The Chemistry of Dienes and Polyenes. Volume 1
Edited by Zvi Rappoport

ISBN: 0-471-96512-X

CHAPTER **13**

Radical addition to polyenes

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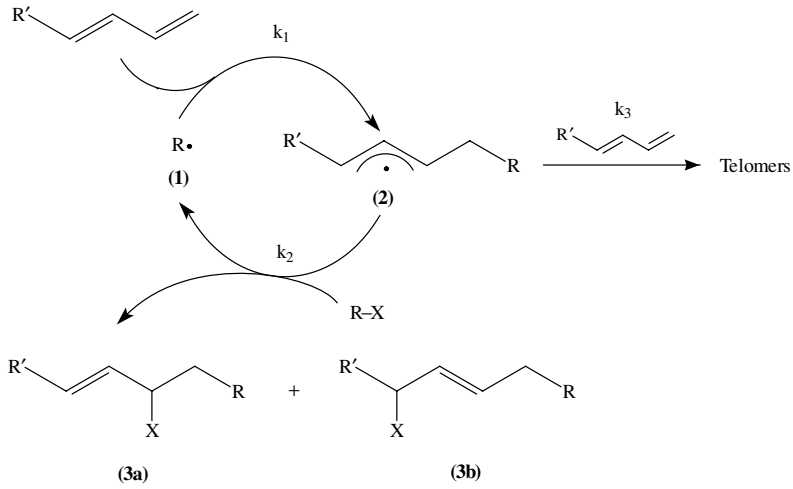
I. INTRODUCTION

Despite the enormous importance of dienes as monomers in the polymer field, the use of radical addition reactions to dienes for synthetic purposes has been rather limited. This is in contrast to the significant advances radical based synthetic methodology has witnessed in recent years. The major problems with the synthetic use of radical addition reactions to polyenes are a consequence of the nature of radical processes in general. Most synthetically useful radical reactions are chain reactions. In its most simple form, the radical chain consists of only two chain-carrying steps as shown in Scheme 1 for the addition of reagent R−X to a substituted polyene. In the first of these steps, addition of radical R• **(1)** to the polyene results in the formation of adduct polyenyl radical **2**, in which the unpaired spin density is delocalized over several centers. In the second step, reaction of **2** with reagent R−X leads to the regeneration of radical **1** and the formation of addition products **3a** and **3b**. Radical **2** can also react with a second molecule of diene which leads to the formation of polyene telomers.



SCHEME 1

Even though more complex schemes involving three or more chain-carrying steps are frequently observed, this most simple mechanism is sufficient to discuss the conditions under which radical chain processes will be synthetically successful. To begin with, the overall rate of product formation is proportional to the square root of the rate of initiation. Once initiated, both chain-carrying steps must occur at rates which are high enough to compete with typical chain-breaking processes such as recombination, disproportionation or reaction with the solvent. It is commonly assumed that successful radical chain reactions can only be achieved if the rate constants k_1 and k_2 are larger than 10^2 M^{-1} s^{-1}[1,2]. While this reactivity requirement is necessary to keep the chain process running at all, synthetically useful chain reactions also have to show sufficient selectivity in a twofold sense. First, reaction of adduct radical **2** with reagent R−X must be significantly faster than reaction with a second polyene molecule. Even though the branching ratio between these two reactions can be influenced to a certain extent by choosing suitable concentrations of R−X and polyene, the rate constant k_2 for reaction between radical **2** and R−X should be at least as large as the propagation rate constant (k_3) for polymerization. Second, the use of polyenes adds an additional selectivity requirement in that the regiochemistry in the initial addition step and in the final reaction of polyenyl radical **2** with reagent R−X should be high for the reaction to be synthetically useful. In the following, we will take a detailed look at each of these criteria to identify the suitability of polyenes in radical chain reactions and identify possible problem areas.

II. REACTIVITY OF POLYENES TOWARDS RADICALS

Absolute rates for the addition of the methyl radical and the trifluoromethyl radical to dienes and a number of smaller alkenes have been collected by Tedder (Table 1)[3]. Comparison of the rate data for the apolar[4] methyl radical and the electrophilic trifluoromethyl radical clearly show the electron-rich nature of butadiene in comparison to ethylene or propene. This is also borne out by several studies, in which relative rates have been determined for the reaction of small alkyl radicals with alkenes. An extensive list of relative rates for the reaction of the trifluoromethyl radical has been measured by Pearson and Szwarc[5,6]. Relative rates have been obtained in these studies by competition with hydrogen

TABLE 1. Absolute rate constants for the addition of methyl and trifluoromethyl radicals to simple alkenes at 164 °C[3]

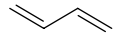
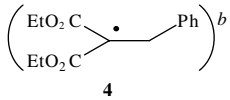
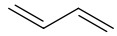
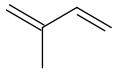
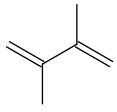
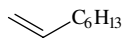
Alkene	k_{ADD} M^{-1} s^{-1}	
	$\bullet CH_3$	$\bullet CF_3$
	3.6×10^5	7.0×10^8
	3.2×10^4	8.1×10^6
	4.5×10^4	3.5×10^6

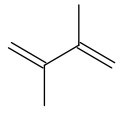
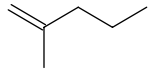
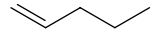
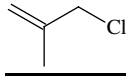
TABLE 2. Relative rate constants for the addition of the trifluoromethyl radical and the diethyl α-benzylmalonyl radical to simple alkenes and dienes

Alkene	$k_{REL}(\bullet CF_3)^a$	k_{REL}  **4** ^{b}
	1.0	—
	1.47	—
	2.10	70
	0.54	82
	0.13	—
	—	1.0

[a] References 5 and 6, in the gas phase at 65 °C.
[b] References 7 and 8, in CH_3CO_2H at 60 °C.

abstraction from 2,3-dimethylbutane (Table 2). Even though the analytical method has been a point of controversy[9], the relative rate data for pairs of alkenes leave little doubt about the high reactivity of dienes towards electrophilic radicals. The higher addition rate to dienes results in this case from lower activation barriers, while preexponential factors are rather similar in most cases. The electrophilic dicyanomethyl radical[10] has also been shown to add significantly faster to 2,3-dimethyl-1,3-butadiene than to other structurally similar alkenes (Table 3)[11]. Dicyanomethyl radicals have in this instance been generated by photochemical initiated addition of bromomalononitrile to alkenes. The diethyl α-benzylmalonyl radical **(4)** has been characterized as ambiphilic due to its bell-shaped reactivity profile in alkene addition reactions[7]. Addition of **4** to styrene and 2,3-dimethyl-1,3-butadiene occurs at comparable rates while addition to 1-octene or to acrylates is

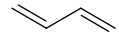
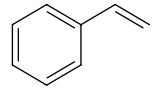
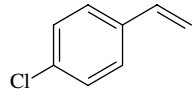
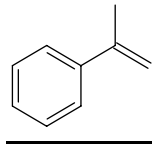
TABLE 3. Relative rate constants for the addition of the dicyanomethyl radical to simple alkenes and dienes in 1,2-dichloroethane at 28 °C[11]

Alkene	k_{REL} (•CH(CN)$_2$)
	100
	6.7
	0.44
	0.52

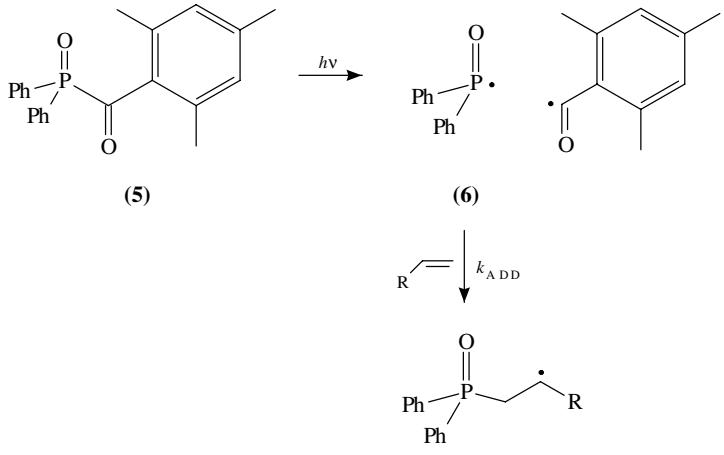
slower by almost two orders of magnitude (Table 2). From the absolute rate constant for addition of **4** to 1-octene of $k_{ADD} = 9.8 \times 10^4$ M^{-1} s^{-1} at 60 °C in acetic acid, the rate for addition to 2,3-dimethyl-1,3-butadiene can be calculated as $k_{ADD} = 6.9 \times 10^6$ M^{-1} s^{-1}[7,8]. Comparable rates for the addition to butadiene and substituted styrenes have also been found in the trichloromethyl radical addition to alkenes[12]. Again, the technique of competition kinetics has been used to obtain these values (Table 4).

Due to the significant importance of dienes as monomers, absolute as well as relative rate data have been determined for the addition of initiator derived radicals. Photolysis of (2,4,6-trimethylbenzoyl)diphenylphosphine oxide (TMDPO) **5** leads to the formation of

TABLE 4. Relative rate constants for the addition of the trichloromethyl radical to substituted styrenes and butadiene in $BrCCl_3$ at 80 °C[12]

Alkene	k_{REL}(•CCl_3)
	1.0
	0.5
	0.5
	2.1

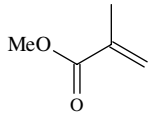
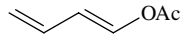
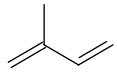
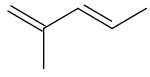
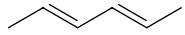
diphenylphosphonyl radical **6**. Subsequent addition of **6** to alkenes and dienes has been shown to proceed rapidly (equation 1) by time-resolved EPR spectroscopy (Table 5)[13,14].



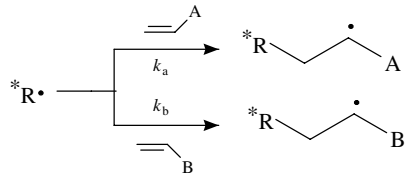
(5) **(6)** (1)

The phosphonyl radical **6** cannot easily be classified as nucleophilic or electrophilic, since the bimolecular rate constants for addition to a wide range of alkenes vary by no more than one order of magnitude. A similar observation can be made for relative addition rates of other initiator derived radicals, in which the radical centers are substituted by electron-donating as well as electron-withdrawing substituents. The end group analysis of diene polymers using isotopically labeled initiators has proven especially fruitful in this regard[15,16a]. In this method, isotopically labeled initiators are reacted with a mixture of alkenes. The ratio of the rate constants for addition of initiator derived radicals to both monomers can then be determined by end group analysis of the resulting copolymer. ^{13}C-NMR spectroscopy appears to be the method of choice if ^{13}C-enriched initiator is

TABLE 5. Absolute rate data for the addition of the diphenylphosphonyl radical to various alkenes in benzene at 20 °C[13,14]

Polyene	Bimolecular rate constant k_{ADD} ($M^{-1}\,s^{-1}$)	Reference
	$(1.6 \pm 0.4) \times 10^7$	13
	$(1.5 \pm 0.2) \times 10^7$	13
	$(1.4 \pm 0.2) \times 10^7$	14
	$(1.2 \pm 0.2) \times 10^7$	14
	$(2.9 \pm 0.2) \times 10^6$	14

available that carries the label sufficiently close to the alkene addition site (equation 2).



(2)

As a point of reference, relative rates for methyl methacrylate have also been included in Table 6. While addition to butadiene or isoprene is significantly faster as compared to methyl methacrylate for electrophilic or ambident radicals, little rate variation is found for the 1-phenylethyl radical.

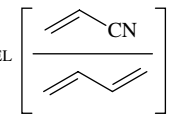
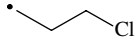
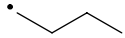
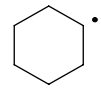
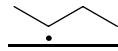
The dependence of relative rates in radical addition reactions on the nucleophilicity of the attacking radical has also been demonstrated by Minisci and coworkers (Table 7)[17]. The evaluation of relative rate constants was in this case based on the product analysis in reactions, in which substituted alkyl radicals were first generated by oxidative decomposition of diacyl peroxides, then added to a mixture of two alkenes, one of them the diene. The final products were obtained by oxidation of the intermediate allyl radicals to cations which were trapped with methanol. The data for the acrylonitrile–butadiene

TABLE 6. Relative bimolecular addition rates for the reaction of initiator derived radicals obtained by polymer end group analysis[15,16a]

Alkene	Relative addition rates k_{rel}			
	NC, H_3C^*, CH_3^*, •	MeO_2C, H_3C^*, CH_3^*, •	Ph, $*$, H, CH_3, •	O, Ph, O•
CO_2Me	1.0[a]	1.0[b]	1.0[c]	1.0
	7.0	3.0	1.3	6.4
	3.3	1.9	0.7	3.5
	6.5	4.2	1.2	8.3
Ph, Ph	1.4	1.1	0.7	13.0

[a] At 60 °C in benzene, Reference 16a
[b] At 60 °C in benzene, Reference 16b
[c] At 100 °C in toluene, Reference 16a.

TABLE 7. Relative rate constants for the addition of substituted alkyl radicals to the acrylonitrile/butadiene pair in methanol at 0 °C[17]

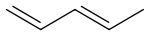
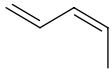
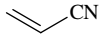
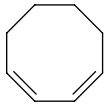
Radical	k_{REL} 
$ClCH_2\bullet$	1.2
$H_3C\bullet$	1.7
	1.7
	3.1
$CH_3CH_2\bullet$	6.2
	9.0
	9.3
	11.6
	15.8

pair collected in Table 7 is rather typical and shows how the relative addition rate mainly depends on two effects. First, the addition to the electron-deficient alkene becomes comparatively faster with an increasing number of alkyl substituents at the radical center. Second, substitution of the alkyl groups by electronegative chlorine atoms reduces the relative addition rate. Both effects can readily be explained with substituent effects on the nucleophilicity of the radicals. The relative addition rate does not, however, exceed a value of 20 even for the most nucleophilic alkyl radicals.

In many synthetically useful radical chain reactions, hydrogen donors are used to trap adduct radicals. Absolute rate constants for the reaction of the resulting hydrogen donor radicals with alkenes have been measured by laser flash photolysis techniques and time-resolved optical absorption spectroscopy for detection of reactant and adduct radicals[18a]. Addition rates to acrylonitrile and 1,3-pentadienes differ by no more than one order of magnitude, the difference being most sizable for the most nucleophilic radical (Table 8). The reaction is much slower, however, if substituents are present at the terminal diene carbon atoms. This is a general phenomenon known from addition reactions to alkenes, with rate reductions of *ca* 100 observed at ambient temperature for the introduction of methyl groups at the attacked alkene carbon atom[18b]. This steric retardation of the addition process either completely inhibits the chain reaction or leads to the formation of unwanted products.

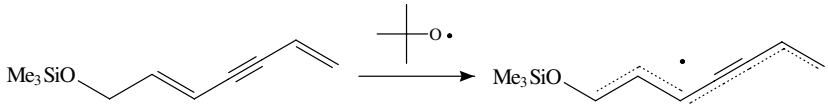
One side reaction commonly encountered in the reaction of alkyl-substituted polyenes with oxygen-centered radicals is hydrogen abstraction from the alkyl group in positions adjacent to the polyene π-system. For reactions of the *tert*-butyloxy radical, this reaction becomes so dominant that it can be used to form polyenyl radicals by hydrogen abstraction

TABLE 8. Absolute rate constants for the addition of triethylsilyl, tri-*n*-butylgermyl and tri-*n*-butylstannyl radicals to alkenes[18a]

Alkene	$Et_3Si\bullet$		*n*-$Bu_3Ge\bullet$		*n*-$Bu_3Sn\bullet$	
	T(K)	k_{ADD} ($M^{-1}\,s^{-1}$)[a]	T(K)	k_{ADD} ($M^{-1}\,s^{-1}$)[b]	T(K)	k_{ADD} ($M^{-1}\,s^{-1}$)[c]
	299	1.4×10^8	297	4.6×10^7	298	6.8×10^7
	—	—	298	4.0×10^7	298	6.8×10^7
	302	1.1×10^9	300	1.8×10^8	299	8.8×10^7
	299	3.8×10^6	299	6.4×10^5	297	$< 7 \times 10^4$

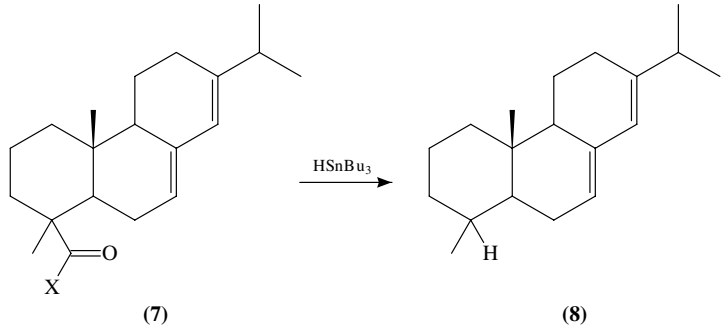
[a]Di-*tert*-butyl peroxide/Et_3SiH (1:1) as solvent.
[b]Di-*tert*-butyl peroxide + 15% (vol) *n*-Bu_3GeH as solvent.
[c]Di-*tert*-butyl peroxide + 10% (vol) *n*-Bu_3SnH as solvent.

from alkyl-substituted polyenes (equation 3)[19].



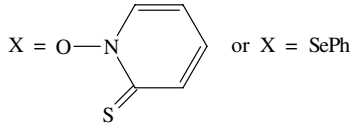
(3)

In most other cases, however, the diene system simply becomes too unreactive to participate in radical chain reactions. Thus, the reductive decarboxylation of ester **7** by Barton-POC ester methodology[20] or as the selenoester[21] gives the reduced product **8**, cleanly without any trace of product in which the diene system has participated in the reaction (equation 4)[20,21].



(7) **(8)**

(4)



or X = SePh

Based on the data collected in this section, one must conclude that the addition of radicals to dienes is certainly rapid enough to compete against the typical chain-breaking processes and that especially the addition of electrophilic radicals to polyenes appears to bear significant potential. Terminally substituted polyenes are likely to be unsuitable for radical addition reactions due to their lower addition rates and to undesirable side reactions.

III. REACTIVITY OF POLYENYL RADICALS

Little quantitative information is available for the kinetics of the reaction of polyenyl radicals. The propagation rate constants for polymerization reactions might be indicative, however, of the characteristics of free polyenyl radicals in solution[6,22,23]. From Table 9 it can be seen that the propagation rate constants for butadiene and isoprene are smaller by a factor of 10 to 20 as compared to those for acrylonitrile and typical acrylates. From Section 2, an increase in rate would have been expected on changing from acrylates to dienes. The lower rates actually observed must therefore be attributed to the lower reactivity of the allyl radicals formed during diene polymerization. The sluggish reactivity of polyenyl radicals is usually rationalized through the high resonance stabilization of these species[24–29]. The stabilization energy for the allyl radical obtained in various ways amounts to 13.2–14.6 kcal mol^{-1}. A limiting value for the stabilization energy of indefinitely long polyenyl radicals has been estimated to be between 24 and 33.3 kcal mol^{-1}. Even if reaction occurs at the terminal positions of the polyenyl radical system, partial loss of the stabilization energy and an increased activation barrier will result for this reaction.

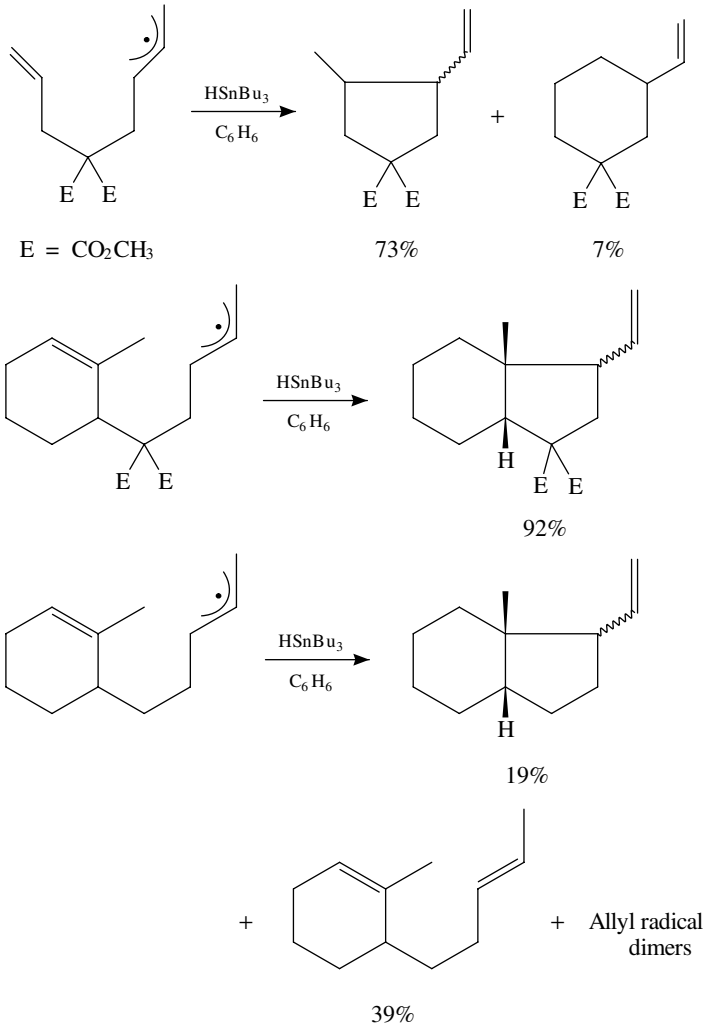
Cases in which allyl radicals display sufficient reactivity to participate successfully in radical chain reactions include the addition of bromotrichloromethane to butadiene[30,31], the reaction of cyclopentadiene with tosyl cyanide[32], the addition of thiols[33–36a], stannanes[35,37–39] and hydrogen halides[35,40]. All these reactions follow the simple two-step radical chain mechanism depicted in Scheme 1, and the low reactivity of the intermediate allyl radicals can be compensated by using the trapping agent in excess or even as the solvent. In chain reactions with three or more chain-carrying radicals, this compensation is not possible anymore, because the concentration of the reaction partners has to be chosen such that the selectivity requirements for all intermediate radicals are satisfied[1]. Complex radical chain reactions with polyenes as one of the reactants are therefore not known.

The reactivity of allyl radicals does, however, appear to be sufficient for intramolecular radical reactions. In a systematic study, Stork and Reynolds investigated the feasibility of allyl radical 5-*exo* cyclizations[41]. It was found that cyclization proceeds readily for a variety of systems, especially for those with geminal 3,3-diester substitution. Mixtures of *cis/trans*-cyclopentanes are formed as the major products, while 6-*endo* cyclization is hardly observed[42]. Allyl radicals behave in this respect much like alkyl radicals[43]. Cyclization is not even hindered by the presence of substituents at the attacked carbon

TABLE 9. Propagation rate constants (k_{prop}) for the polymerization of selected alkenes and dienes at 60 °C[6,22,23]

Alkene	k_{PROP} (M^{-1} s^{-1})	log A	E_a (kcal mol^{-1})
Butadiene	100	8.1	9.3
Isoprene	50	8.1	9.8
Methyl methacrylate	734	7.0	6.3
Acrylonitrile	1960	—	—

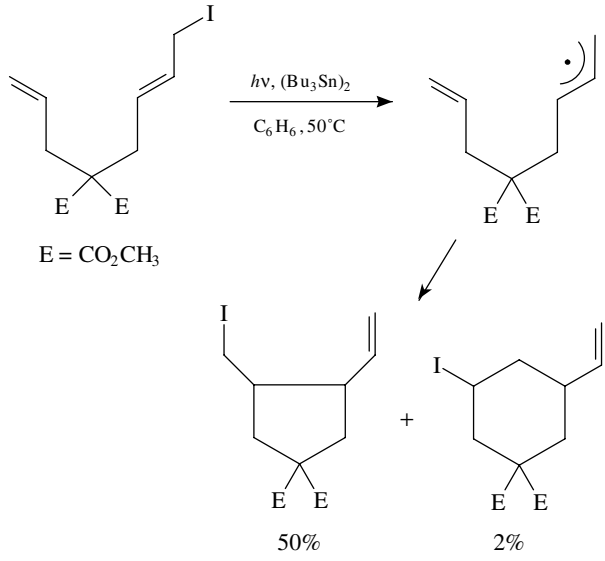
atom. Only in the absence of the accelerating[44] effect of the *gem*-diester substitution does cyclization become too slow to compete with either reduction of the allyl radical or, as a typical side reaction of allyl radicals, dimerization (equation 5). Experimental evidence was also collected to show that allyl radical cyclizations are mainly under kinetic control. The *cis/trans* selectivity in cyclopentane formation depends, however, on the nature of the hydrogen donor.



(5)

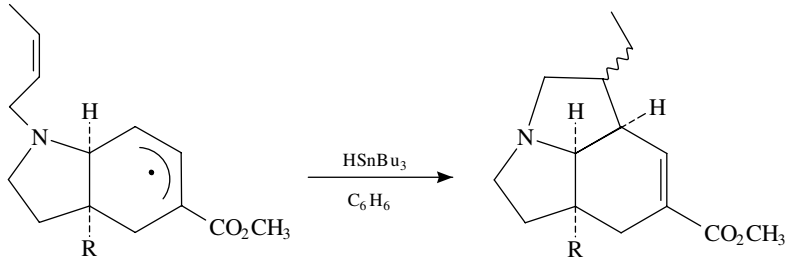
The strong prevalence for allyl radicals to cyclize in 5-*exo* fashion as well as the accelerating effect of geminal diester substitution was also observed in iodide atom transfer reactions of allylic iodides[44]. The ratio of 5-*exo* to 6-*endo* product is even higher than for hydrogen trapping, probably also due to the lower temperature in this photolytically initiated reaction (equation 6). Allylic dimers were again isolated as side products. No

cyclization was observed in the absence of ester groups.



(6)

Cyclization has also been observed for those cases in which allyl radicals are stabilized by additional substituents. Radicals **9**, which carry an ester group at one allyl terminus, cyclize readily in a 5-*exo* fashion to furnish products **10** in good yield. No 6-*exo* product was found in this instance (equation 7)[45].

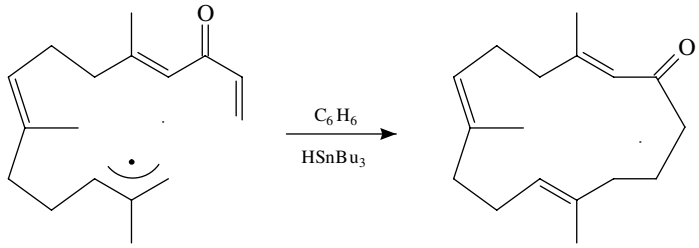


(7)

(9) **(10)**

R = Ph, SPh 60 – 85%

Finally, allyl radicals have successfully been employed in macrocyclization reactions, in which the slower rate of reaction of allyl radicals with hydrogen donors turned out to be advantageous[46]. Thus, radical **11** cyclizes in 14-*endo* mode to provide, after trapping with tin hydrogen, the product **12** as a *E/Z*-mixture of the C2/C3 double bond. No products derived from 6-*exo* or 10-*exo* cyclizations could be found (equation 8). This can be rationalized by assuming a faster rate of addition of the nucleophilic allyl radical to the electron-deficient terminal double bond than to the C6 or C10 double bonds.



(8)

(11) **(12)** 52%

In conclusion, it appears that allyl or polyenyl radicals are much less reactive than alkyl radicals, which restricts the use of polyenes in intermolecular radical chain reactions to simple two-step processes. Allyl radicals are, however, reactive enough to partake in a variety of intramolecular reactions.

IV. REGIOSELECTIVITY OF RADICAL ADDITION REACTIONS TO POLYENES

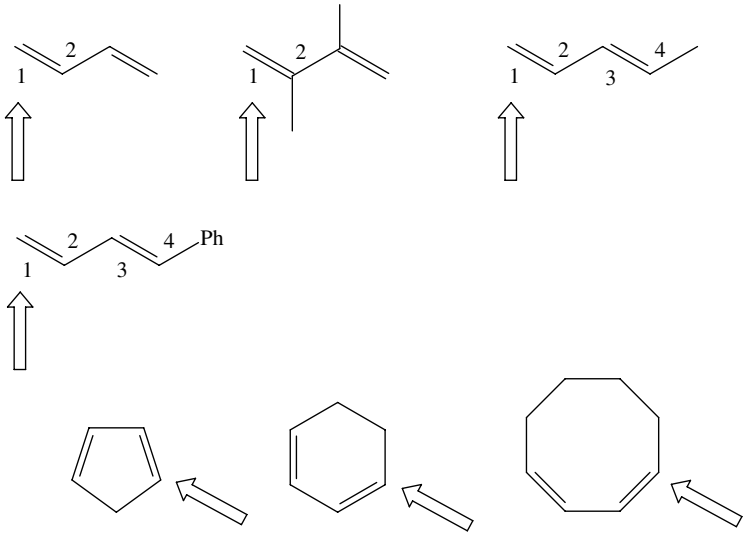
The regioselectivity in radical addition reactions to alkenes in general has successfully been interpreted by a combination of steric and electronic effects[18b,47]. In the absence of steric effects, regiochemical preferences can readily be explained with FMO theory. The most relevant polyene orbital for the addition of nucleophilic radicals to polyenes will be the LUMO; for the addition of electrophilic orbitals it will be the HOMO. Table 10 lists the HOMO and LUMO coefficients (without the phase sign) for the first three members of the polyene family together with those for ethylene as calculated from Hückel theory and with the AM1 semiempirical method[48].

The orbital coefficients obtained from Hückel calculations predict the terminal position to be the most reactive one, while the AM1 model predicts the C1 and C3 positions to be competitive. In polyenes, this is true for the addition of nucleophilic as well as electrophilic radicals, as HOMO and LUMO coefficients are basically identical. Both theoretical methods agree, however, in predicting the C1 position to be considerably more reactive as compared to the C2 position. It must be remembered in this context that FMO-based reactivity predictions are only relevant in kinetically controlled reactions. Under thermodynamic control, the most stable adduct will be formed which, for the case of polyenyl radicals, will most likely be the radical obtained by addition to the C1 position.

TABLE 10. HOMO and LUMO coefficients for ethylene and selected polyenes

Alkene		HMO				AM1			
		C1	C2	C3	C4	C1	C2	C3	C4
1	LUMO	0.71				0.71			
	HOMO	0.71				0.71			
1 2	LUMO	0.60	0.37			0.56	0.43		
	HOMO	0.60	0.37			0.56	0.43		
1 2 3	LUMO	0.52	0.23	0.42		0.45	0.28	0.47	
	HOMO	0.52	0.23	0.42		0.44	0.29	0.47	
1 2 3 4	LUMO	0.46	0.16	0.41	0.30	0.36	0.20	0.44	0.37
	HOMO	0.46	0.16	0.41	0.30	0.36	0.21	0.43	0.37

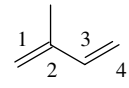
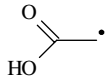
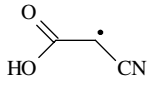
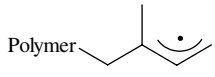
Most of the dienes investigated experimentally show high regioselectivity in radical addition reactions. The preferred position of attack is shown in Scheme 2.



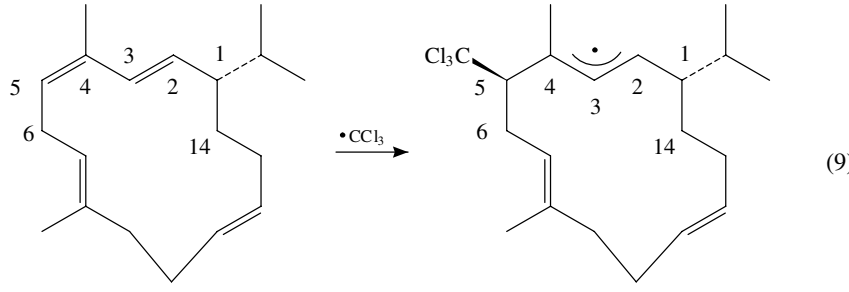
SCHEME 2

In one of the earliest investigations of regioselectivity in radical addition reactions to polyenes, the addition of hydrogen bromide to 1,3-butadiene was observed to yield mainly the 1,4-addition product in the presence of peroxides[40]. The preference for attack at the C1 position of 1,3-butadiene has subsequently been observed for a large number of radicals[3,14,17,30,34,37–39,49–56]. Only for the addition of the methyl radical has the ratio of addition to the C1 vs C2 actually been measured. A value of C1:C2 = 1.0:0.01 has been found[50]. For all other cases, products arising from attack at C2 have not been reported. This is also true for radical addition to 2,3-dimethyl-1,3-butadiene[9,10,32,34,37–39,57]. Additions to 1,3-pentadiene occur predominantly at the C1 position due to the steric effect exerted by the terminal methyl group[10,33,34,37,51,58]. This is a reflection of the reduced addition rate to C4 due to the steric effects of α-substituents[18b]. Rate retardation does not, however, go as far as redirecting addition to the C2/C3 centers, as ESR investigation of the propagating radical chain in the polymerization of 2,4-hexadiene has shown[14]. The early observation of exclusive C4-addition in the reaction of thiophenol with 1-phenyl-1,3-butadiene can also be explained by steric effects[59]. The hydrostannation of cyclic olefins proceeds with exclusive attack of the intermediate stannyl radicals on the terminal diene positions[37,38]. Addition of malonyl or tosyl radicals to cyclopentadiene and cyclohexadiene also takes place at the C1 position[10,32,57,60]. Isoprene represents an interesting case in that the two terminal positions are nonidentical due to their β-substituents. Again, no additions to the non-terminal carbon centers have been reported, but the C1:C4 addition ratio strongly depends on the attacking radical (Table 11). The selectivity pattern in the addition of thiols to chloroprene is almost identical to that observed for isoprene[33,34]. A somewhat more complex situation exists in the radical chain addition of CCl_4 to cembrene **13**[61]. Attack of the trichloromethyl radical occurs exclusively at the C5 center of **13** to form adduct radical **14** (equation 9). The high regio- and stereoselectivity appears

TABLE 11. Regioselectivity in the radical addition to isoprene

Radical	T (°C)	Solvent	 $C_1:C_2:C_3:C_4$	Reference
$Cl_3C\bullet$	80	CCl_4	C4 only	51
	20	C_6H_6	C1 only	13
	25	HOAc	1.0:0.0:0.0:2.8	53
	25	HOAc	1.0:0.0:0.0:7.8	53
	0	CH_3OH	3.4:0.0:0.0:1.0	54b
$Me_3Sn\bullet$	100	Me_3SnH	1.0:0.0:0.0:1.0	38
	20	Isoprene	C1 only	14
$CH_3S\bullet$	25	neat	3.5:0.0:0.0:1.0	33,34
$PhS\bullet$	25	neat	39:0.0:0.0:1.0	33,34
	25	neat	8.9:0.0:0.0:1.0	33,34

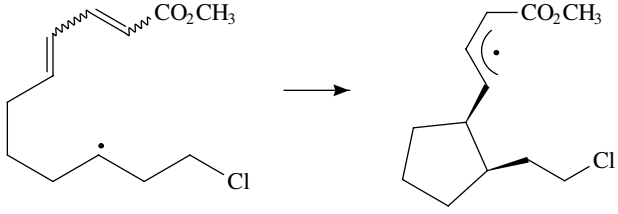
to be the consequence of steric effects as the X-ray structure of **13** shows the C2 position blocked by the isopropyl group from the top side, and by the ring C14 center from the bottom side, while addition can occur unhindered from the top side at C5.



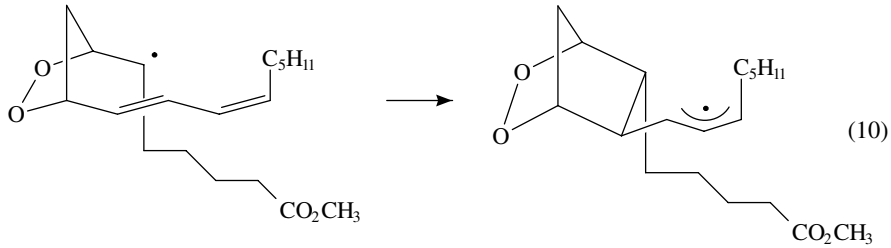
(9)

(13) **(14)**

The regioselectivity in diene addition reactions can also be influenced by ring strain effects in cyclization reactions. The regioselectivity is highly predictable in those cases, in which addition to the preferred diene center forms the preferred ring size. Thus, the cyclization of radical **15** proceeds readily to form the *cis*-disubstituted cyclopentylmethyl radical **16** with high selectivity[39]. Similarly, cyclization of **17** affords exclusively bicyclic radical **18**, in which the additional cyclopentane ring has been formed by addition to the terminal position of the butadiene subunit[62]. This preference for 5-*exo* cyclizations onto dienes is not even disrupted by substituents at the C1 or C4 positions of the diene system, as seen for radical **19**, which cyclizes to **20** (equation 10)[63]. This is in contrast to alkyl radical cyclizations to alkenes, in which major amounts of 6-*endo* cyclization is observed for 5-substituted systems[43].

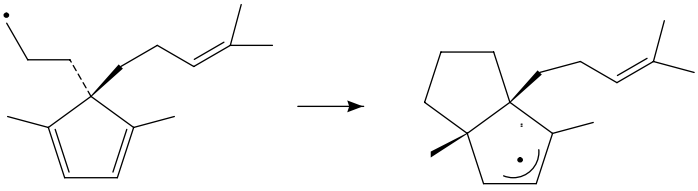


(15) **(16)**



(10)

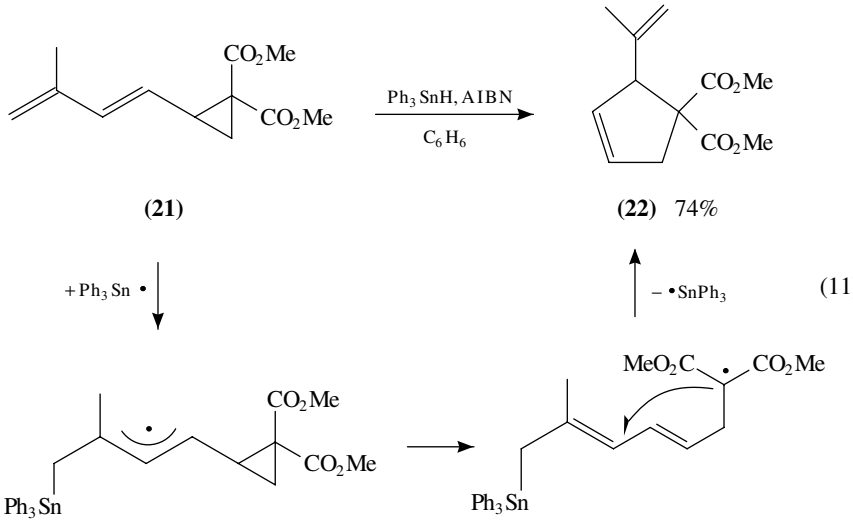
(17) **(18)**



(19) **(20)**

An interesting example of the situation in which the preferred addition site does not lead to the preferred ring size has been provided by Miura and coworkers with the extended vinylcyclopropane rearrangement of substrate **21**[64]. Formation of vinylcyclopentyl derivative **22** requires the addition of the triphenylstannyl radical to the unsubstituted terminus

of the diene moiety in **21** to form intermediate allyl radical **23**. Cyclopropane ring opening then gives acyclic radical **24**, which cyclizes in a 5-*exo*-trig fashion to yield, after elimination of triphenylstannyl radical, product **22** (equation 11). The attack at the C2 center of the diene system in the cyclization step is the only known example in which addition to the central carbon atoms of the diene unit occurs readily. In this particular case, the unusual regiochemistry is caused by the favorable cyclization geometry as well as by the presence of the triphenylstannyl leaving group in the γ-position.



(11)

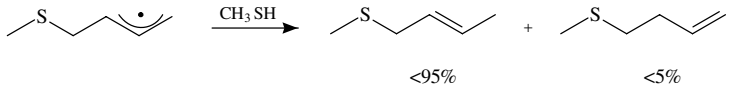
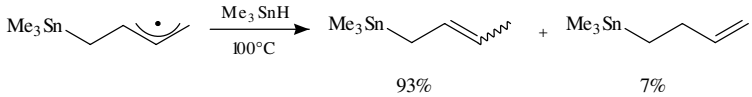
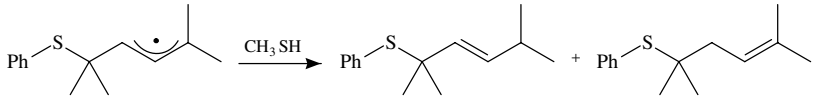
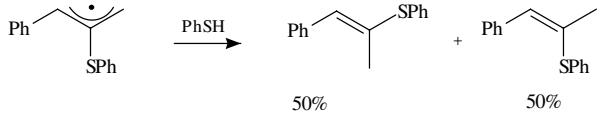
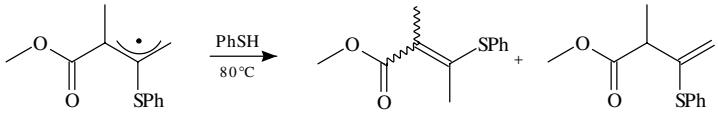
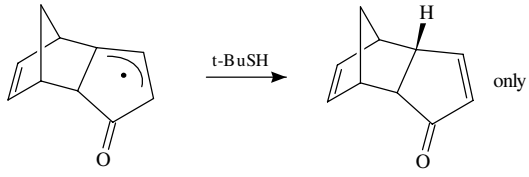
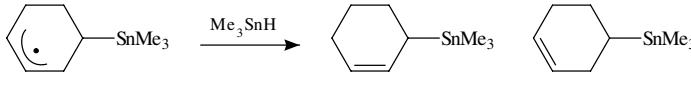
In conclusion, the regiochemistry of radical attack at dienes appears to be rather predictable by considering steric and electronic effects. Attack is almost always preferred at the terminal carbon atoms of the diene. α-Substituents retard the addition significantly in all known cases while the steric effects of β-substituents depend on the nature of the attacking radical.

V. REGIOSELECTIVITY IN REACTIONS OF POLYENYL RADICALS

A. Trapping with Closed-shell Molecules

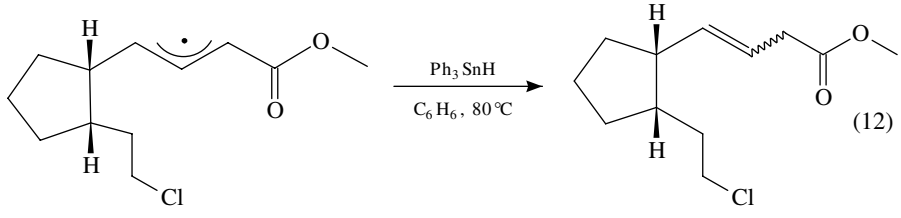
Allyl radicals substituted at only one of the terminal carbon centers usually react predominantly at the unsubstituted terminus in reactions with nonradicals. This has been shown in reactions of simple dienes such as butadiene, which react with hydrogen bromide, tetrachloromethane or bromotrichloromethane to yield overall 1,4-addition products[35,58]. The reaction of allyl radicals with hydrogen donors such as thiols[33,34,36a] or tin hydrides[37–39] has been investigated and reviewed repeatedly. In most cases, the thermodynamically more favorable product is formed predominantly. This accords with formation of either the higher substituted alkene or the formation of conjugated π-systems. Not in all cases, however, is the formation of the thermodynamically more favorable product identical to overall 1,4-addition to the diene. In those cases in which allyl radicals are formed through reaction of dienes with tin hydrides or thiols, the

TABLE 12. Examples for the trapping of allyl radicals with thiols and tin hydrides

	Reference
	33
	38
	33
	36a
	36b
	36c
	38

reaction with thiols appears to proceed with slightly higher regioselectivity. The rule of predominant formation of the thermodynamically more favorable product also pertains to the *E*:*Z* selectivity of the product alkenes[36]. Table 12 gives some representative examples.

The few cases in which thermodynamic control is not effective appear to be dominated by steric effects[39]. Thus, trapping of radical **25** with triphenyltin hydride regioselectively yields product **26**, in which the double bond is separated from the ester through a methylene bridge (equation 12).



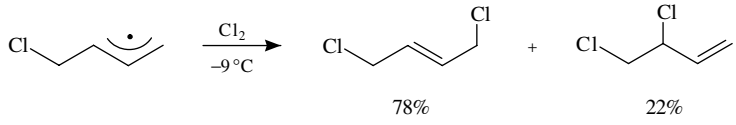
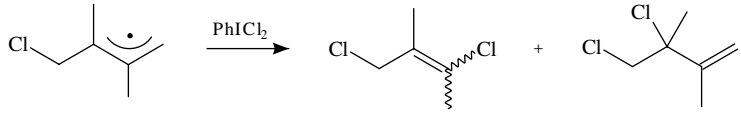
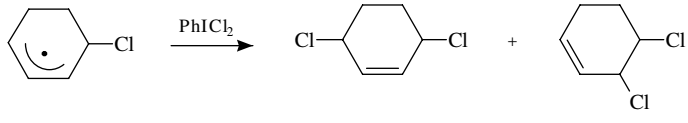
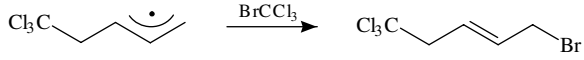
(12)

(25) **(26)** 60%

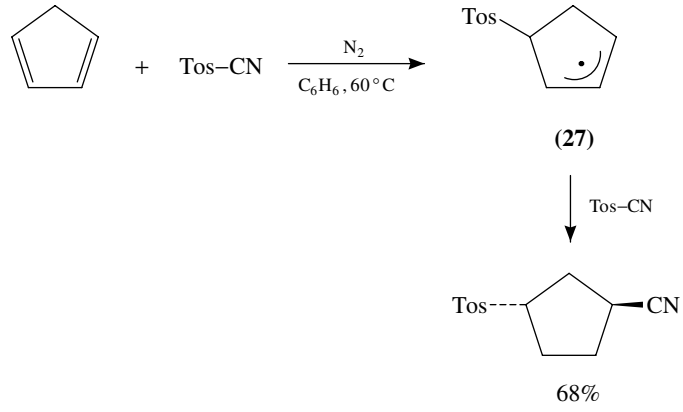
Allyl radicals are also formed during the radical halogenation of dienes[65,66]. The regioselectivities obtained in these reactions depend markedly on the reaction conditions, because formation of the reaction products is also possible through polar reaction pathways. In those cases in which proper care has been taken to ensure a radical mechanism, the halogenation of dienes proceeds with much lower regioselectivity in the halogen transfer step as compared to the hydrogen transfer reactions considered before (Table 13). The reagent used to deliver the halogen, in contrast, appears to have only a small influence. Many results for the trapping of allyl radicals with bromine exist from the allylic halogenation with *N*-bromosuccinimide. The regioselectivity of this reaction has been reviewed[67].

The addition of tosyl cyanide to cyclopentadiene leads to intermediate formation of radical **27**, which then is trapped by tosyl cyanide by cyano group transfer. The *trans*-

TABLE 13. Examples for the trapping of allyl radicals with halogen donors

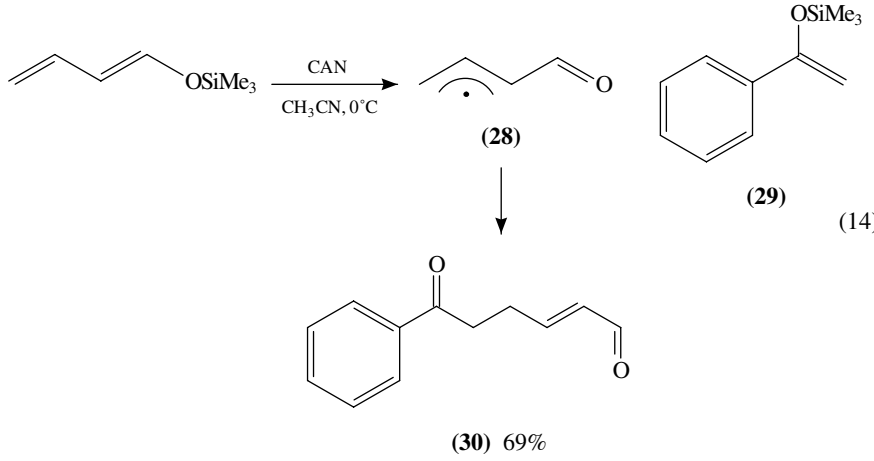
	Reference
 78% 22%	65
 52% 48%	66
 50% 50%	66
	30, 31, 35

1,4-addition product is formed exclusively (equation 13).



(13)

Only a few examples exist for the intermolecular trapping of allyl radicals with alkenes[68,69]. The reaction of α-carbonyl allyl radical **28** with silyl enol ether **29** occurs exclusively at the less substituted allylic terminus to form, after oxidation with ceric ammonium nitrate (CAN) and desilylation of the adduct radical, product **30** (equation 14). Formation of terminal addition products with *trans*-configuration has been observed for reaction of **28** with other enol ethers as well.



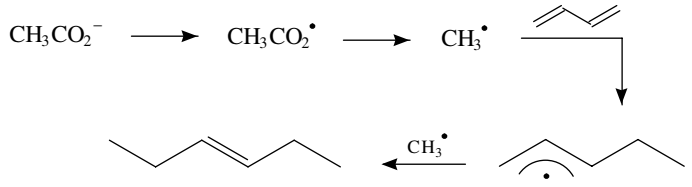
(14)

Intramolecular trapping of allyl radicals by carbon–carbon double bonds has, of course, been observed to occur readily and with high selectivity (see Sections III and IV).

B. Trapping with Radicals

The trapping of allyl radicals with other open-shell species can be studied in all reactions in which a sufficiently high concentration of radicals is created and in which the concentration of nonradical trapping agents is low. This prerequisite has been met in Kolbe electrolysis reactions, in which radicals are generated by one-electron oxidation of carboxylate anions. One of the simplest systems, the reaction of methyl radicals with

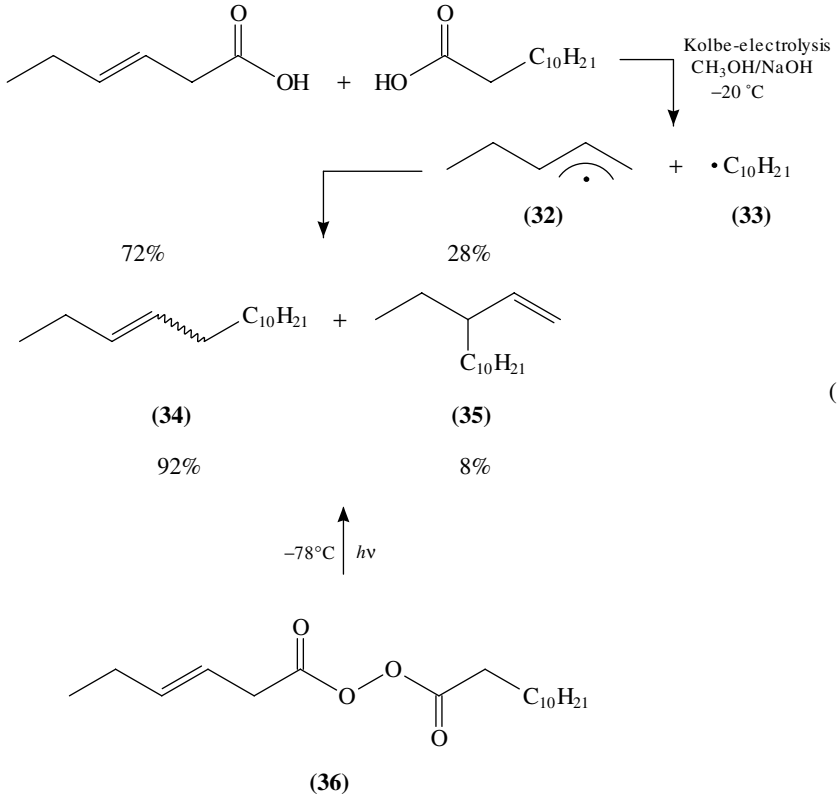
butadiene, has been studied in this way[52]. Methyl radicals are obtained by oxidation of acetate anions and subsequent decarboxylation of the resulting acetyloxy radicals. Addition to butadiene then leads to the adduct allyl radical **31**, which is trapped by a second methyl radical to form the overall 1,4-addition product *trans*-3-hexene exclusively (equation 15).



(15)

(31)

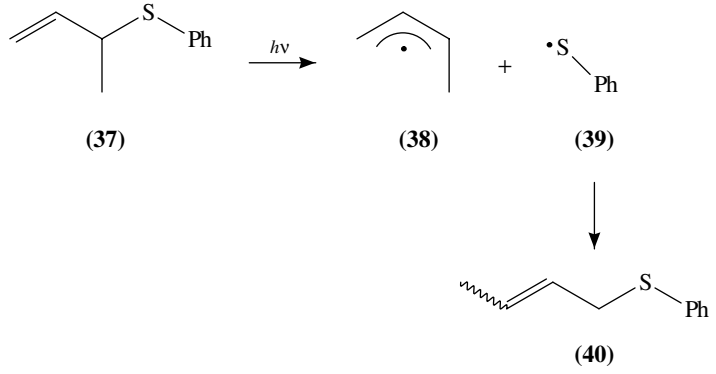
Allyl radicals can, of course, also be generated by electrolysis of the corresponding β,γ-unsaturated carboxylic acids together with a second carboxylic acid. This 'mixed Kolbe electrolysis' method has been used to study the recombination of allyl radical **32** with the undecyl radical **33**[70]. Recombination leads to the formation of adducts **34** and **35** in a ratio of 72:28, again preferring the product with the higher substituted double bond (equation 16).



(16)

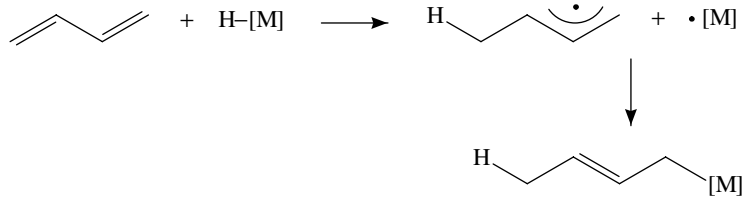
(36)

The same intermediate radicals can be formed by photolysis of the mixed diacyl peroxide **36**[70]. The resulting radical pair recombines, after decarboxylation, in a ratio of 92:8 (equation 16). The higher regioselectivity in this latter case appears to result from the limited mobility of the intermediate radicals in the solid state (at −78 °C). This experiment illustrates that a meaningful comparison of selectivities requires experimental data obtained under comparable reaction conditions. Photolytically generated radical pairs have also been used to investigate the regioselectivity in the recombination of allyl radical **38** with thiophenyl radical **39**. Terminal trapping is, as seen before for radical **32**, the preferred mode of action since photolysis of thiol ether **37** gives product **40** exclusively (equation 17)[71].



(37) **(38)** **(39)** **(40)** (17)

Many more examples have been collected for the reaction of transition metal hydride complexes with 1,3-dienes, which appear to proceed via radical pair mechanisms, even without photochemical activation[72–77]. The following general mechanism has been assumed to be operative for the reaction of $HMn(CO)_5$[72,73], $HFe(CO)_4SiCl_3$[74,75], $HFe(CO)_2Cp$[76] and $HCo(CO)_4$ (H-[M]) (equation 18)[77].

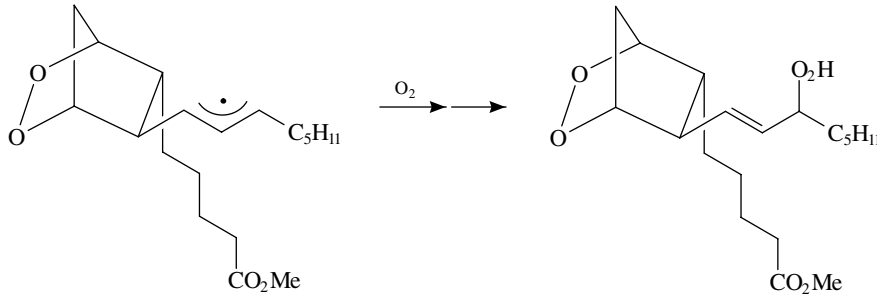


(18)

The mechanistic proposal of rate-limiting hydrogen atom transfer and radical recombination is based on the observed rate law, the lack of influence of CO pressure, kinetic isotope effects [studied with $DMn(CO)_5$] and CIDNP evidence. In all known cases, exclusive formation of the overall 1,4-addition product has been observed for reaction of butadiene, isoprene and 2,3-dimethyl-1,3-butadiene. The preferred trapping of allyl radicals at the less substituted side by other radicals has actually been so convincing that its observation has been taken as a mechanistic probe[78].

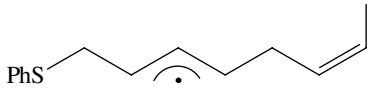
Oxygen can also be considered an open-shell trapping agent in its ground state triplet state. An example for the highly regioselective trapping of a sterically demanding allyl radical by oxygen has been provided in the study of the biomimetic synthesis

of prostaglandins[62]. As seen before in the tin hydride trapping of allyl radicals, the bicyclic substituent in **41** reduces the reactivity of one of the allylic radical centers dramatically and reaction occurs regioselectively only at one end of the allyl system to yield hydroperoxide **42** (equation 19)[79]. Trapping by oxygen proceeds much less selectively in more symmetrically substituted allyl radicals such as **43**, which yields peroxy radicals **44** and **45** in a ratio of 27:73 (equation 20)[79].

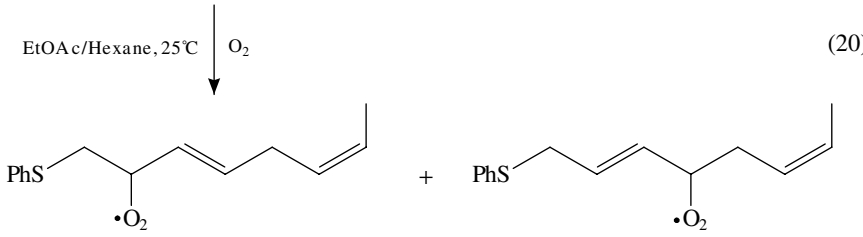


(41) **(42)**

(19)



(43)



(20)

(44) **(45)**

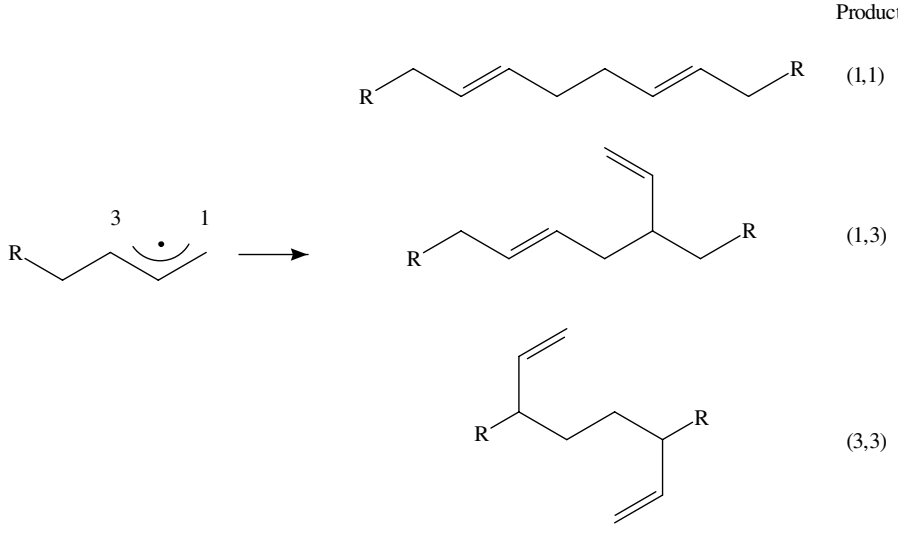
27 : 73

A number of earlier investigations of the regioselectivity in the reaction of allyl radicals with other radicals has been plagued by severe analytical problems[41,80].

C. Dimerization of Allyl Radicals

The regioselectivity in the dimerization of allyl radicals has been studied by a variety of methods. One of the earliest investigations into this field employed the Kolbe electrolysis

to generate carboxylate derived radicals in the presence of dienes[49]. The complex product mixture obtained could only be analyzed at that time to contain major amounts of product resulting from recombination at the least substituted allyl terminus. The same difficulty was encountered in the dimerization of allyl radicals, which result from the addition of alkoxy radicals to butadiene[81a]. Again, the major product appeared to result from recombination at the less substituted center of the intermediate allyl radical. Generally, the recombination of allyl radicals with an unsymmetrical substitution pattern can produce (1,1)-, (1,3)- or (3,3)-coupling products (Scheme 3). Products (1,1) and (1,3) frequently occur as mixtures of *Z*- and *E*-isomers.



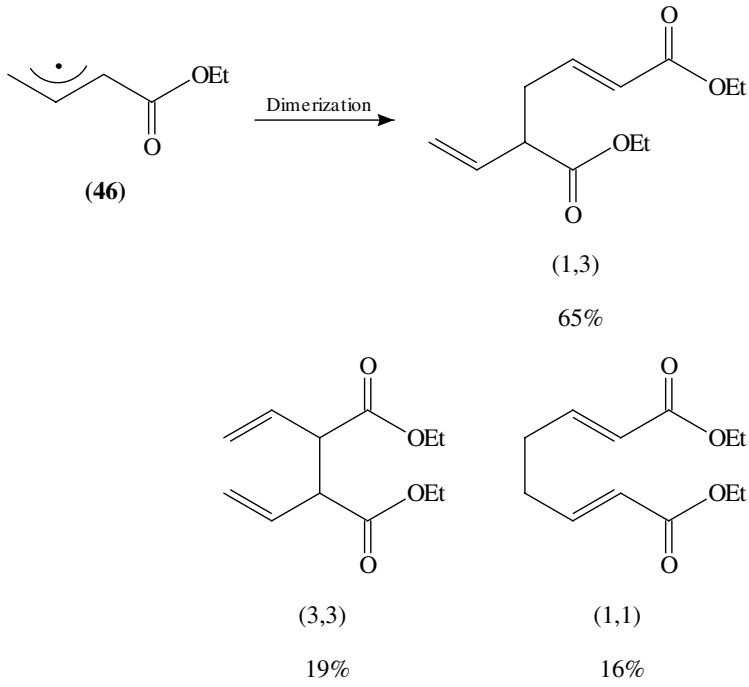
SCHEME 3

Assuming that the allyl C1 and C3 centers have an intrinsic reactivity, which is independent of the direct coupling partner (C1 or C3 of the second allyl radical), the results of a variety of different experimental investigations can be examined comparatively. If this assumption holds true, the relative product distribution for an allyl radical with intrinsic reactivity of **A** at C1 and of **B** at C3 should be given by equation 21.

$$(1,1):(1,3):(3,3) = \mathbf{A}^2 : 2\mathbf{AB} : \mathbf{B}^2 \tag{21}$$

Despite the fact that a quantitative product analysis is often difficult to achieve in these reactions, the product distribution expected from equation 21 is indeed found in many cases. Table 14 lists some representative examples.

In all cases, reaction at the less substituted allyl terminus is preferred by a factor of two or more, even though the actual degree of regioselectivity depends strongly on the substitution pattern. Those cases in which the product distribution deviates strongly from that predicted by equation 21 include allyl radicals connected to other π-systems. A point in case is the recombination of 1-ethyloxycarbonyl allyl radical **46**, which predominantly yields the (1,3)-recombination product (equation 22)[71].



(46)

(1,3)

65%

(3,3)

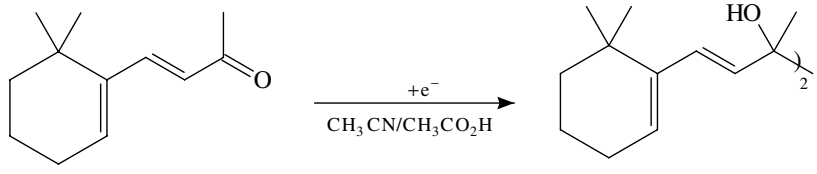
19%

(1,1)

16%

(22)

The product distribution observed in the dimerization of polyene-substituted ketyl radicals is also remarkable in that only products involving dimerization at the carbonyl carbon atom are observed (equation 23)[82,83]. This finding is quite independent of the reducing agent, since ketyl radicals formed by reduction with low-valent transition metal complexes behave analogously[84–86].

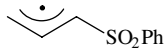
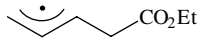
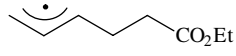
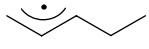
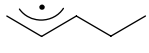
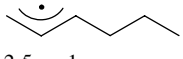
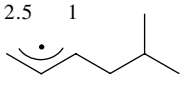
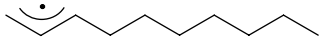
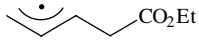


(23)

In summary, it appears that the trapping of allyl radicals with closed-shell trapping agents is quite selective, especially in those cases in which the allyl radical contains one substituted and one unsubstituted terminus. Trapping with radicals appears to produce mixtures of isomers, especially in the dimerization of allyl radicals. The observed regioselectivities do, however, depend on the reaction conditions, allowing for some control of the reaction outcome for a given substrate.

Reviewing now the last four sections, it is obvious that the major problem in radical chain reactions involving dienes or polyenes is the low reactivity of the diene (or polyene) adduct radicals. This allows for the occurrence of allyl radicals in intramolecular reactions but poses a major problem in intermolecular radical chain reactions. The obvious solution to this problem is to use methods in which radicals are produced stoichiometrically and not

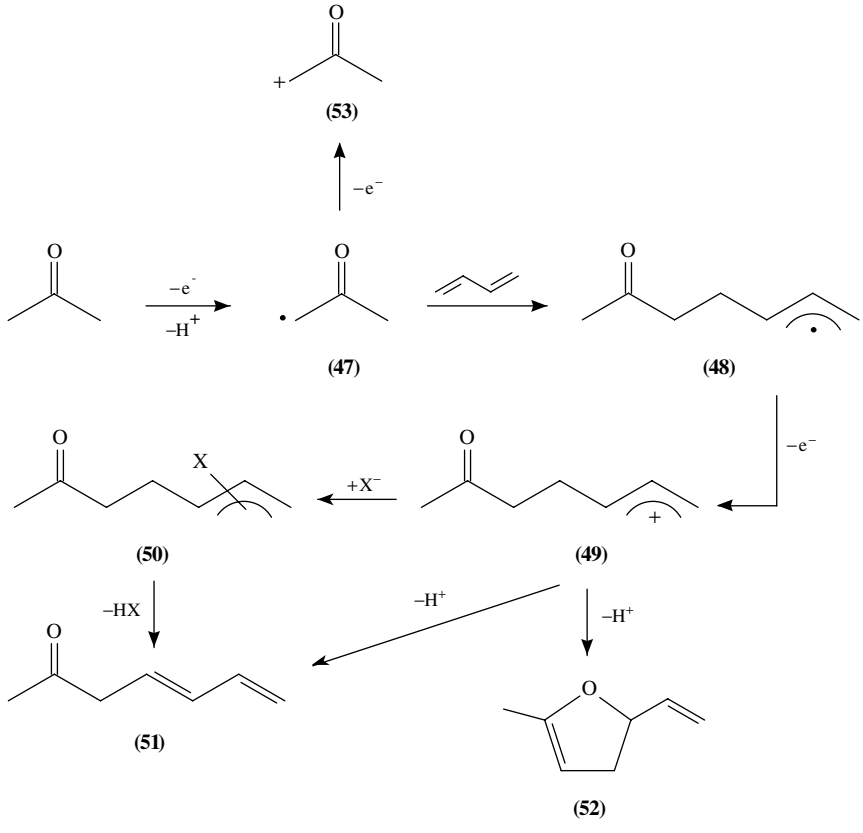
TABLE 14. Relative reactivities at allyl radical termini calculated from product distributions from allyl radical recombination

Relative reactivities	T (°C)	Method	Reference
>3.9 <1 	−78	Carbanion oxidation	81b
2.7 1 	0	Kolbe electrolysis	81c
2.9 1 	0	Kolbe electrolysis	81c
1.7 1 	35	Photolysis	71
1.9 1 	−10	Kolbe electrolysis	81d
1.9 1 	−10	Kolbe electrolysis	81d
2.5 1 	0	Kolbe electrolysis	54b
H>4.0 <1.6 	−20	Diene addition	54a
>6.9 <1 	0	Kolbe electrolysis	81d

in radical chain processes. Not surprisingly, most examples of the successful use of dienes in radical reactions are located in this area. Even though the use of non-chain methods does solve the problem of adduct radical reactivity, the problem of competing polymerization still persists. It is therefore mandatory also for nonchain methods to convert the adduct radicals to product faster than addition to a second polyene molecule. With the trapping of polyene radicals by closed-shell molecules being too slow, three further possibilities exist: (1) trapping with other radicals; (2) oxidation to polyene cations; or (3) reduction to polyene anions. Since option (1) has been shown before to proceed with low selectivity at times and not much is known about option (3), we have to restrict ourselves here to consideration of (2), which has been applied successfully in many cases.

VI. NON-CHAIN RADICAL REACTIONS—OXIDATION AS AN ALTERNATIVE TERMINATING STEP

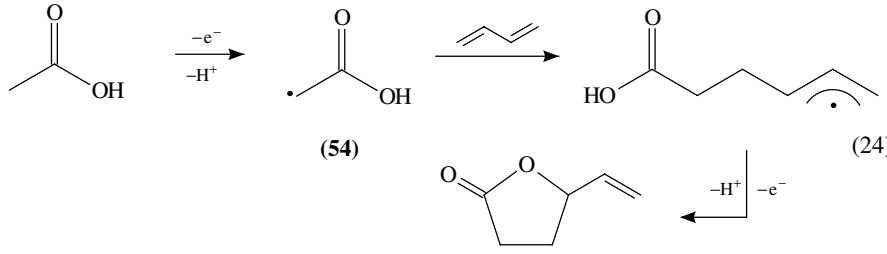
A general mechanistic scheme for the radical addition-adduct radical oxidation sequence is given in Scheme 4. Initial radicals are usually derived from easily enolizable compounds such as ketones, esters and, most frequently, 1,3-dicarbonyl compounds by oxidation with metal salts. The resulting α-carbonyl radical **47** is more difficult to oxidize and addition to dienes can occur. The resulting adduct radical **48** has a much lower oxidation potential as compared to **47.** Oxidation to cation **49** is therefore faster than repeated addition to diene molecules and polymerization can be prevented. Depending on oxidants and reaction conditions, a number of possibilities exist to convert cation **49** to stable products. Trapping of the cation by nucleophiles is frequently observed to produce products of type **50**, which can also be formed directly through inner-sphere electron transfer to radicals **48**. Cation **49** can also deprotonate to form **51**, which can alternatively be formed via **50** through elimination of HX. Finally, **49** is often trapped intramolecularily by the carbonyl functionality of the initial radical to form, after deprotonation, substituted di- and tetrahydrofurans such as **52**. If carboxylic acids or esters are used as enolizable compounds, γ-lactones are formed instead. For this mechanistic scheme to work, the oxidant must be strong enough to effect



SCHEME 4

rapid oxidation of the enolate and the adduct radical **48**. If the oxidant is too strong, however, oxidation of enol radical **47** to form cation **53** will be too rapid and no addition to diene will be observed.

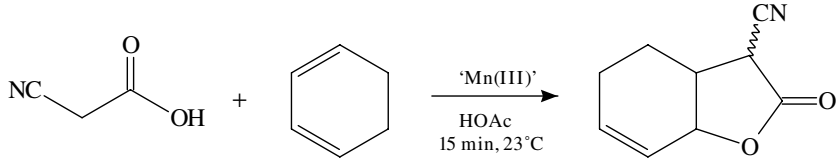
Among the preferred and also first oxidants to be used for this purpose was manganese(III) acetate in acetic acid, for which the formula $Mn_3O(OAc)_7$ might be appropriate[53,87]. Oxidation of acetic acid, for example, leads to radical **54** which, upon addition to butadiene and oxidation of the adduct radical, leads to γ-lactone **55** (equation 24).



(24)

(55) 30%

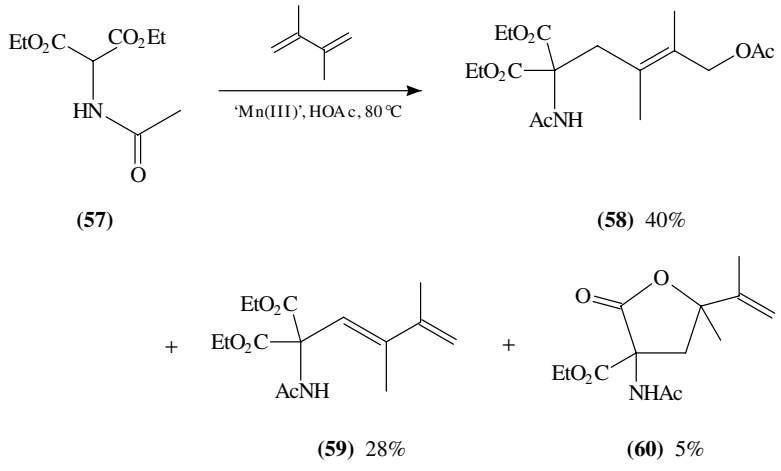
The low yield in this reaction might be caused by a number of reasons. First, the overall reaction is only rapid for readily enolizable compounds. 1,3-Dicarbonyl compounds will therefore be a better choice as compared to acetic acid. Second, to prevent oxidation of radical **54**, it is advantageous to work with excess diene and therefore speed up trapping of **54** through diene addition. Finally, lactone **55** can, as an enolizable compound itself, also be oxidized by manganese(III) acetate and form various oxidation products. Shorter reaction time and the use of understoichiometric amounts of oxidant might therefore benefit the overall result. All these factors have been taken into account in the synthesis of bicyclic γ-lactone **56**, which has been obtained from cyanoacetic acid and 1,3-cyclohexadiene in 78% yield within 15 min reaction time (equation 25)[60,88].



(56) 78%

(25)

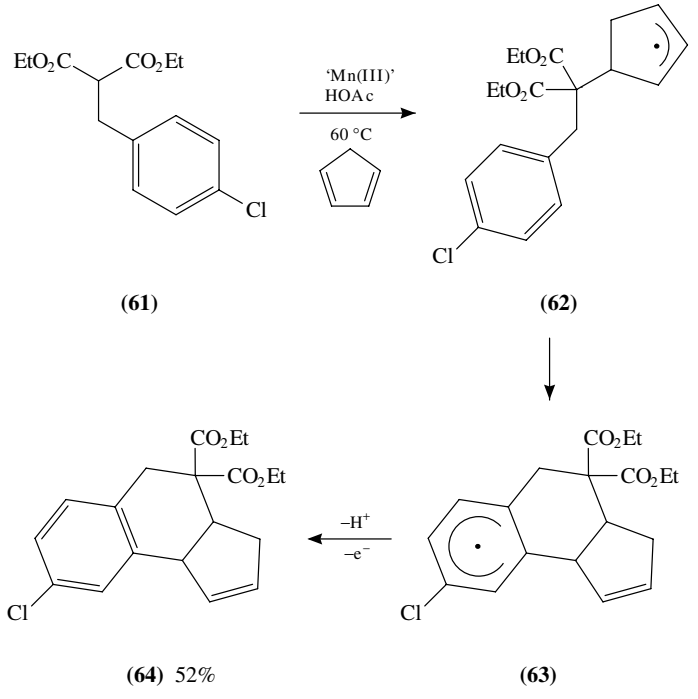
Using esters instead of acids reduces the rate of formation of lactones and gives rise to trapping by solvent as well as the formation of overall diene substitution products. Oxidation of amidomalonic ester **57**, for example, yields as major products the acetic acid trapping product **58** and the diene substitution product **59**, but only 5% of lactone **60** (equation 26). The oxidation of the initially formed amidomalonic ester radical, of increased importance in this case due to the amide substituent, could be largely reduced through addition of sodium acetate or trifluoroacetic acid, which are known to reduce the oxidation potential of the Mn(III) acetate.



(57) **(58)** 40% **(59)** 28% **(60)** 5%

(26)

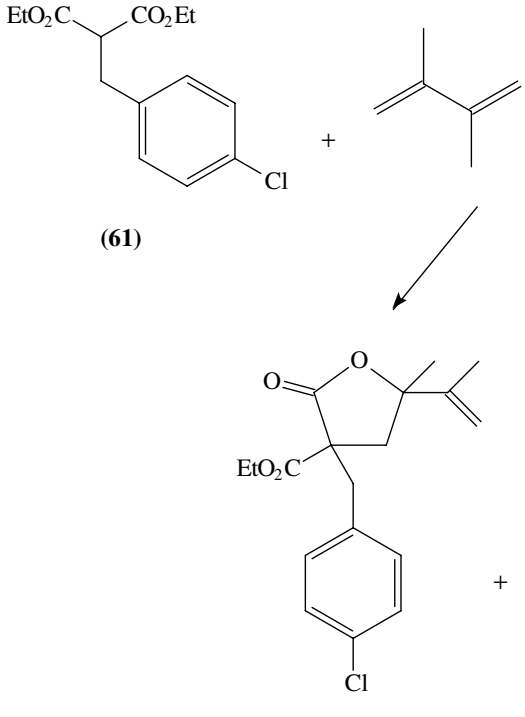
Further variations of the general scenario described in Scheme 4 consist in trapping adduct radical **48** before oxidation occurs[7]. This can be achieved if intramolecular radical additions are possible, as is the case in radical **62**. Oxidation of **62** to the corresponding allyl cation is slower than 6-*exo*-cyclization to the chlorobenzene ring to form radical **63**, which subsequently is oxidized to yield tetrahydronaphthalene **64** as the main product (equation 27). This sequence does not work well for other dienes such as 2,3-dimethyl-1,3-butadiene, for which oxidation of the intermediate allyl radical is too rapid to allow radical cyclization onto the aromatic π-system.



(61) **(62)** **(63)** **(64)** 52%

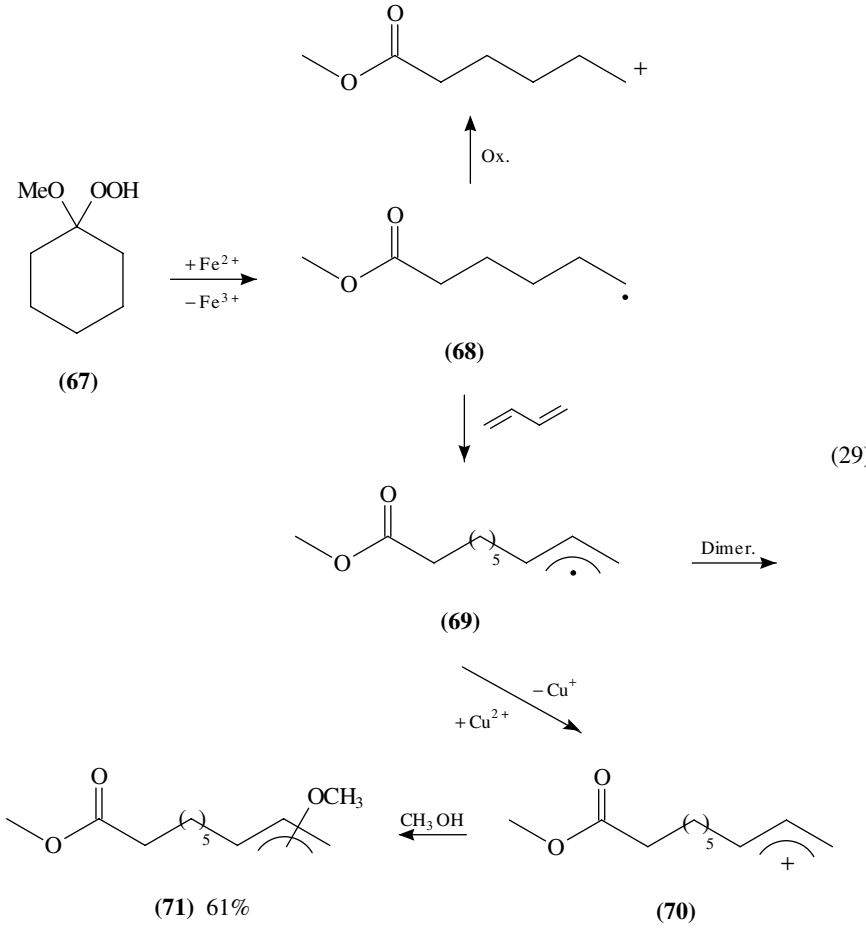
(27)

The competition between intramolecular and intermolecular trapping of the intermediate allyl cation **49** (Scheme 4) can be influenced to a large part by the ligands of the oxidizing metal salts. Intramolecular trapping by carbonyl groups becomes much more dominant when ligands of low nucleophilicity, such as perchlorate, are used in aprotic solvents. This is illustrated by reaction of α-benzylmalonate **61** with 2,3-dimethyl-1,3-butadiene, which yields a mixture of products **65** and **66** with manganese(III) acetate[7], but only intramolecular trapping product **65** when iron(III) perchlorate nonahydrate in acetonitrile is used as oxidant (equation 28)[89,90].



(28)

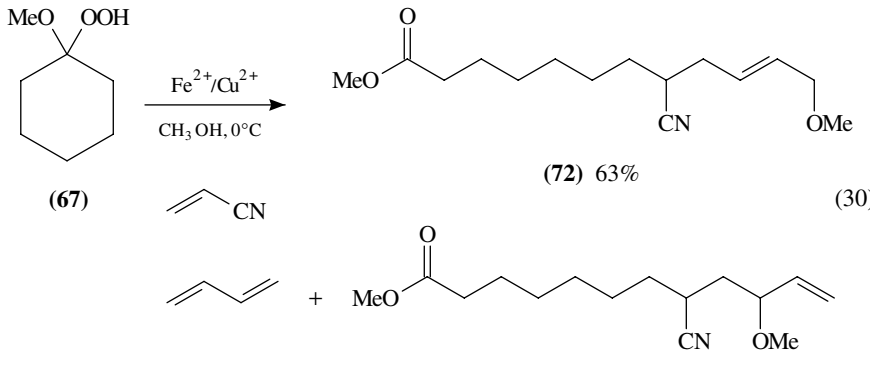
Iron(II) salts, usually in conjunction with catalytic amounts of copper(II) compounds, have also been used to mediate radical additions to dienes[91,92]. Radicals are initially generated in these cases by *reductive* cleavage of peroxyesters of hydroperoxides to yield, after rearrangement, alkyl radicals. Addition to dienes is then followed by oxidation of the allyl radical and trapping by solvent. Hydroperoxide **67**, for example, is reduced by ferrous sulfate to acyclic radical **68**, which adds to butadiene to form adduct radical **69**. Oxidation of **69** by copper(II) and reaction of the resulting allyl cation **70** with methanol yield product **71** in 61% yield (equation 29).



(29)

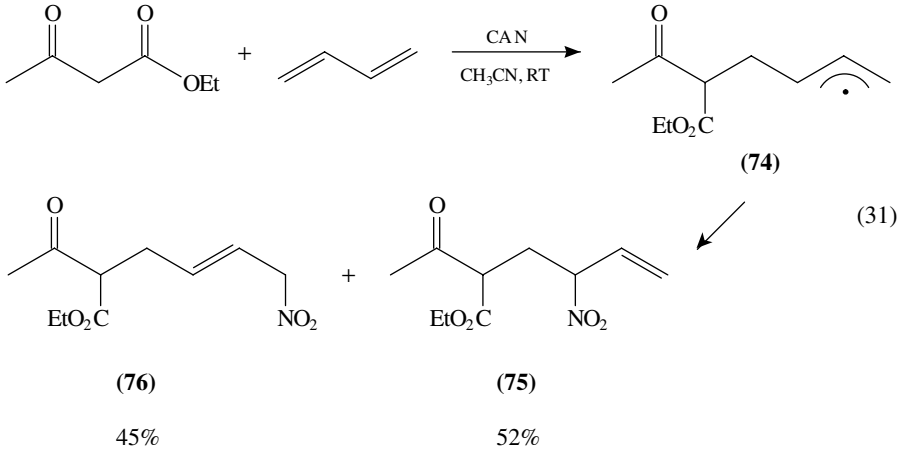
The concentration of copper(II) has a pronounced effect on the course of the reaction. In the presence of very low copper(II) concentrations, oxidation of allyl radical **69** is slow and major amounts of allyl radical dimer are formed. In the presence of very high concentrations of copper(II), radical **68** is oxidized rapidly before addition to diene can take place. An optimum yield of product **71** can therefore only be achieved at certain copper(II) concentrations. The metal-ion-promoted addition of chloramines to butadiene appears to follow the same mechanism[93].

This scheme can be extended by using mixtures of dienes with electron-deficient alkenes such as acrylonitrile. Due to its nucleophilic nature, addition of radical **68** to acrylonitrile is faster than addition to butadiene. The resulting ambiphilic adduct radical then adds to butadiene to form a relatively unreactive allyl radical. Oxidation and trapping of the allyl cation by methanol lead, as before, to products such as **72** and **73**, which are composed of four components: the radical precursor **67**, acrylonitrile, butadiene and methanol (equation 30)[17,94].



(30)

Reactions involving ceric ammonium nitrate (CAN) as oxidant give nitrates instead of acetates or methyl ethers as final trapping products[8,55,56]. Oxidation of the adduct allyl radicals **48** (Scheme 4) appears in this case to follow a ligand transfer mechanism rather than a stepwise electron transfer/nucleophilic addition sequence. The oxidation of ethyl acetoacetate in the presence of butadiene, for example, leads to adduct radical **74**, which is trapped by CAN to form the two possible products **75** and **76** in high yield but low selectivity (equation 31). A similar sequence has been used starting from silyloxycyclopropanes, which yield β-carbonylalkyl radicals after CAN oxidation. Addition to butadiene and trapping with CAN again forms a mixture of nitrates, which have in this case been used as substrates for the palladium(II) catalyzed coupling with carbon- and nitrogen-centered nucleophiles[56].



(31)

For completeness, it must also be noted that the oxidation of enolizable compounds and intermediate allyl radicals can be achieved electrochemically[54b]. The resulting product mixtures, however, proved much more complex as compared to oxidation by transition metal salts.

VII. ACKNOWLEDGEMENT

Generous support by the Fonds der Chemischen Industrie is gratefully acknowledged.

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The Chemistry of Dienes and Polyenes. Volume 1
Edited by Zvi Rappoport

ISBN: 0-471-96512-X

CHAPTER **14**

Palladium-catalyzed oxidation of dienes

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I. INTRODUCTION

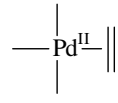
Palladium-catalyzed oxidation of hydrocarbons has been a matter of intense research for about four decades. The field was initiated by the development of the aerobic oxidation of ethylene to acetaldehyde catalyzed by palladium chloride and co-catalyzed by cupric chloride (the Wacker process, equation 1)[1].

$$CH_2{=}CH_2 + 1/2\,O_2 \xrightarrow[CuCl_2]{PdCl_2} CH_3CHO \qquad (1)$$

A number of reviews dealing with the palladium-catalyzed oxidation of unsaturated hydrocarbons have been written[2–8]. The present review will focus on the palladium-catalyzed oxidation of dienes including both conjugated and nonconjugated dienes. Since this topic has been thoroughly reviewed up to *ca* 1979 in the book by Henry[2] the present review will mainly cover the time period 1979–95. During this time several reviews[3–7] have been written which partly cover the present topic.

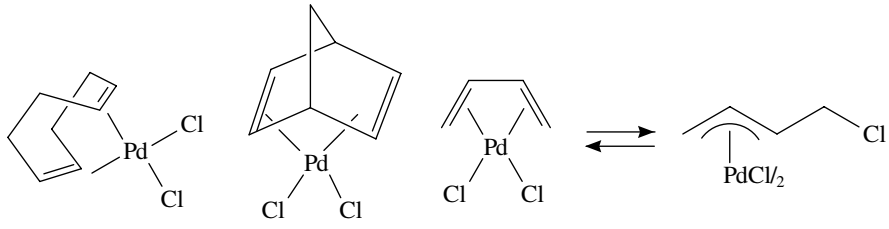
A. Principle for the Oxidation of Unsaturated Hydrocarbons

In most palladium-catalyzed oxidations of unsaturated hydrocarbons the reaction begins with a coordination of the double bond to palladium(II). In such palladium(II) olefin complexes **(1)**, which are square planar d^8 complexes, the double bond is activated towards further reactions, in particular towards nucleophilic attack. A fairly strong interaction between a vacant orbital on palladium and the filled π-orbital on the alkene, together with only a weak interaction between a filled metal d-orbital and the olefin π^*-orbital (back donation), leads to an electrophilic activation of the alkene[9].



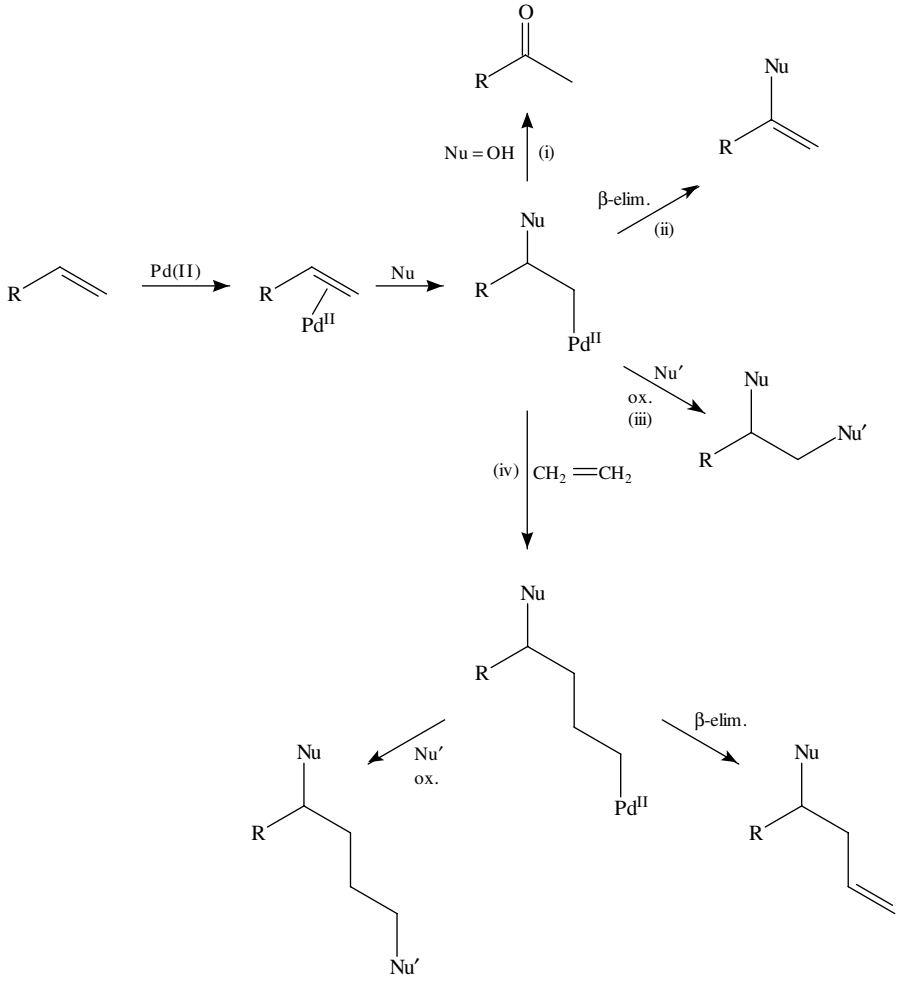
(1)

If the unsaturated hydrocarbon is a diene, both double bonds may coordinate to palladium(II). (Diene)palladium(II) complexes have been isolated and characterized. For example, **2** and **3** are stable complexes in which both double bonds are coordinated to the metal[10]. Conjugated dienes constitute a special case and although η^4-diene complexes, e.g. **4**, are postulated as intermediates, they have not yet been isolated. The butadiene complex **4** is in equilibrium with the π-allyl complex **5** in solution, and attempts to isolate the diene complex from this mixture lead to formation of a yellow crystalline complex **5**[11].



(2) **(3)** **(4)** **(5)**

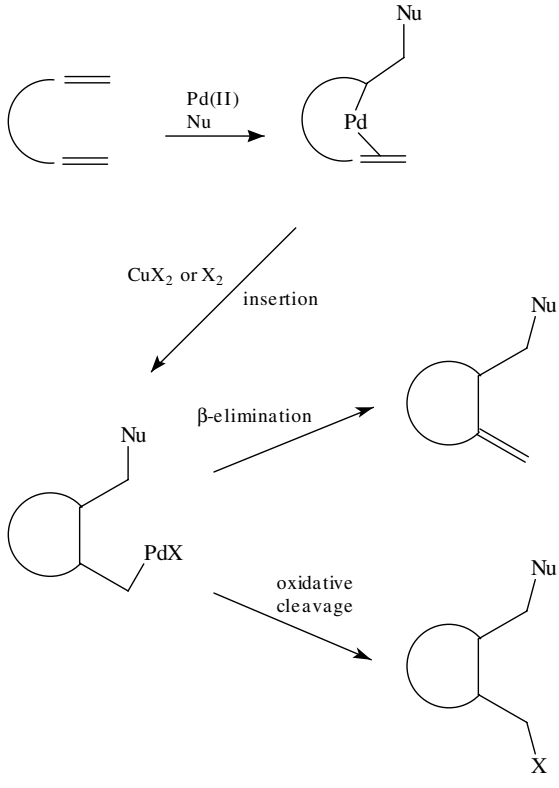
A common pathway in palladium-catalyzed oxidation reactions is that the π-olefin complex formed reacts with a nucleophile, either external or coordinated, and the new organometallic intermediate may then undergo a number of different reactions (Scheme 1): (i) an intramolecular hydride shift leads to ketone formation; (ii) a β-elimination results in the formation of a vinyl functionalized olefin; (iii) an oxidative cleavage of the palladium–carbon bond produces a 1,2-functionalized olefin[7]; and (iv) an insertion reaction, exemplified by insertion of an olefin, leads to formation of a new palladium–carbon bond, which may be cleaved according to one of the previous processes (β-elimination or oxidative cleavage). In all cases palladium has removed 2 electrons from the organic molecule, which becomes oxidized. These electrons, which end up on Pd(0), are in turn transferred to the oxidant and Pd(II) is regenerated. In this way a palladium(II)-catalyzed oxidation is realized.



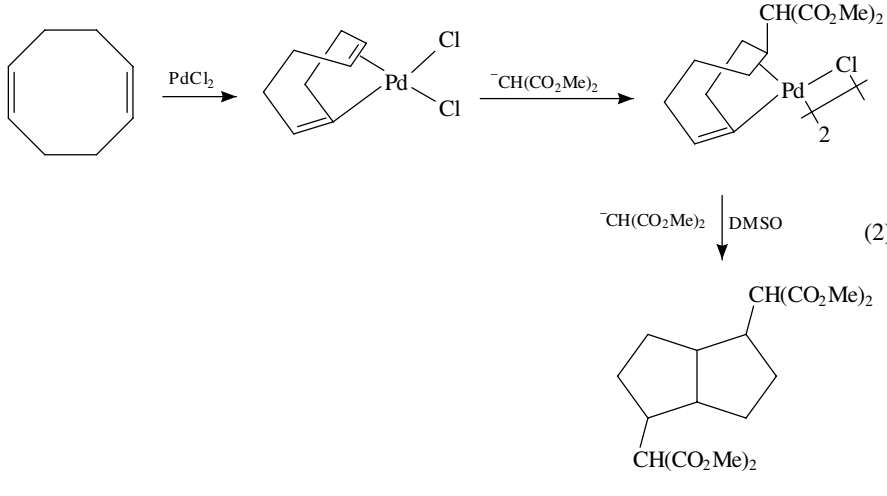
SCHEME 1

II. NONCONJUGATED DIENES

As mentioned above nonconjugated dienes give stable complexes where the two double bonds can form a chelate complex. A common pathway in palladium-catalyzed oxidation of nonconjugated dienes is that, after a first nucleophilic addition to one of the double bonds, the second double bond inserts into the palladium–carbon bond. The new (σ-alkyl)palladium complex produced can then undergo a β-elimination or an oxidative cleavage reaction (Scheme 2). An early example of this type of reaction, although not catalytic, was reported by Tsuji and Takahashi (equation 2)[12].

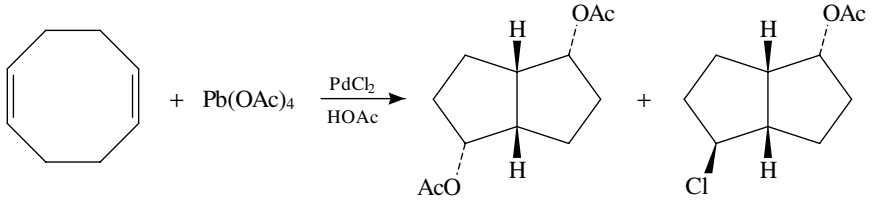

Nu
Pd(II)
Nu
Pd
CuX2 or X2
insertion
Nu
β-elimination
Nu
PdX
oxidative
cleavage
Nu
X

SCHEME 2


PdCl2
Cl
Pd
Cl
⁻CH(CO2Me)2
CH(CO2Me)2
Cl
Pd
2
⁻CH(CO2Me)2
DMSO
CH(CO2Me)2
CH(CO2Me)2

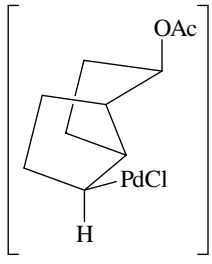
(2)

In this reaction the first addition product was isolated. In catalytic reactions this is not the case and in these reactions the first (σ-alkyl)palladium complex formed from the nucleophilic addition reacts further. For example, in the palladium-catalyzed oxidation of 1,5-cyclooctadiene with $Pb(OAc)_4$ in acetic acid the corresponding diacetate **6** was obtained in 76% yield together with some chloroacetate (equation 3)[13,14]. Adduct **7** is the suggested intermediate. An additional number of such palladium-catalyzed cyclizations of nonconjugated dienes have been reported[15–21]. In this system the two nucleophiles incorporated are either two acetates or one acetate and one chloride. For example, norbornadiene gives a mixture of three products, **8**, **9a** and **9b**, where the chloroacetate **8** is the main product (equation 4)[15]. Another example is the reaction of vinylnorbornene **10**, which gives a substituted brendane system **11** in good selectivity and yield[16,20]. The latter compound was transformed to the important synthetic intermediate **12** containing 5 stereogenic centers (equation 5). This transformation was done via hydrolysis, oxidation to ketone and subsequent Beyer-Villiger oxidation.

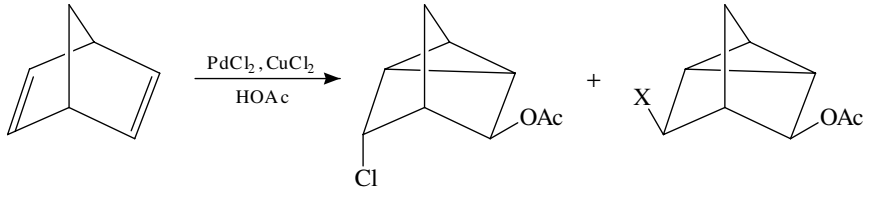


(6) 76% trace

(3)



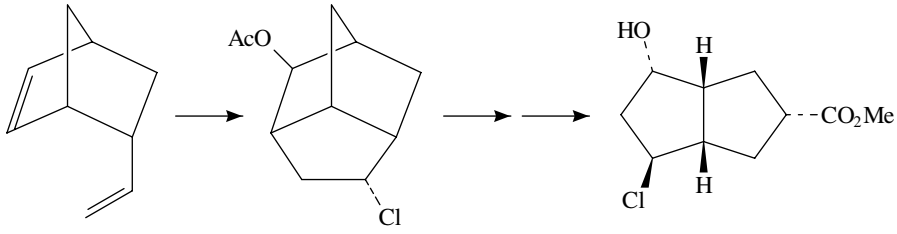
(7)



(8) 56%

(9a) X = Cl (13%)
(9b) X = OAc (13%)

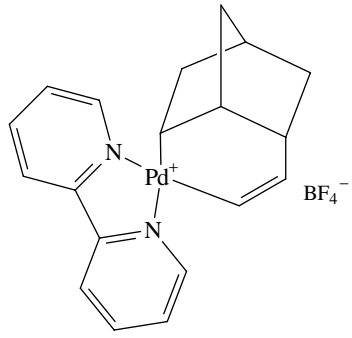
(4)



(10) **(11)** **(12)**

Isolated intermediate:

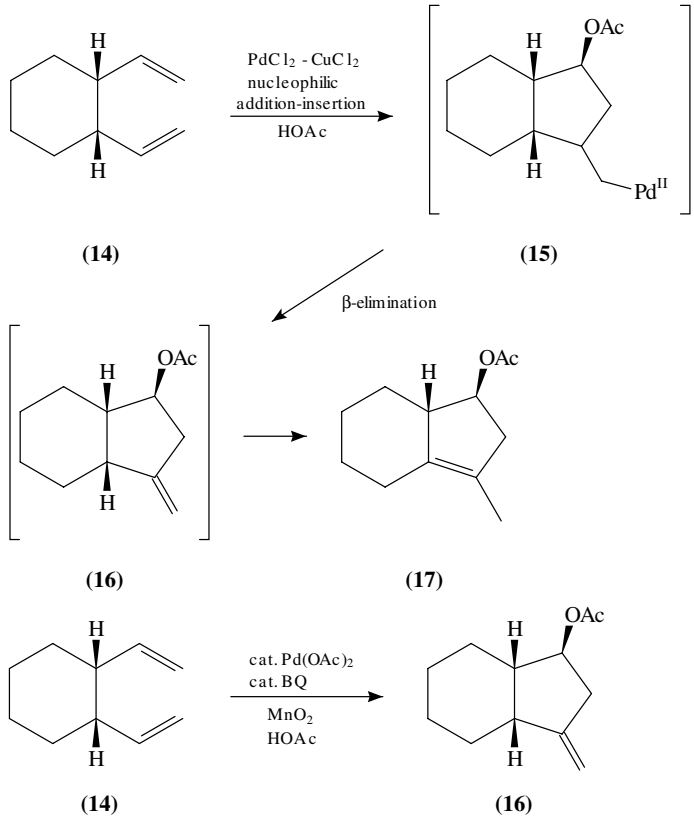
(5)



(13)

The palladium-catalyzed oxidations of the nonconjugated dienes to give products such as **6**, **8**, **9** and **11** involve three fundamental organometallic reactions: nucleophilic addition–insertion–oxidative cleavage of the Pd–C bond. It is interesting to note that in the formation of **6** and **11** all three reactions are highly stereoselective. It is generally assumed that the first two reactions are always stereospecific, while the oxidative cleavage may occur with either retention or inversion. The organopalladium intermediate was trapped by the addition of $AgBF_4$ and bipyridyl and in this way the cationic complex **13** was isolated.

When the $PdCl_2$–$CuCl_2$ system was applied to 1,2-divinylcyclohexane **14**, only one nucleophile is added to the diene system (equation 6)[16]. After nucleophilic addition and insertion the σ-palladium complex **15** formed undergoes a β-elimination. The primary product **16** generated undergoes a double bond isomerization to give **17**, which is the product observed. The latter reaction has been improved and developed into a synthetically useful reaction[3,4,22–25]. By changing the oxidation system to MnO_2/*p*-benzoquinone(BQ)[26] in acetic acid with $Pd(OAc)_2$ as catalyst, the product **16** with the *exo* methylene compound was obtained (equation 7)[22]. In the copper-catalyzed reaction the latter compound was postulated as the primary product, which under the reaction conditions undergoes an isomerization to the observed product. With MnO_2/BQ as the oxidation system, **16** does not isomerize.

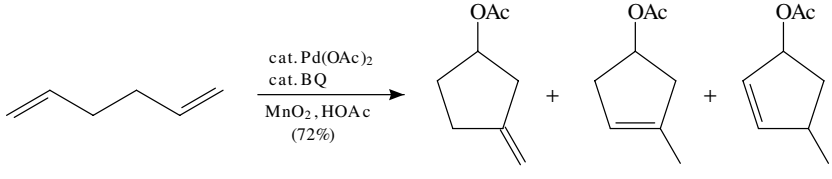


(14) **(15)** (6)

(16) **(17)**

(14) **(16)** (7)

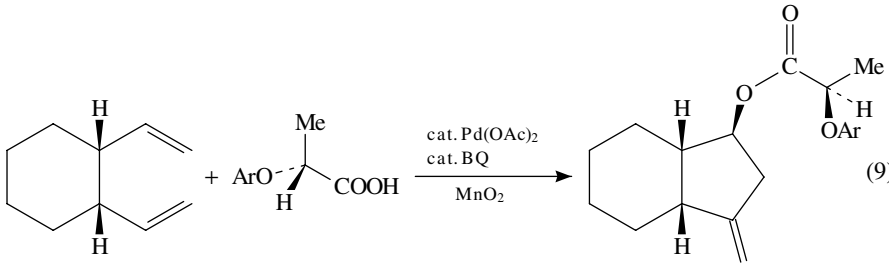
Acyclic dienes also undergo the palladium-catalyzed cyclization with the MnO_2/BQ oxidation system[22]. Thus, simple 1,5-hexadiene afforded a 72% isolated yield of cyclized products **18**, **19** and **20**, with an isomer distribution of 65:25:10, respectively (equation 8). In general, the selectivity and/or yield was lower for the acyclic dienes.



(18) **(19)** **(20)**

65 : 25 : 10 (8)

The palladium-catalyzed oxidation of the 1,2-divinylcyclohexane system was applied to diastereoselective reactions with the use of chiral acids as nucleophiles[25]. With this technique an asymmetric induction of up to 76% was obtained in the formation of **21** from **14** (equation 9). The use of molecular sieves was essential in order to obtain a good asymmetric induction.

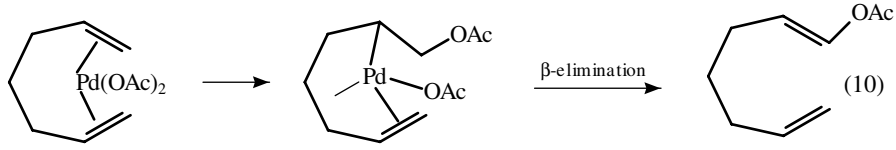


(9)

(14) **(21)**

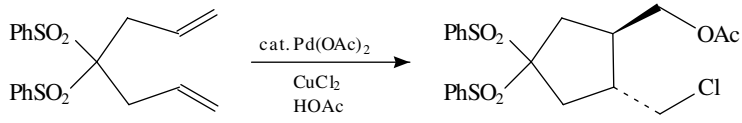
Ar = 2,4-$Cl_2C_6H_3$ 76% de

The use of 1,6-diene systems usually does not result in cyclization reactions with palladium(II) salts. For example, with 1,6-heptadiene a β-elimination takes place from the σ,π-intermediate to give diene **22** as the major product (equation 10)[27]. However, more recently Trost and Burgess[21] have shown that with a 4,4-bis(phenylsulfonyl) derivative of 1,6-heptadiene **(23)** an insertion takes place to give a 5-membered ring product (**24**, equation 11). The final step of the latter reaction is oxidative cleavage of the palladium–carbon bond by $CuCl_2$ to produce a carbon–chlorine bond.



(10)

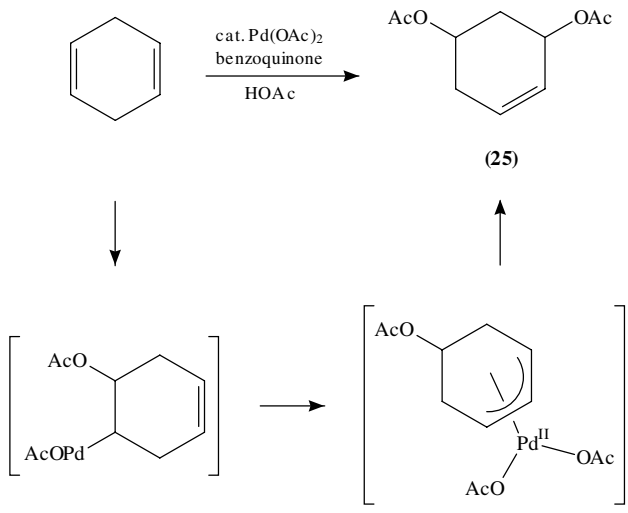
(22)



(11)

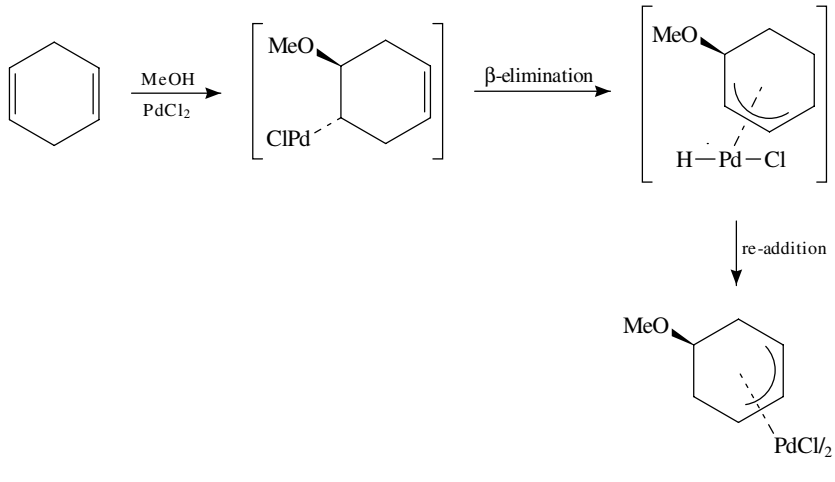
(23) **(24)**

Palladium-catalyzed oxidation of 1,4-dienes has also been reported. Thus, Brown and Davidson[28] obtained the 1,3-diacetate **25** from oxidation of 1,4-cyclohexadiene by benzoquinone in acetic acid with palladium acetate as the catalyst (Scheme 3). Presumably the reaction proceeds via acetoxypalladation–isomerization to give a π-allyl intermediate, which subsequently undergoes nucleophilic attack by acetate. This principle, i.e. rearrangement of a (σ,π-allyl)- to a (π-allyl)palladium complex, has been applied in nonoxidative palladium-catalyzed reactions of 1,4-dienes by Larock and coworkers[29]. Åkermark and coworkers have demonstrated the stereochemistry of this process by the transformation of 1,4-cyclohexadiene to the (π-allyl)palladium complex **26** by treatment



SCHEME 3

with palladium chloride in methanol (equation 12)[30]. The (π-allyl)palladium complex, in which the methoxy group is *trans* to palladium, was isolated and used for further organic reactions.



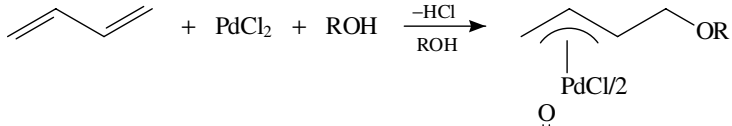
(12)

III. CONJUGATED DIENES

A. Intermolecular Reactions

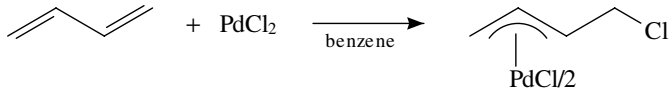
As mentioned in the introduction, π-complexes of conjugated dienes with palladium(II) are not stable enough to be isolated. However, reaction of a conjugated diene with $PdCl_2$ in alcoholic solvents or acetic acid gives a (π-allyl)palladium complex **27** in which the

alcohol or acetic acid has attacked the diene in the 4-position (equation 13)[31,32]. In a non-nucleophilic solvent a 4-chloro-η^3-(1,2,3)-alkenylpalladium complex **28** is formed (equation 14)[11,31].



(13)

R = OMe, OEt, RC(=O) **(27)**

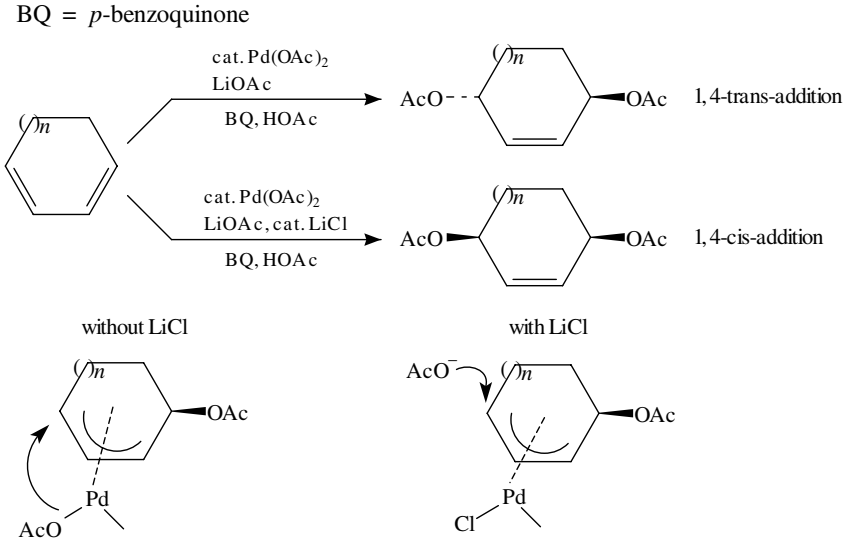


(14)

(28)

In 1971, Brown and Davidson reported that 1,3-cyclohexadiene undergoes a palladium-catalyzed 1,4-diacetoxylation of unspecified stereochemistry[28]. The oxidant employed was *p*-benzoquinone. They were uncertain about the mechanism at the time but later work has shown that the reaction proceeds via a (π-allyl)palladium intermediate and subsequent nucleophilic attack by acetate[6,7].

In 1981, a stereoselective palladium-catalyzed 1,4-diacetoxylation of 1,3-dienes with *p*-benzoquinone (BQ) as the oxidant was reported[33]. It was found that chloride ions can be used as a stereochemical switch. Thus, in the absence of chloride ions *trans* diacetoxylation takes place, whereas in the presence of a catalytic amount of chloride ion (as added LiCl) a *cis* diacetoxylation takes place (Scheme 4). In both cases the reaction is highly 1,4-regioselective. The explanation for



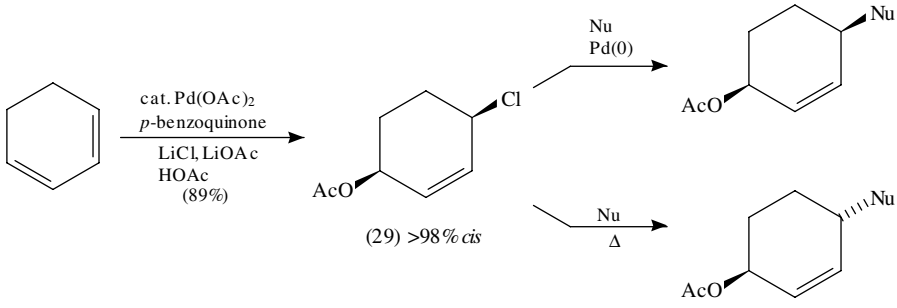
SCHEME 4. Ligand control in Pd-catalyzed 1,4-diacetoxylation

this remarkable ligand control of the stereochemistry is that in the absence of chloride ion, acetate ion will be the counterion on palladium and will undergo a *cis* migration. When chloride ions are present they will displace the acetate on palladium since the Pd−Cl bond is much stronger than the Pd−OAc bond. In this way the chloride blocks the coordination of acetate and, as a result, only external attack by acetate occurs.

The diacetoxylation works well with a number of cyclic and acyclic conjugated dienes and has been applied to the synthesis of natural products[33,34]. For example, the *meso* diacetate from 2,4-hexadiene was used for the enantiodivergent synthesis of the carpenter bee pheromone[34a].

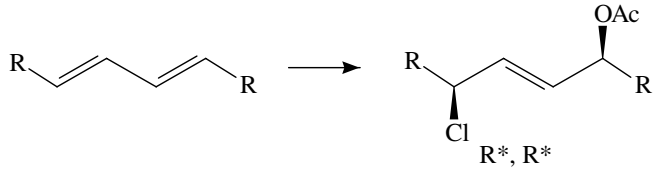
The 1,4-diacetoxylation was also extended to the use of other acyl groups than acetyl. Thus, an unsymmetrical 1,4-acetoxy-trifluoroacetoxylation of 1,3-dienes was developed by the use of added trifluoroacetic acid to the acetic acid used as the solvent[33c]. With the use of acetone as the solvent with an added carboxylic acid a general diacyloxylation was obtained and, for example, the 1,4-dibenzoates of 2-cycloalkene-1,4-diols were prepared directly from the corresponding 1,3-cycloalkadienes[33d].

An increased chloride ion concentration in the palladium-catalyzed oxidation of 1,3-cyclohexadiene resulted in a highly stereo- and regioselective 1,4-chloroacetoxylation[35]. The product selectivity was also high. Thus, palladium-catalyzed chloroacetoxylation afforded an 89% isolated yield of chloroacetate **29** which was >98% *cis* (Scheme 5). Only 1–2% of diacetate was observed in the crude product.

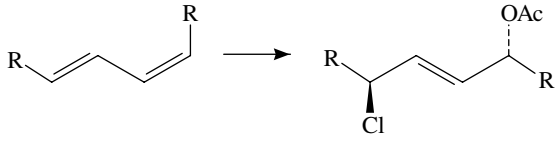


SCHEME 5

The chloroacetoxylation is a quite general reaction and works well with a number of conjugated dienes. Some additional examples are given in Scheme 6 and in equations 15 and 16. The reaction is highly *syn* stereoselective for a number of cyclic dienes tried. Also, for acyclic dienes the reaction leads to a 1,4 *syn* addition and the reaction takes place with good stereospecificity (94–96% *syn*). Thus (*E*,*E*)-dienes give the R*R* isomer whereas (*E*,*Z*)-dienes produce the R*S* isomer (equations 15 and 16). The reaction has also been extended to include other carboxylic acids than acetic acid (chloroacyloxylation)[33d].

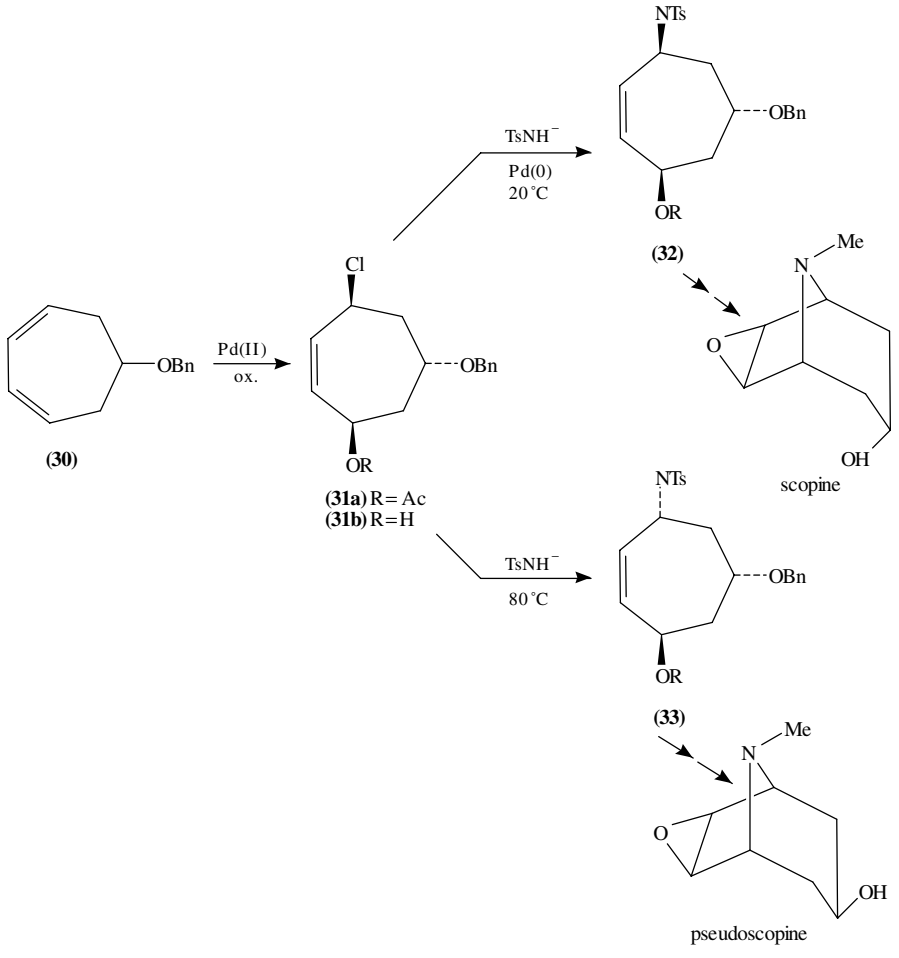


(15)



(16)

R*, S*

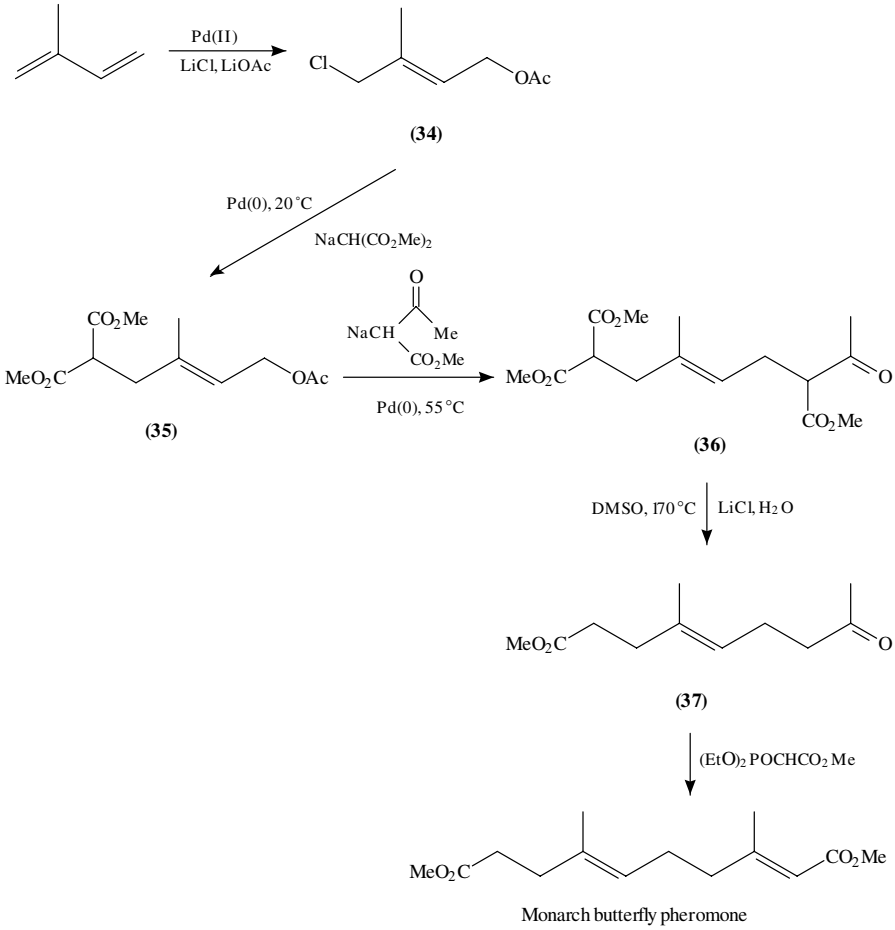


SCHEME 6

The chloroacetoxylation reaction is synthetically useful since the chloride can be substituted with either retention [Pd(0)-catalyzed reaction] or inversion (S_N2 reaction) by a number of nucleophiles. In this way both the *cis* and *trans* isomers are accessible and have been prepared from a number of allylic acetates (Schemes 5 and 6). In a subsequent reaction the allylic acetate can be substituted by employing a copper- or palladium-catalyzed reaction. The latter reactions are stereospecific.

An example of the use of the dual stereoselectivity offered by the chloroacetates is given in Scheme 6 for the synthesis of scopine and pseudoscopine[36]. Palladium-catalyzed chloroacetoxylation of diene **30** gave chloroacetate **31a** in 63% yield with high diastereoselectivity (>95% 1β,4β,6α) with the benzyloxy group *trans* to the chloro and acetoxy groups. Subsequent palladium(0)-catalyzed reaction of the allylic chloride **31** with $TsNH^-$ afforded **32**. The corresponding S_N2 reaction between **31** and the tosylamide anion at elevated temperature afforded the isomeric *trans* product **33**. The amido alcohol derivatives **32** and **33** were subsequently transformed to scopine and pseudoscopine, respectively, via stereoselective epoxidation and cyclization.

This sequential substitution of the chloro and acetoxy groups makes the chloroacetates useful as building blocks. An example of the use of the chloroacetate **34** from isoprene for the synthesis of the Monarch butterfly pheromone is given in Scheme 7[37]. Two different nucleophiles, sodium dimethyl malonate and sodium methyl acetoacetate, were employed in Pd(0)-catalyzed allylic substitutions. The transformation of **34** to **36** was also made

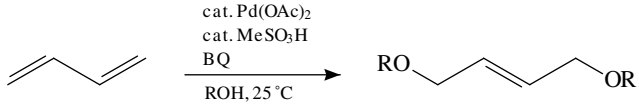


SCHEME 7

in one pot. Double decarboxylation of **36** afforded **37**, which was transformed to the pheromone via a Wittig–Horner reaction.

The principle of this stereoselective functionalization of 1,3-dienes has been applied in organic synthesis of several other natural products[38–44].

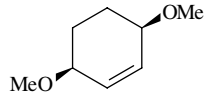
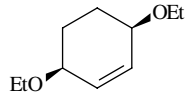
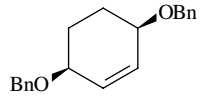
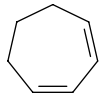
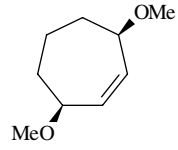
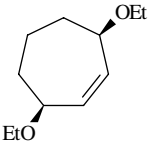
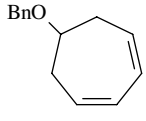
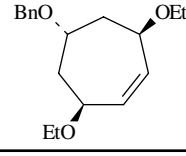
The 1,4-oxidation has also been extended to the use of alcohols as nucleophiles[45]. By performing the reaction in an alcohol as the solvent with $Pd(OAc)_2$ as catalyst and *p*-benzoquinone as the oxidant, a 1,4-dialkoxylation was obtained (equation 17). It was essential to add a catalytic amount of acid to get a reaction. The reaction is highly regio- and stereoselective and 1,3-cyclohexadiene and 1,3-cycloheptadiene afforded exclusively 1,4-*syn* addition products (Table 1).



(17)

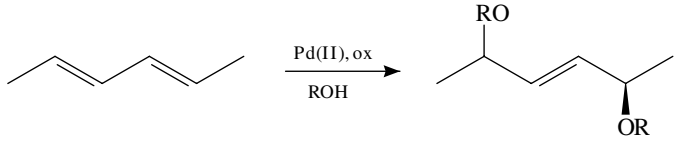
R = Me, Et, Bn

TABLE 1. Pd-catalyzed 1,4-dialkoxylations of 1,3-dienes

1,3-Diene	Alcohol	Product	% Yield	Stereochemistry
	MeOH		63	>98.8% *cis*
	EtOH		72	>98% *cis*
	BnOH		53	>98% *cis*
	MeOH		69	>98% *cis*
	EtOH		82	>98% *cis*
	EtOH		69	>95% 1β, 4β, 6α

The stereochemistry of the dialkoxylation arises from two external attacks by the alcohol, one on the π-diene complex and the second on the intermediate π-allyl complex. This is in accordance with the other palladium-catalyzed 1,4-*syn* additions discussed above.

Also, the 1,4-dialkoxylation of acyclic 1,3-dienes was stereoselective. For example, the reaction of (*E*,*E*)-2,4-hexadiene gave the *d*,*l* products **38** by a 1,4-*syn* addition. The double bond was exclusively of *E* configuration (equation 18).

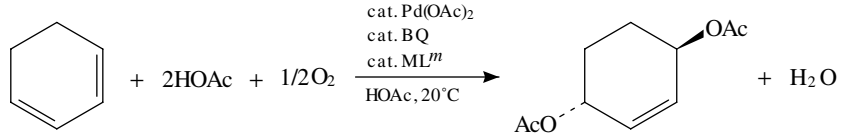


(18)

(38a) R = Me, 45%, >97% *dl*, >98% *E*

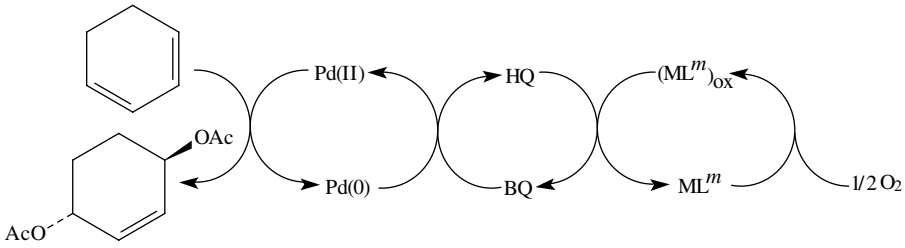
(38b) R = Et, 45%, >96% *dl*, >98% *E*

A mild aerobic palladium-catalyzed 1,4-diacetoxylation of conjugated dienes has been developed and is based on a multistep electron transfer[46]. The hydroquinone produced in each cycle of the palladium-catalyzed oxidation is reoxidized by air or molecular oxygen. The latter reoxidation requires a metal macrocycle as catalyst. In the aerobic process there are no side products formed except water, and the stoichiometry of the reaction is given in equation 19. Thus 1,3-cyclohexadiene is oxidized by molecular oxygen to diacetate **39** with the aid of the triple catalytic system Pd(II)−BQ−ML^m where ML^m is a metal macrocyclic complex such as cobalt tetraphenylporphyrin (Co(TPP)), cobalt salophen (Co(Salophen) or iron phthalocyanine (Fe(Pc)). The principle of this biomimetic aerobic oxidation is outlined in Scheme 8.



(39)

(19)



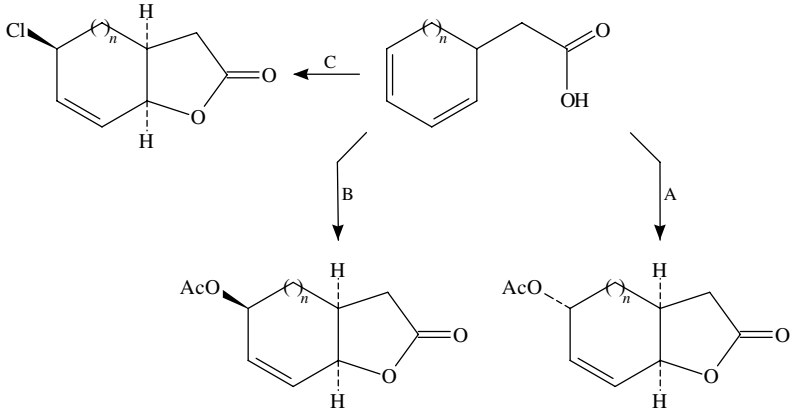
SCHEME 8

Further development of this aerobic oxidation was done by utilizing a quinone containing cobalt tetraphenyl porphyrin[47]. This gives a more efficient electron transfer between quinone and porphyrin and results in a faster aerobic 1,4-diacetoxylation of the diene. The

use of a zeolite encapsulated metal macrocycle (iron phthalocyanine or cobalt salophene) gave a more stable metal macrocyclic catalyst that was filtered off and reused many times in the aerobic 1,4-diacetoxylation[48].

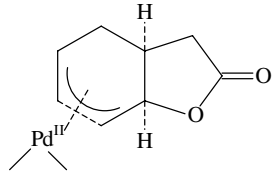
B. Intramolecular Reactions

If one of the nucleophiles is situated in the side chain of the diene an intramolecular palladium-catalyzed 1,4-oxidation takes place. The first example of this type of reaction was the 1,4-oxylactonization (Scheme 9)[49].



SCHEME 9. Pd-catalyzed oxylactonization: cat.$Pd(OAc)_2$, *p*-benzoquinone (BQ), acetone–HOAc (4 : 1); A: no LiCl, B: cat LiCl, C: excess LiCl

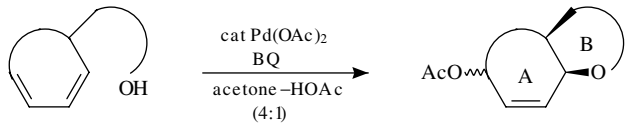
In this reaction a useful stereocontrol was obtained by the use of LiCl as a catalytic additive. Without added LiCl a 1,4-*trans* acetoxylactonization took place, while in the presence of a catalytic amount of LiCl a 1,4-*cis* acetoxylactonization occurred. This is in analogy with the diacetoxylation of conjugated dienes discussed above where chloride ions block the coordination of acetate to palladium[34]. At an increased chloride ion concentration (as added LiCl) a highly regio- and stereoselective 1,4-*cis* chlorolactonization took place. The presence of the π-allylpalladium intermediate **40** was demonstrated by its isolation and stereochemical assignment. The *trans* stereochemistry between palladium and oxygen in the π-allylpalladium complex **40** was established by the use of reporter ligands and NOE measurements[49b].



(40)

The analogous reaction of alcohol derivatives **41** gave fused tetrahydrofurans and fused tetrahydropyrans **42**[50]. As in the lactonization reaction the stereochemistry can be tuned

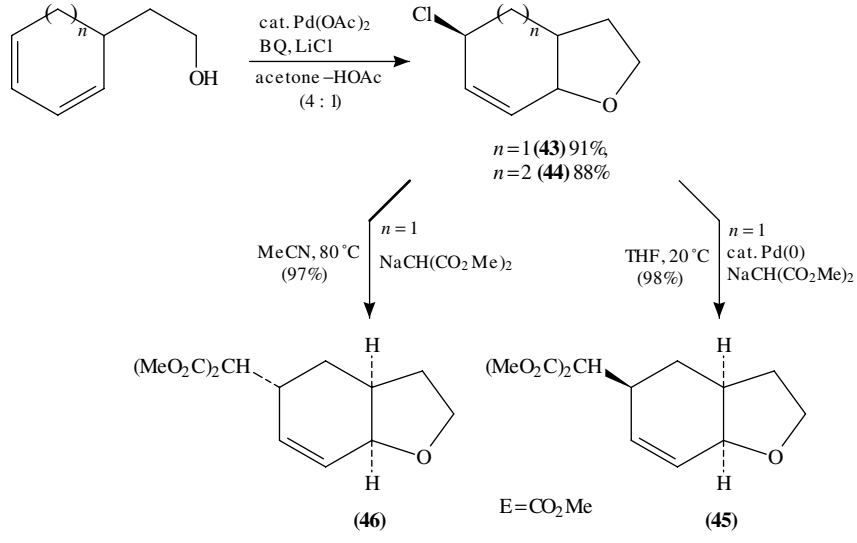
TABLE 2. Pd-catalyzed 1,4-oxylactonization



(41) (42)

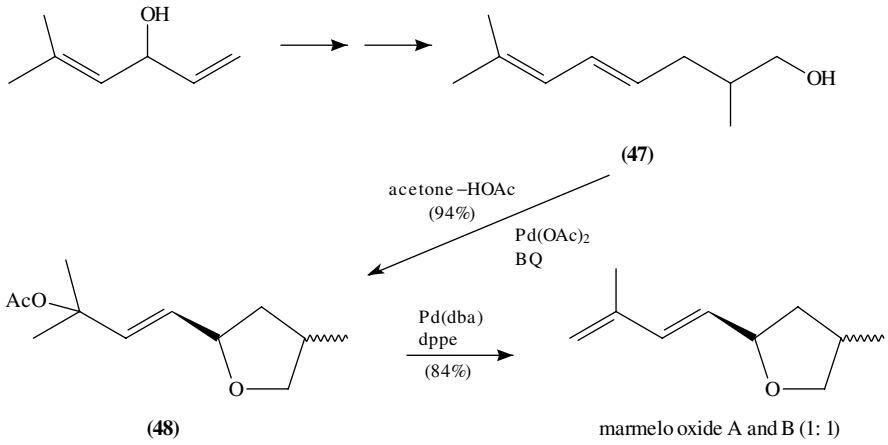
Ring size A	B	Cl^-	% Yield	*cis/trans* (of addition)
6	5	—	87	<2/98
6	5	cat.	82	91/9
6	6	—	87	<2/98
6	6	cat.	78	91/9
7	5	—	90	<2/98
7	5	cat.	81	>98/2

by the ligand control with addition of LiCl. In this way stereoselective 1,4-*trans* and 1,4-*cis* additions were obtained (Table 2). At a higher chloride concentration a 1,4-*cis* oxychlorination took place in high regio- and stereoselectivity to give **43** and **44**. This reaction opens up an entry into stereodefined heterocycles and a stereodivergent transformation of **43** with Pd(0) catalysis or classical S_N2 substitution afforded **45** and **46**, respectively (Scheme 10).



SCHEME 10. E = CO_2Me

The reaction was applied to an acyclic system for the synthesis of furanoid terpenes (Scheme 11)[51]. The palladium-catalyzed intramolecular reaction of **47** afforded **48** which was transformed to the target molecule. The latter product was obtained as a 1:1 mixture of marmelo oxide A and B, which is the isomeric mixture found in nature.

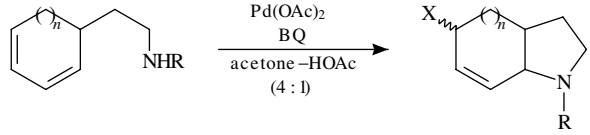


SCHEME 11

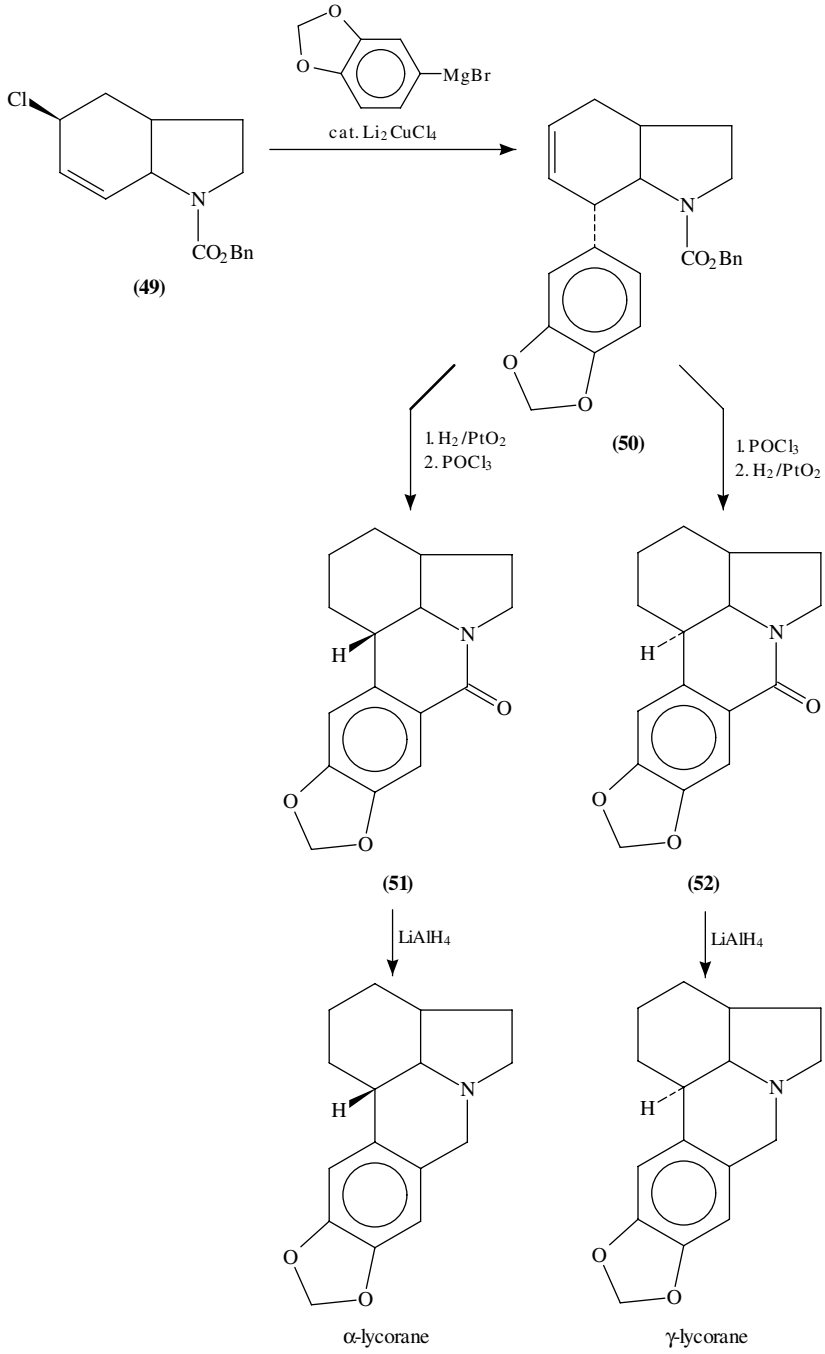
The use of a nitrogen nucleophile in the side chain (as an amide) also leads to an intramolecular 1,4-addition under the standard conditions for the palladium-catalyzed 1,4-oxidation reactions[52]. Nitrogen nucleophiles employed for this reaction comprise tosylamides, carboxamides, carbamates and ureas. The reactions are run in acetone-acetic acid with *p*-benzoquinone (BQ) as the oxidant. In most cases highly stereo- and regioselective reactions were obtained and some examples are given in Table 3.

One of these products **(49)** was used as a key intermediate for the synthesis of the *Amaryllidaceae* alkaloids α- and γ-lycorane (Scheme 12)[53]. A copper-catalyzed Grignard reaction with **49** afforded **50** via a selective γ-*anti* displacement of the chloride. Hydrogenation followed by Bischler–Napieralski cyclization gave **51**. Interestingly, reversal of the latter two steps gave the isomer **52** where an epimerization at the benzylic carbon had occurred in the cyclization step (>99% selectivity). Subsequent reduction of the amide in each case afforded the target molecules α- and γ-lycorane, respectively. The purity of the final product was very high with respect to the opposite stereoisomer. Thus <0.2% of γ-lycorane was present in α-lycorane and vice versa.

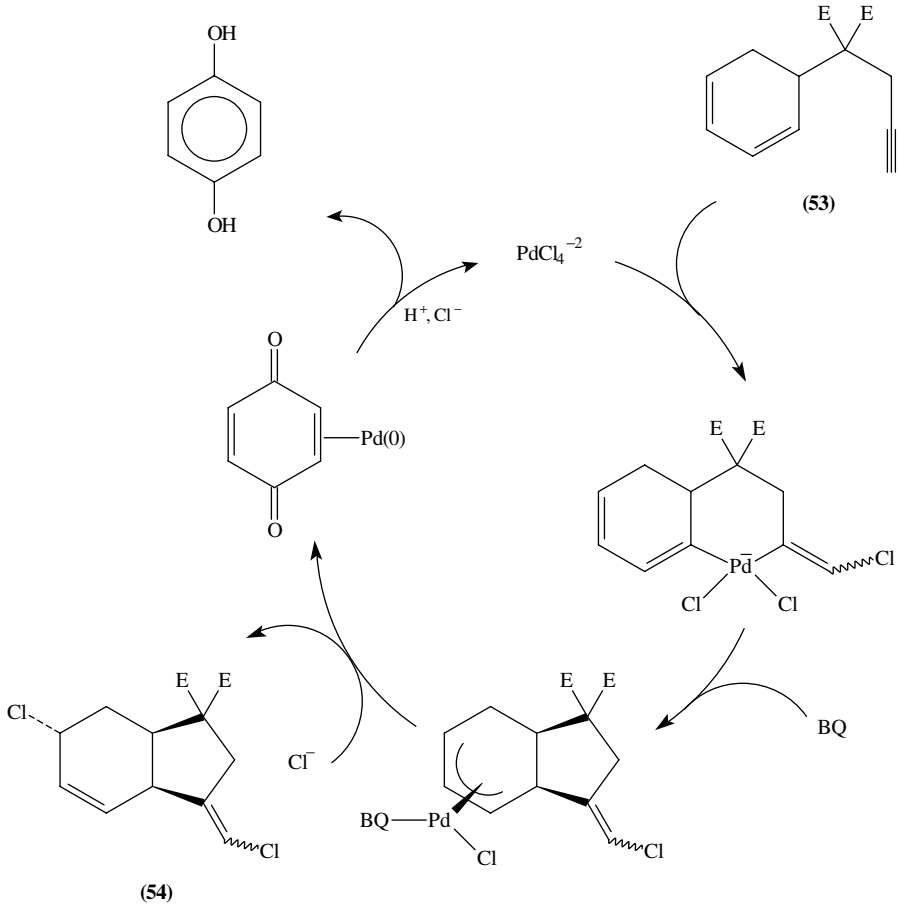
TABLE 3. Pd-catalyzed 1,4-oxyamination



Ring size,	R	Additive	X	% Yield	Stereochemistry of addition
6 ($n = 1$)	Ts	LiOAc	AcO	82	>93% *trans*
6 ($n = 1$)	Ts	LiCl(cat.)	AcO	65	>98% *cis*
6 ($n = 1$)	Ts	LiCl	Cl	90	>98% *cis*
6 ($n = 1$)	CO_2Bn	LiCl	Cl	97	>98% *cis*
7 ($n = 2$)	Ts	LiCl	Cl	86	>98% *cis*

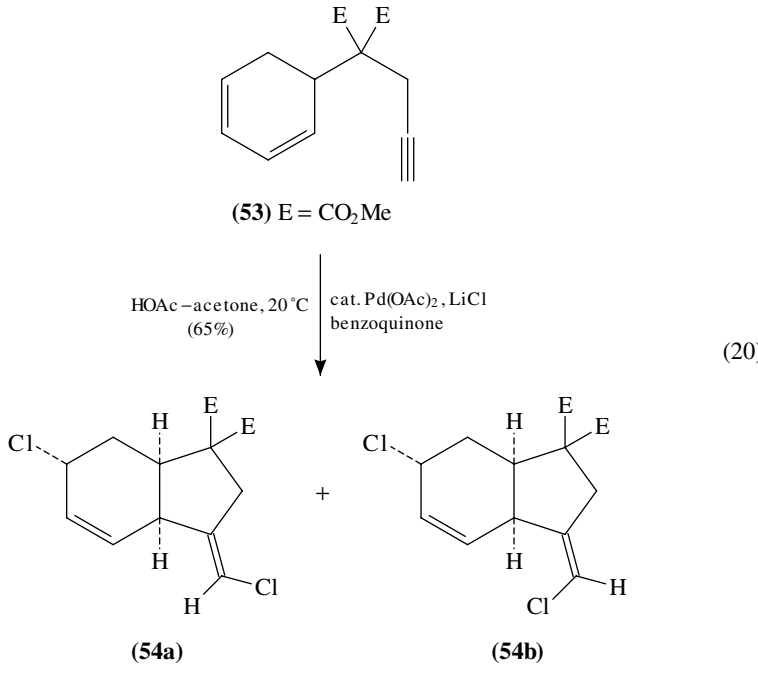

Cl
N
CO2Bn
(49)
O
O
MgBr
cat. Li2CuCl4
N
CO2Bn
O
O
(50)
1. H2/PtO2
2. POCl3
1. POCl3
2. H2/PtO2
H
N
O
O
O
(51)
(52)
LiAlH4
LiAlH4
α-lycorane
γ-lycorane

SCHEME 12



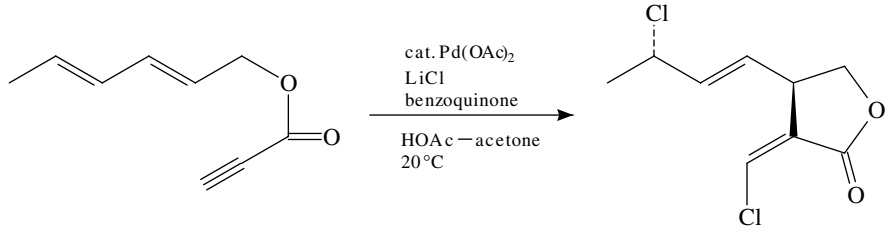
SCHEME 13. E = CO_2Me

The intramolecular palladium-catalyzed 1,4-oxidation has been extended to include carbon nucleophiles. There is an apparent problem with the use of carbon nucleophiles in an oxidation reaction due to the ease of oxidation of the carbanion to a radical. To overcome these problems, masked carbanions such as vinylpalladium and allylsilanes were employed in intramolecular palladium-catalyzed reaction of conjugated dienes[54,55]. In the first approach a vinylpalladium species is generated from an acetylene in the side chain. Subsequent vinylpalladation of the diene produces a (π-allyl)palladium complex. A benzoquinone-induced chloride attack on the π-allyl complex gives the product. The reaction works well with the use of either $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ as catalyst. The addition across the diene is highly regio- and stereoselective and takes place in a 1,4-*anti* fashion in agreement with the mechanism (Scheme 13). Reaction of dieneyne **53** gave a 65% yield of carbocyclization product as a 1:1.5 mixture of the chlorovinylic isomers **54a** and **54b** (equation 20)[54]. The *E* and *Z* isomerism at the chlorovinyl function originates from a nonstereoselective chloropalladation of the triple bond[56].



(20)

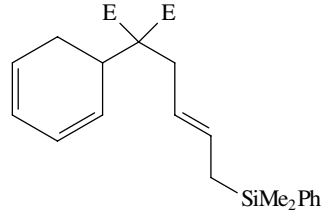
An example of this reaction in an acyclic case is given in equation 21. Dienyne **55** afforded compound **56** in a highly selective 1,4-addition. In this case the relative amount of the trans chloropalladation adduct was higher than in the reaction of **53** and the chlorovinyl group was 90% *E*[54].



(21)

In the second approach[55] an allylsilane was employed as carbon nucleophile in the side chain. Allylsilanes have been frequently used as masked allyl carbanions, usually in reactions with a keto function[57]. Palladium-catalyzed reaction of allylsilane **57** with LiCl under similar conditions as used for the other intramolecular 1,4-oxidations afforded **58** (equation 22). Interestingly, the carbochlorination over the diene was highly 1,4-*syn*

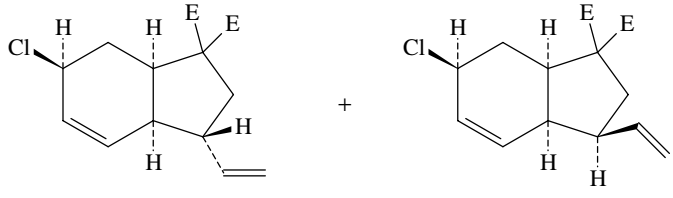
selective. The stereoselectivity is opposite to that obtained from dienyne **53** in equation 20 (*vide supra*).



(57) E = CO_2Me

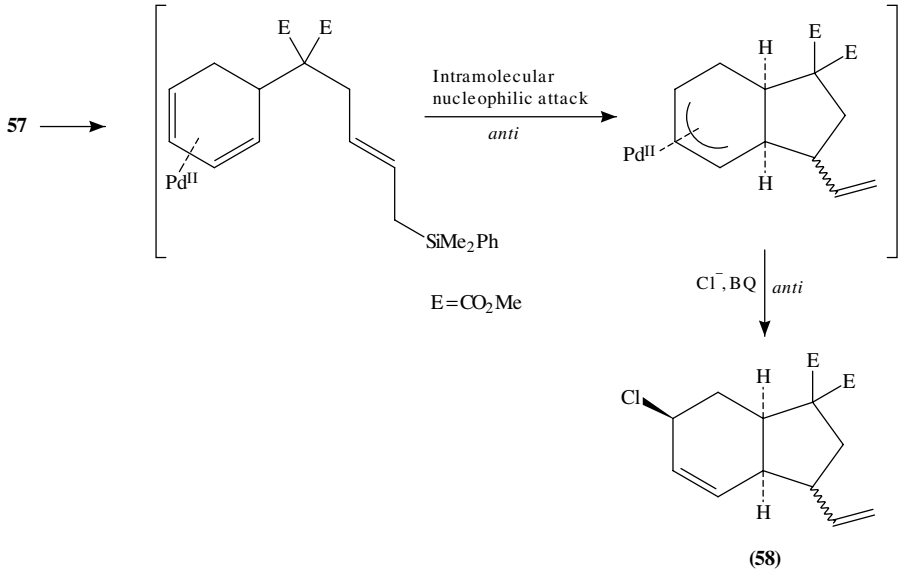
benzoquinone, LiCl
acetone–HOAc (2:1) (68%)
cat. Li_2PdCl_4

(22)



(58α) : **(58β)**

3 : 1



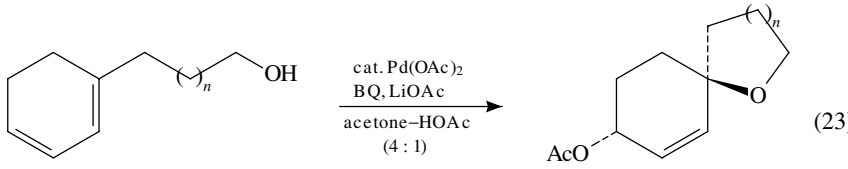
E=CO_2Me

(58)

SCHEME 14

The mechanism of this new reaction is shown in Scheme 14. Coordination of the diene to palladium(II) makes the diene double bond electrophilic enough to be attacked by the allylsilane. The attack by the allylsilane takes place on the face of the diene opposite to that of the palladium (*anti*). This is the first example of an anti attack by an allylsilane on a π-(olefin)metal complex. Benzoquinone (BQ)-induced *anti* attack by chloride ion produces the product **58**.

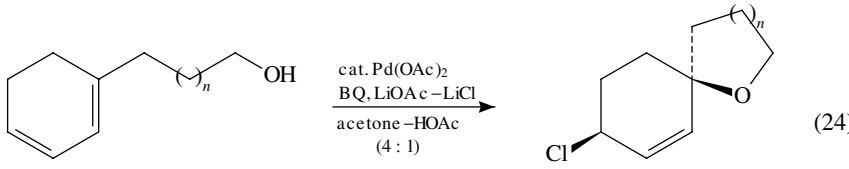
If the side chain with the nucleophile is situated in the 1-position of the conjugated diene, a palladium-catalyzed spirocyclization occurs. In this case stereoselective oxaspirocyclizations were obtained from the diene alcohols **59** and **60** (equation 23–25)[58]. The reaction worked well for the formation of a tetrahydrofuran and tetrahydropyran in the spirocyclization. In the absence of chloride ions **59** gave high yields of the acetoxy oxaspirocyclic compound **61** via a 1,4-*anti* addition across the diene (equation 23). In the presence of stoichiometric amounts of LiCl a 1,4-*syn* oxychlorination took place and allylic chloride **62** was obtained (equation 24). Under chloride-free conditions, cycloheptadiene alcohol **60** afforded oxaspirocyclic acetate **63** (equation 25).



(23)

(59a) $n = 1$
(59b) $n = 2$

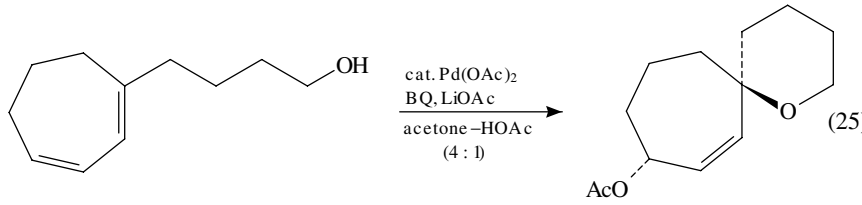
(61a) 86% (>98% *trans*)
(61b) 82% (>98% *trans*)



(24)

(59a) $n = 1$
(59b) $n = 2$

(62a) 70% (>98% *cis*)
(62b) 73% (>98% *cis*)

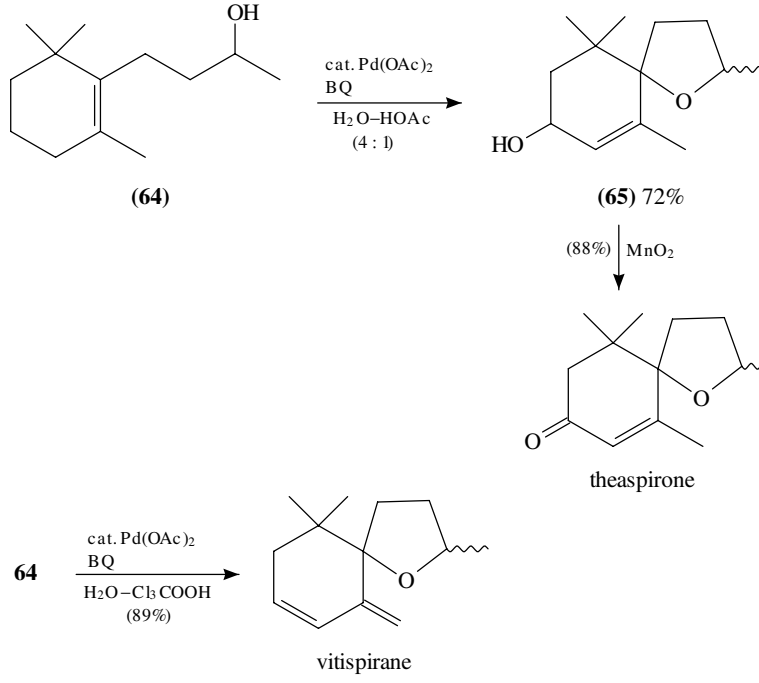


(25)

(60)

(63) 82% (>94% *trans*)

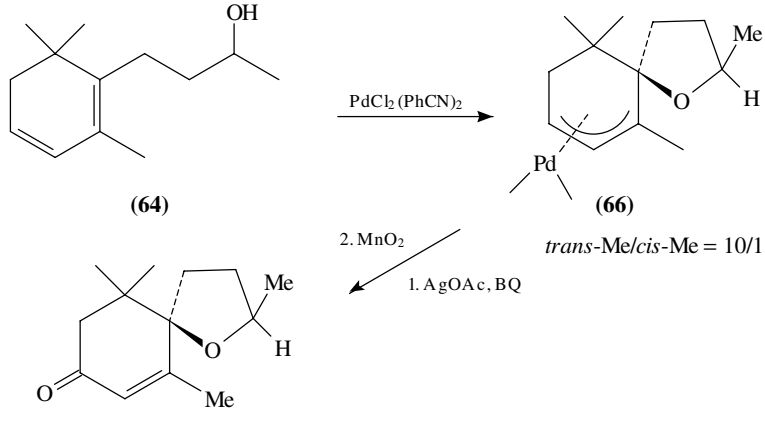
The oxaspirocyclization was applied to the synthesis of theaspirone and vitispirane (equations 26 and 27)[59]. Under slightly modified reaction conditions where water is employed as the major solvent, palladium-catalyzed 1,4-oxidation of **64** afforded **65**. Alcohol **65** was oxidized to theaspirone, which was obtained as a 1:1 isomeric mixture of *cis* and *trans* isomers. When the analogous reaction was performed at a lower pH by the use of trifluoroacetic acid, vitispirane was formed in high yield, again as a 1:1 isomeric mixture of stereoisomers.



(26)

(27)

In a stoichiometric reaction the (π-allyl)palladium complex **66** was isolated and characterized[58b]. In a subsequent reaction the π-allyl complex was reacted with benzoquinone in acetic acid to give an allylic acetate, which was hydrolyzed and oxidized to theaspirone. Interestingly, a quite high diastereoselectivity for the *trans* methyl isomer was obtained in the palladium-mediated spirocyclization (equation 28).

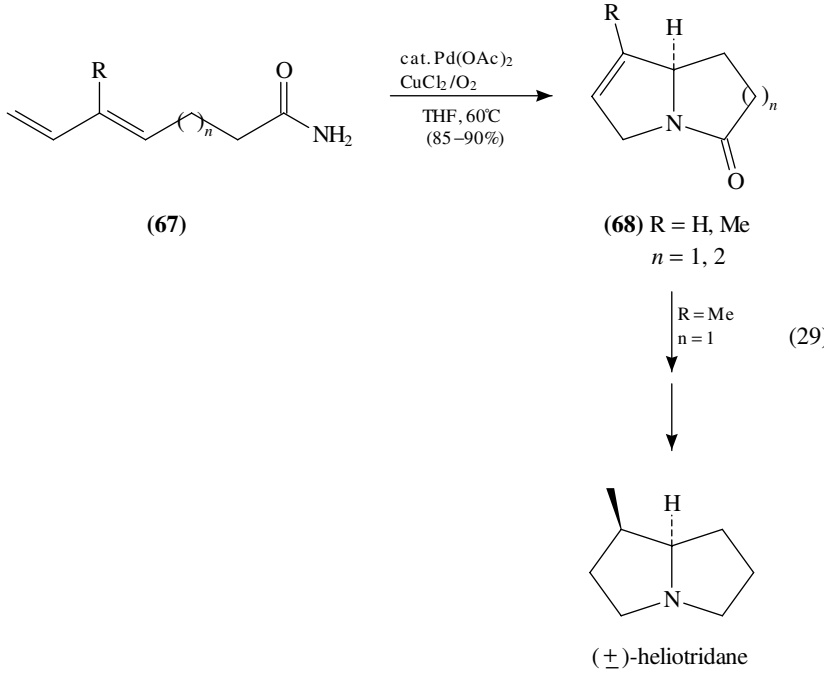


(28)

In the catalytic reaction this diastereoselectivity drops, and it was demonstrated that the π-allyl complex with the *cis* tetrahydrofuran is kinetically favored and is trapped by the

oxidant to give the product. In the stoichiometric reaction the thermodynamically favored π-allyl complex **66** with the *trans* tetrahydrofuran is formed.

An intramolecular palladium-catalyzed tandem cyclization of dienamides **67** in which the amide nucleophile adds twice has been developed (equation 29)[60]. This reaction constitutes a formal [4 + 1] cycloaddition and provides a new route to pyrrolizidine and indolizidine alkaloids. Reaction of dienamides **67** in the presence of catalytic amounts of $Pd(OAc)_2$ and $CuCl_2/O_2$ as the oxidant afforded bicyclic compounds **68** in good yields. The pyrrolizidine derivative **68** (R = Me, n = 1) was transformed to the alkaloid (±)-heliotridane.



(67)

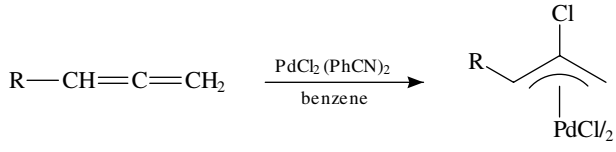
(68) R = H, Me
n = 1, 2

(±)-heliotridane

(29)

IV. ALLENES

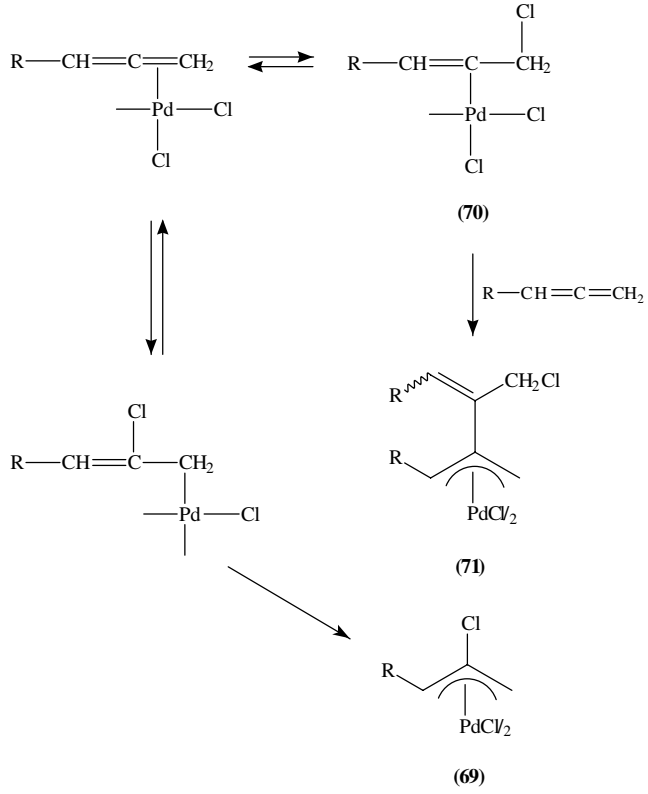
Reaction of allenes with $PdCl_2(PhCN)_2$ in benzene leads to the formation of 2-chloro π-allyl complexes **69** (equation 30)[61].



(30)

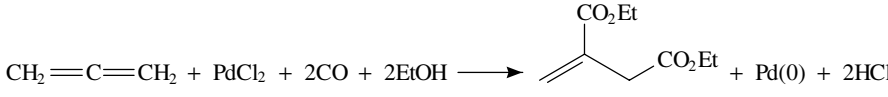
(69) R = H, R = alkyl

If an excess of allene is used, two allenes are incorporated in the π-allyl complex formed. The latter complex, **71**, is formed via a trapping of a vinyl complex **70** (Scheme 15).



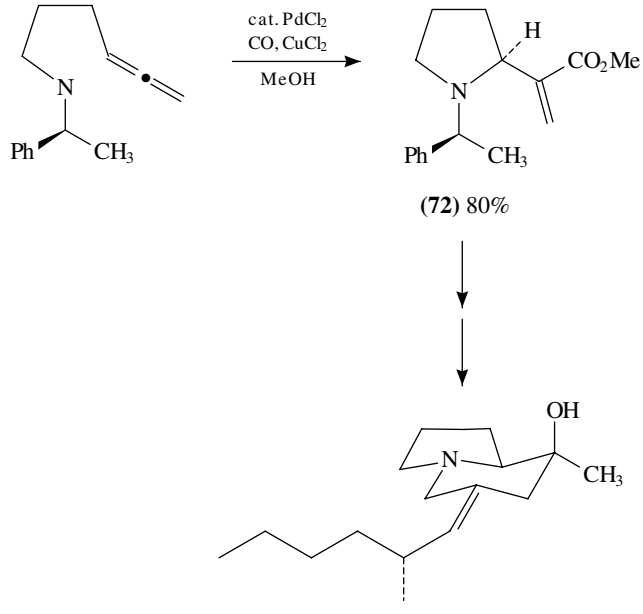
SCHEME 15

Attempts to employ allenes in palladium-catalyzed oxidations have so far given dimeric products via π-allyl complexes of type **71**[62,63]. The fact that only very little 1,2-addition product is formed via nucleophilic attack on π-allyl complex **69** indicates that the kinetic chloropalladation intermediate is **70**. Although formation of **70** is reversible, it is trapped by the excess of allene present in the catalytic reaction to give dimeric products. The only reported example of a selective intermolecular 1,2-addition to allenes is the carbonylation given in equation 31, which is a stoichiometric oxidation[64].



(31)

An example of an intramolecular palladium-catalyzed oxidation of an allene involving carbonylation was used in the synthesis of pumilotoxin 251 D (equation 32)[65]. Intramolecular aminopalladation of the allene followed by carbonylation of the palladium–carbon bond and subsequent oxidative cleavage of the acylpalladium intermediate by $CuCl_2$ afforded pyrrolidine **72** in which the chirality at the carbon at the 2-position was established.



(32)

pumilotoxin 251 D

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The Chemistry of Dienes and Polyenes. Volume 1
Edited by Zvi Rappoport

ISBN: 0-471-96512-X

CHAPTER **15**

Structural effects on dienes and polyenes

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I. DIENES AND POLYENES

A. Introduction

Polyenes are hydrocarbons with multiple double bonds. Dienes are simply special cases of polyenes. There are three types of polyenes:

1. Alternating polyenes in which single and double bonds alternate. There are two subtypes of alternating polyenes: conjugated alternating polyenes, of which 1,3,5-hexatriene and cycloheptatriene are examples; and cross-conjugated polyenes such as 2-vinyl-1,3-butadiene. The most important of the cross-conjugated dienes are the fulvenes[1].

2. Adjacent polyenes are hydrocarbons with double bonds between each pair of atoms in the polyene system; they are called cumulenes[2]. Two types of cumulenes exist: those with an even number of adjacent double bonds and those with an odd number. The former can exhibit chirality, the latter geometric isomerism. Allenes (propadienes) are the simplest members of the even-numbered type of cumulenes.

3. Isolated polyenes are those in which the double bonds are separated by one or more sp^3 hybridized carbon atoms. As their behavior is essentially that of ordinary molecules containing a double bond, they will not be considered further.

In this work we present a description of the quantification of structural effects on reactivities and properties of polyene systems.

II. THE NATURE OF STRUCTURAL EFFECTS

A. Introduction

Models for the quantitative description of the structural effects of substituents bonded to dienes or polyenes are described in this work. Also described are substituent effects of dienyl and polyenyl substituents.

In the second half of the nineteenth century the structural theory of organic chemistry was developed. It led to the concept that chemical, physical and biological properties of all kinds must vary with structural change. The earliest structure–property relationships (SPR) were qualitative. With the development of methods of quantitative measurement of these properties data accumulated. Attempts were then made to develop quantitative models of the structural dependence of these properties. These methods for the quantitative description of structural effects will now be described.

B. Structure–Property Quantitative Relationships (SPQR)

Quantitative descriptions of the structural dependence of properties are called structure–property quantitative relationships (SPQR). The four types of these relationships are:

1. Quantitative structure–chemical reactivity relationships (QSRR). Chemical reactivities involve the formation and/or cleavage of chemical bonds. Examples of chemical reactivity data are equilibrium constants, rate constants, polarographic half wave potentials and oxidation–reduction potentials.

2. Quantitative structure–chemical property relationships (QSCR). Chemical properties involve a difference in intermolecular forces between an initial and a final state. Examples of chemical property data are equilibrium constants for hydrogen bonding; charge transfer complex formation, conformational equilibria, partition coefficients; chromatographic properties such as capacity factors in high performance liquid chromatography, retention times in gas chromatography, and R_F values in thin layer and paper chromatography; melting and boiling points; solvent effects on equilibrium or rate constants; and solubilities.

3. Quantitative structure–physical property relationships (QSPR). Physical properties are either ground state properties or properties which depend on the difference in energy between the ground state and an excited state. Bond lengths, bond angles and dipole moments are ground state properties; infrared, ultraviolet, nuclear magnetic resonance and other types of spectra, ionization potentials and electron affinities are properties which depend on the energy difference between states.

4. Quantitative structure–activity relationships (QSAR). Any property associated directly or indirectly with a living organism is a biological activity. The bioactive substrates studied include pure enzymes, tissue homogenates, single celled organisms, whole tissues and large multicellular organisms. The data may be obtained in vitro or in vivo. They include rate and equilibrium constants for enzyme reactivity and for binding to receptor sites, various kinds of toxicity determinations such as lethal dose and lethal concentration, and minimum effective concentrations.

1. The nature of SPQR

There are several different types of chemical species (molecules, ions, radicals, carbenes; nitrenes, benzynes, etc.) for which SPQR can be determined. Three kinds of structure are possible:

1. Species with the structure XGY where X is a variable substituent, Y is a constant active site (an atom or group of atoms at which a measurable phenomenon takes place) and G is a constant skeletal group to which X and Y are bonded.

2. Species with the structure XY in which the variable substituent X is directly attached to the constant active site Y.

3. Species in which substituent and active site are the same, the entire species is the active site and it varies. These species are designated X_Y.

The purpose of SPQR is to provide a quantitative description of the change in some measurable quantity Q that occurs when a change is made in the structure of the species by varying the substituent X. All of the other pertinent variables such as the conditions of the measurement are held constant. Thus:

$$(\partial Q/\partial \mathrm{X})_{\mathrm{G,Y},T,P,\mathrm{Sv,I},\ldots} = Q_{\mathrm{X}} \tag{1}$$

where Q_X is the measured quantity when the substituent is X, G is the skeletal group, Y the active site, T the temperature, P the pressure, Sv the solvent, I the ionic strength, all of which are constant throughout the data set.

We assume that Q_X will be a linear function of some number of parameters which represent the effects of the structural variation of X. Then:

$$Q_{\mathrm{X}} = a_1 p_{1\mathrm{X}} + a_2 p_{2\mathrm{X}} + a_3 p_{3\mathrm{X}} + \cdots + a_0 \tag{2a}$$

$$= \sum_{i=1}^{n} a_i p_{i\mathrm{X}} + a_0 \tag{2b}$$

where the p_i are the parameters which account for the structural effect of X on Q. These parameters have been obtained in various ways:

1. From quantum chemical calculations[3]. This method is most suitable for electrical effect parameters.

2. From molecular mechanics calculations[4] for steric effect parameters.

3. From a reference set by definition (primary values). This method assumes that structural effects on the data set to be studied are a linear function of those which occur in the reference set. Secondary values of these parameters can be estimated by various methods.

4. From comparative molecular field analysis (COMFA)[5]. This method can be used for electrical, steric and polarizability parameters.

5. From molecular geometry for steric parameters.

6. From topological methods. This method is best restricted to steric effect and polarizability parameters.

Once suitable parameters are available the values of Q can be correlated with them by means of either simple linear regression analysis if the model requires only a single variable, or multiple linear regression analysis if it requires two or more variables. Such a correlation results in a SPQR. In this work we consider only those parameters that are defined directly or indirectly from suitable reference sets or, in the case of steric parameters, calculated from molecular geometries.

2. The uses of SPQR

SPQR have three major uses:

1. Mechanistic. QSRR and those QSAR which involve enzyme reactivity can provide information about the sensitivity of a reaction to electrical effects, its electronic demand, the composition of the electrical effect and the sensitivity to steric effects. QSAR which involve binding to receptor sites can provide information about the nature of the receptor site. Other QSAR can shed light on the bioactivity-determining step.

2. Predictive. All SPQR can be used to predict reactivities, chemical and physical properties and bioactivities. There are manifold practical applications of such predictions. Particular examples include the design of bioactive molecules such as medicinal drugs and

pesticides. In addition to the maximization of activity and minimization of side effects, desirable pharmaceutical properties such as improved solubility, longer shelf life and controlled release can be developed. They are also a major method in environmental science where they can be used to predict toxicities, biodegradabilities and other properties of environmental interest.

3. Archival. SPQR provide a concise, efficient and convenient method for storing the results of experimental studies on the effect of structural changes upon properties.

C. The Types of Structural Effects

Structural effects are conveniently divided into three categories:

1. Electrical effects. These effects cause a variation in the electron density at the active site. They account for the ability of a substituent to stabilize or destabilize a cation, anion, radical, carbene or other chemical species.

2. Steric effects. These effects result from the repulsion between valence electrons in orbitals on atoms which are in close proximity but not bonded to each other.

3. Inter- and intramolecular force effects. These effects result either from the interactions between the substituent and its immediate surroundings such as the medium, a surface or a receptor site, or from the effect of the substituent on the interactions of the skeletal group G and the active site Y with their surroundings.

Electrical effects are the major factor in chemical reactivities and physical properties. Intermolecular forces are usually the major factor in bioactivities. Either electrical effects or intermolecular forces may be the predominant factor in chemical properties. Steric effects only occur when the substituent and the active site are in close proximity to each other and even then rarely account for more than twenty-five percent of the overall substituent effect.

III. ELECTRICAL EFFECTS

A. Introduction

The earliest successful parameterization of electrical effects is that of Hammett[6–8]. Burkhardt reported the existence of QSRR two years before Hammett but did not develop a general relationship[9]. Hammett defined the σ_m and σ_p constants using the ionization constants (K_X) of 3- and 4-substituted benzoic acids in water at 25 °C as the reference set and hydrogen as the reference substituent (i.e. K_H) to which all others are compared. For hydrogen the values of the σ_m and σ_p constants were defined as zero.

$$\sigma_X \equiv \log \frac{K_X}{K_H} \tag{3}$$

These parameters were intended to apply to XGY systems in which the skeletal group is phenylene. Hammett found it necessary to define an additional set of parameters, σ_p^-, in order to account for substituent effects in 4-substituted benzene systems with an active site that has a lone pair on the atom adjacent to the benzene ring. The reference set was the ionization constants of 4-substituted phenols in water at 25 °C. Brown and his coworkers[10,11] later defined another set of constants, σ_p^+, to account for substituent effects in benzene derivatives with electronically deficient active sites. The reference set was the rate constants for the solvolysis of 4-substituted cumyl chlorides in 90% aqueous acetone at 25 °C. Finally, Wepster and coworkers[12] and Taft[13] both independently proposed constants intended to represent substituent effects in benzene derivatives with minimal delocalized effect. Using the Taft notation these constants are written as σ_p^0. The reference systems had a methylene group inserted between the benzene ring and the active

site ($XGCH_2Y$, where Y is 1,4-phenylene) as it was argued that the methylene group acted as an insulator preventing conjugation between X and Y. These parameters all differ in electronic demand. They are used in the Hammett equation (equation 3) which may be written in the form:

$$Q_X = \rho\sigma_X + h \tag{4}$$

where Q_X is the value of the quantity of interest when the substituent is X, and σ_X is either σ_{mX}, σ_{pX}, σ^0_{pX}, $\sigma_{pX}{}^+$, or $\sigma_{pX}{}^-$; ρ and h are the slope and intercept of the line. In using the Hammett equation it is necessary to make an *a priori* choice of parameters based on the location of the substituent and a knowledge of the electronic demand in the data set which is to be modelled. If such knowledge is unavailable, as is often the case, it is necessary to correlate the data set with each different parameter. The parameter which gives the best fit is then assumed to be the proper choice and the electronic demand associated with it is that of the data set.

Taft and his coworkers[14–16] developed a diparametric model which separated the electrical effect into contributions from the 'inductive' (actually the field) and resonance effects. This separation depends on the difference in the extent of electron delocalization when a substituent is bonded to an sp^3-hybridized carbon atom in one reference system and to an sp^2-hybridized carbon atom in another. As the first case represents minimal delocalization and the second extensive delocalization, we have referred to the two effects as the localized and delocalized electrical effects. This diparametric electrical effect model can be written in the form:

$$Q_X = L\sigma_{lX} + D\sigma_{DX} + h \tag{5}$$

where σ_l and σ_D are the localized and delocalized electrical effect parameters respectively, L and D are their coefficients while h is the intercept. Taft and coworkers[16] stated that four σ_D constants are required in order to account for all types of electronic demand: σ_{RX}, σ^0_{RX}, $\sigma_{RX}{}^+$, and $\sigma_{RX}{}^-$. They correspond to the σ_p constants described above. Charton noted that in cases of very large electron demand two additional σ_D constants were required: $\sigma_R{}^{\oplus}$ for highly electron-deficient (positive) active sites[17] and $\sigma_R{}^{\ominus}$ for active sites that have a large electron excess (negative)[18].

An alternative diparametric model was proposed by Yukawa and Tsuno[19] for use with electron-deficient active sites. The equation was originally written as:

$$Q_X = \rho\sigma_X + \rho r(\sigma_X{}^+ - \sigma_X) \tag{6}$$

A later version has the form[20]:

$$Q_X = \rho\sigma_X + \rho r(\sigma_X{}^+ - \sigma^0_X) \tag{7}$$

A similar relationship:

$$Q_X = \rho\sigma_X + \rho r(\sigma_X{}^- - \sigma_X) \tag{8}$$

has been proposed for active sites with an electron excess[21]. These relationships are termed the YT equations. They resemble the Hammett equation in being able to include both *meta*- and *para*-substituted compounds in the same data set. To do this it must be assumed that ρ_m is equal to ρ_p. This assumption is a reasonable approximation but in some cases the difference between ρ_m and ρ_p ($\Delta\rho$) is significant. If the molecular geometry of the system of interest does not differ much from that of the benzoic acids, then $\Delta\rho$ is likely to be negligible.

Like the case of the Hammett equation, the use of the LD equation (equation 5) for the description of chemical reactivities required either an *a priori* knowledge of the type

of σ_D substituent constant required, or a comparison of the results obtained using each of the available σ_D constants. The use of the YT equation has generally been restricted to electronically deficient active sites. Clearly there was a need for a more general model of electrical effects that would avoid the *a priori* parameter choice. A triparametric model of the electrical effect has been introduced[22] that can account for the complete range of electrical effects on chemical reactivities of closed-shell species (carbenium and carbanions), that is, reactions which do not involve radical intermediates. The basis of this model was the observation that the σ_D constants differ in their electronic demand. On the assumption that they are generally separated by an order of magnitude in this variable, it is possible to assign to each σ_D type a corresponding value of the electronic demand, η. Thus, the equation:

$$\sigma_{DX} = a_1\eta + a_0 = \sigma_{ex}\eta + \sigma_{dx} \tag{9}$$

is obeyed. The intercept of this linear relationship represents the intrinsic delocalized (resonance) effect, σ_{dX}. This is the delocalized effect observed when the electronic demand of the data set studied is zero. The slope represents the sensitivity of the X group to the electronic demand of the active site. On substituting equation 9 into the LD equation we obtain the triparametric LDR equation:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + h \tag{10}$$

The σ_l values are identical to σ_I. The symbol was changed in order to be consistent with the other symbols used in the equation.

When the composition of the electrical effect, P_D, is held constant the LDR equation simplifies to the CR equation:

$$Q_X = C\sigma_{ldX} + R\sigma_{eX} + h \tag{11}$$

where σ_{ld} is a composite parameter. It is defined by the relationship:

$$\sigma_{ldX} = l\sigma_{lX} + d\sigma_{dX} \tag{12}$$

Lower-case letters are used for the coefficients in equations that represent a substituent constant as a function of other substituent constants. The difference between pure and composite parameters is that the former represent a single effect while the latter represent a mixture of two or more. The percent composition of these parameters is given by:

$$P_D = \frac{100d}{l + d} \tag{13}$$

If the constant value of P_D is written as k', then the σ_{ldX} parameter for a given value of k' is:

$$\sigma_{ldXk'} = \sigma_{lX} + [k'/100 - k']\sigma_{DX} \tag{14}$$

Writing:

$$k^* = k'/(100 - k') \tag{15}$$

gives:

$$\sigma_{ldXk'} = \sigma_{lX} + k^*\sigma_{dX} \tag{16}$$

The Yukawa–Tsuno (YT) equation for 4-substituted benzene derivatives is approximately equivalent to the CR equation[23,24]. This observation has led to the development of a modified Yukawa–Tsuno (MYT) equation which has the form:

$$Q_X = \rho\sigma_X + R\sigma_{eX} + h \tag{17}$$

with σ taking the value σ_m for 3-substituted benzene derivatives and σ_{50} for 4-substituted benzene derivatives, while σ_{eX} for 3-substituted benzene derivatives is 0. The σ_{50} constants have k' equal to 50 and η equal to zero; they are therefore equal to the sum of the σ_l and σ_d values.

If the sensitivity to electronic demand is held constant, the LDR equation reverts to the LD equation (equation 5). By means of an equation analogous to the MYT equation, the modified LD (MLD) equation is:

$$Q_X = \rho'\sigma_X + D\sigma_{DX} + h \tag{18}$$

where σ is σ_m for 3-substituted and σ_l for 4-substituted while σ_D is 0 for 3-substituents; 3- and 4-substituted benzene derivatives can be combined into a single data set. Again, the use of the MLD equation is restricted to systems for which $\Delta\rho$ is not significant.

When both the electronic demand and the composition of the electrical effect are held constant, a set of composite parameters having the form:

$$\sigma_{k'/kX} = l\sigma_{lX} + d\sigma_{dX} + r\sigma_{eX} \tag{19}$$

is obtained, where k' and k are given by equations 20a and 20b:

$$k' = P_D = \frac{100d}{(l+d)} \tag{20a}$$

$$k = \eta = r/d \tag{20b}$$

The Hammett substituent constants are special cases of these parameters.

The $\sigma_{k'/k}$ values describe the overall electrical effect of the X group. They are obtained from the expression:

$$\sigma_{k'/kX} = \sigma_{lX} + [P_D/(100 - P_D)](\sigma_{dX} + \eta\sigma_{eX}) \tag{21a}$$

$$= \sigma_{lX} + k^*(\sigma_{dX} + k\sigma_{eX}) \tag{21b}$$

A plot of the $\sigma_{k'/kX}$ values for a group with P_D on the x axis, η on the y axis and $\sigma_{k'/k}$ on the z axis produces a surface that characterizes the electrical effect of the X group.

B. Electrical Effects of Dienyl and Polyenyl Substituents

Values of electrical effect substituent constants for a few dienyl and polyenal groups have been reported[25]. They are set forth in Table 1 together with values of diynyl and phenyl groups for comparison. Also reported in Table 1 are values for some other types of substituents[22,25] for purposes of comparison.

1. Classification of substituent electrical effects

It is traditional to classify substituents as either electron acceptors (electron withdrawing, electron sink), EA; or electron donors (electron releasing, electron source), ED. There is a third category as well, however, that consists of groups whose electrical effect is not significantly different from zero (NS groups). Groups vary in the nature of their electrical effect to a greater or lesser extent depending on the electronic demand of the phenomenon being studied, the skeletal group, if any, to which they are bonded, and the experimental conditions. Very few groups are in the same category throughout the entire range of P_D and η normally encountered. We have observed earlier that a plot of the $\sigma_{k'/k,X}$ values for a group with $X = P_D$, $Y = \eta$ and $Z = \sigma_{k'/k}$, produces a surface that characterizes the

TABLE 1. Values of σ_l, σ_d, and σ_e[a]

X	σ_l	Ref.	σ_d	Ref.	σ_e	Ref.
Alternating Dienes and Polyenes						
Conjugated						
CH=CH−CH=CH_2	0.12	25	−0.37	25	−0.12	25
H_2C=C−CH=CH_2	0.14	*24a*	−0.24	*26a*	−0.086	*27a*
CH=CH−CH=CHPh	0.13	25	−0.48	25	−0.12	25
$(CH=CH)_2$CH=CH_2	0.12	25	−0.51	25	−0.12	25
H_2C=C−CH=CH−CH=CH_2	0.09	*24a*	−0.28	*26a*	−0.085	*27a*
$(CH=CH)_2$CH=CHPh	0.07	*24a*	−0.45	*26a*	−0.15	*27a*
$(CH=CH)_3$CH=CH_2	0.06	*24a*	−0.46	*26a*	−0.15	*27a*
Cross-conjugated						
CH=C$(CH=CH_2)_2$	0.15	*24a*	−0.58	*26a*	−0.17	*27a*
Adjacent						
CH=C=CH_2	0.12	25	−0.02	25	−0.11	25
Vinyl						
CH=CH_2	0.11	25	−0.08	25	−0.12	25
CH=CHPh	0.13	25	−0.33	25	−0.12	25
Ethynyl						
C≡CH	0.29	25	−0.02	25	−0.10	25
C≡C−C≡CH	0.39	25	0.04	25	−0.10	25
C≡CPh	0.33	25	−0.25	25	−0.14	25
Aryl						
Ph	0.12	22	−0.12	22	−0.12	22
C_6H_4Ph-4	0.13	25	−0.17	25	−0.12	25
1-Naph	0.14	*b*	−0.23	*b*	−0.12	*b*
2-Naph	0.13	22	−0.16	22	−0.12	22
Other groups						
Me	−0.01	22	−0.14	22	−0.030	22
Et	−0.01	22	−0.12	22	−0.036	22
i-Pr	0.01	22	−0.15	22	−0.040	22
t-Bu	−0.01	22	−0.15	22	−0.036	22
c-Pr	0.01	22	−0.17	22	−0.069	22
CF_3	0.40	22	0.13	22	−0.026	22
CHO	0.30	22	0.27	22	−0.10	22
Ac	0.30	22	0.25	22	−0.095	22
$CONH_2$	0.28	22	0.12	22	−0.055	22
CO_2Me	0.32	22	0.16	22	−0.070	22
CO_2Et	0.30	22	0.18	22	−0.064	22
CN	0.57	22	0.12	22	−0.055	22
NH_2	0.17	22	−0.68	22	−0.13	22
NHAc	0.28	22	−0.35	22	−0.088	22
NMe_2	0.17	22	−0.66	22	−0.24	22
NO_2	0.67	22	0.18	22	−0.077	22
N_3	0.43	25	−0.27	25	−0.12	22
PMe_2	0.10	22	−0.50	22	−0.27	22
$POMe_2$	0.30	22	0.14	22	−0.036	22
$PO(OMe)_2$	0.36	22	0.24	22	−0.033	22
OH	0.35	22	−0.57	22	−0.044	22
OMe	0.30	22	−0.55	22	−0.064	22
OEt	0.28	22	−0.55	22	−0.070	22
OAc	0.38	22	−0.24	22	−0.005	22
OPh	0.40	22	−0.51	22	−0.083	22

(*continued overleaf*)

TABLE 1. (*continued*)

X	σ_l	Ref.	σ_d	Ref.	σ_e	Ref.
SH	0.27	22	−0.40	22	−0.098	22
SMe	0.30	22	−0.38	22	−0.13	22
SAc	0.39	22	−0.08	22	−0.057	22
SEt	0.26	22	−0.39	22	−0.12	22
SPh	0.31	22	−0.34	22	−0.17	22
SOMe	0.54	27	−0.01	27	−0.037	*b*
SOPh	0.51	27	−0.02	27	−0.052	*b*
SO_2Me	0.59	22	0.13	22	−0.052	22
SO_2Ph	0.56	22	0.08	22	−0.082	22
SeMe	0.28	22	−0.40	22	−0.14	22
F	0.54	22	−0.48	22	0.041	22
Cl	0.47	22	−0.28	22	−0.011	22
Br	0.47	22	−0.27	22	−0.018	22
I	0.40	22	−0.20	22	−0.057	22
H	0	22	0	22	0	22

[a]Numbers in italics in the columns headed Ref. refer to equations in the text used to estimate the values reported; numbers in ordinary typeface refer to references to the source from which the values were taken.
[b]M. Charton, unpublished results

electrical effect of the X group. A matrix of these values can be obtained by calculating them for values of P_D in the range 10 to 90 in increments of 10 and values of η in the range −6 to 6 in increments of 1. The resulting 9 by 13 matrix has 117 values. We define $\sigma_{k'/k,X}$ values greater than 0.05 as EA, $\sigma_{k'/k,X}$ values less than −0.05 as ED and $\sigma_{k'/k,X}$ values between 0.05 and −0.05 as NS. The variability of the electrical effect of a group can be quantitatively described by the percent of the matrix area in the P_D–η plane in which the group is in each category (P_{EA}, P_{ED} and P_0). Approximate measures of these quantities are given by the relationships:

$$P_{EA} = \frac{n_{EA}}{n_T},\ P_0 = \frac{n_{NS}}{n_T},\ P_{ED} = \frac{n_{ED}}{n_T} \tag{22}$$

where n_{EA}, n_{NS}, n_{ED} and n_T are the number of EA, the number of NS, the number of ED and the total number of values in the matrix. Matrices for a number of substituents are given in Table 2, values of P_{EA}, P_0 and P_{ED}, for many substituents are reported in Table 3. We may now classify groups into seven types:

1. Entirely electron acceptor (EA) ($P_{EA} = 100$). Examples: CF_3, $PO(OMe)_2$, $POPh_2$.
2. Predominantly electron acceptor (PA) ($100 > P_{EA} \geqslant 75$). Examples: NO_2, HCO, CN.
3. Largely electron acceptor (LA) ($75 > P_{EA} \geqslant 50$). Examples: Cl, C≡CPh, OCN.
4. Ambielectronic (AM) ($50 > P_{EA}$ or P_{ED}). Examples: SH, CH_2Ph, $SiMe_3$.
5. Largely electron donor (LD) ($75 > P_{ED} \geqslant 50$). Examples: Me, OH, NH_2.
6. Predominantly electron donor (PD) ($100 > P_{ED} \geqslant 75$). Examples: *P=PMe*, *P=POMe*.
7. Entirely electron donor (ED) ($P_{ED} = 100$). Example: *P=PNMe*$_2$.

The values in italics are based on estimated substituent constants.

2. The nature of substituent electrical effects

The overall electrical effect of a substituent as was noted above is a function of its σ_l, σ_d and σ_e values. It depends on the nature of the skeletal group G, the active site Y, the

TABLE 2. Substituent matrices[a]

	P_D								
η	10	20	30	40	50	60	70	80	90
CH=CH−CH=CH_2									
6	0.00	*−0.15*	*−0.35*	*−0.61*	*−0.97*	*−1.51*	*−2.42*	*−4.24*	*−9.69*
5	0.01	*−0.12*	*−0.30*	*−0.53*	*−0.85*	*−1.33*	*−2.14*	*−3.76*	*−8.61*
4	0.03	*−0.09*	*−0.24*	*−0.45*	*−0.73*	*−1.16*	*−1.86*	*−3.28*	*−7.53*
3	0.04	*−0.06*	*−0.19*	*−0.37*	*−0.61*	*−0.98*	*−1.58*	*−2.80*	*−6.45*
2	0.05	−0.03	*−0.14*	*−0.29*	*−0.49*	*−0.80*	*−1.30*	*−2.32*	*−5.37*
1	**0.07**	0.00	*−0.09*	*−0.21*	*−0.37*	*−0.62*	*−1.02*	*−1.84*	*−4.29*
0	**0.08**	0.03	−0.04	*−0.13*	*−0.25*	*−0.44*	*−0.74*	*−1.36*	*−3.21*
−1	**0.09**	**0.06**	0.01	−0.05	*−0.13*	*−0.26*	*−0.46*	*−0.88*	*−2.13*
−2	**0.11**	**0.09**	**0.06**	0.03	−0.01	*−0.08*	*−0.18*	*−0.40*	*−1.05*
−3	**0.12**	**0.12**	**0.12**	**0.11**	**0.11**	**0.10**	**0.10**	**0.08**	**0.03**
−4	**0.13**	**0.15**	**0.17**	**0.19**	**0.23**	**0.28**	**0.38**	**0.56**	**1.11**
−5	**0.15**	**0.18**	**0.22**	**0.27**	**0.35**	**0.46**	**0.66**	**1.04**	**2.19**
−6	**0.16**	**0.21**	**0.27**	**0.35**	**0.47**	**0.65**	**0.94**	**1.52**	**3.27**
H_2C=C−CH=CH_2									
6	**0.06**	−0.05	*−0.18*	*−0.36*	*−0.62*	*−0.99*	*−1.62*	*−2.88*	*−6.66*
5	**0.07**	−0.03	*−0.15*	*−0.31*	*−0.53*	*−0.87*	*−1.42*	*−2.54*	*−5.89*
4	**0.08**	−0.01	*−0.11*	*−0.25*	*−0.44*	*−0.74*	*−1.22*	*−2.20*	*−5.12*
3	**0.08**	0.02	*−0.07*	*−0.19*	*−0.36*	*−0.61*	*−1.02*	*−1.85*	*−4.34*
2	**0.09**	0.04	−0.04	*−0.13*	*−0.27*	*−0.48*	*−0.82*	*−1.51*	*−3.57*
1	**0.1**	**0.06**	0.00	*−0.08*	*−0.19*	*−0.35*	*−0.62*	*−1.16*	*−2.79*
0	**0.11**	**0.08**	0.04	−0.02	*−0.10*	*−0.22*	*−0.42*	*−0.82*	*−2.02*
−1	**0.12**	**0.10**	**0.07**	0.04	−0.01	*−0.09*	*−0.22*	*−0.48*	*−1.25*
−2	**0.13**	**0.12**	**0.11**	**0.09**	**0.07**	0.04	−0.02	*−0.13*	*−0.47*
−3	**0.14**	**0.14**	**0.15**	**0.15**	**0.16**	**0.17**	**0.18**	**0.21**	**0.30**
−4	**0.15**	**0.17**	**0.18**	**0.21**	**0.24**	**0.30**	**0.38**	**0.56**	**1.08**
−5	**0.16**	**0.19**	**0.22**	**0.27**	**0.33**	**0.43**	**0.58**	**0.90**	**1.85**
−6	**0.17**	**0.21**	**0.26**	**0.32**	**0.42**	**0.55**	**0.78**	**1.24**	**2.62**
CH=CH−CH=CHPh									
6	0.00	*−0.17*	*−0.38*	*−0.67*	*−1.07*	*−1.67*	*−2.67*	*−4.67*	*−10.6*
5	0.01	*−0.14*	*−0.33*	*−0.59*	*−0.95*	*−1.49*	*−2.39*	*−4.19*	*−9.59*
4	0.02	*−0.11*	*−0.28*	*−0.51*	*−0.83*	*−1.31*	*−2.11*	*−3.71*	*−8.51*
3	0.04	*−0.08*	*−0.23*	*−0.43*	*−0.71*	*−1.13*	*−1.83*	*−3.23*	*−7.43*
2	0.05	−0.05	*−0.18*	*−0.35*	*−0.59*	*−0.95*	*−1.55*	*−2.75*	*−6.35*
1	**0.06**	−0.02	*−0.13*	*−0.27*	*−0.47*	*−0.77*	*−1.27*	*−2.27*	*−5.27*
0	**0.08**	0.01	*−0.08*	*−0.19*	*−0.35*	*−0.59*	*−0.99*	*−1.79*	*−4.19*
−1	**0.09**	0.04	−0.02	*−0.11*	*−0.23*	*−0.41*	*−0.71*	*−1.31*	*−3.11*
−2	**0.10**	**0.07**	0.03	*−0.03*	*−0.11*	*−0.23*	*−0.43*	*−0.83*	*−2.03*
−3	**0.12**	**0.10**	**0.08**	0.05	0.01	−0.05	*−0.15*	*−0.35*	*−0.95*
−4	**0.13**	**0.13**	**0.13**	**0.13**	**0.13**	**0.13**	**0.13**	**0.13**	**0.13**
−5	**0.14**	**0.16**	**0.18**	**0.21**	**0.25**	**0.31**	**0.41**	**0.61**	**1.21**
−6	**0.16**	**0.19**	**0.22**	**0.29**	**0.37**	**0.49**	**0.69**	**1.09**	**2.29**
$(CH=CH)_2$−CH=CH_2									
6	−0.02	*−0.19*	*−0.41*	*−0.70*	*−1.11*	*−1.73*	*−2.75*	*−4.80*	*−10.9*
5	0.00	*−0.16*	*−0.36*	*−0.62*	*−0.99*	*−1.54*	*−2.47*	*−4.32*	*−9.87*
4	0.01	*−0.13*	*−0.30*	*−0.54*	*−0.87*	*−1.37*	*−2.19*	*−3.84*	*−8.79*
3	0.02	*−0.10*	*−0.25*	*−0.46*	*−0.75*	*−1.19*	*−1.91*	*−3.36*	*−7.71*
2	0.04	*−0.07*	*−0.20*	*−0.38*	*−0.63*	*−1.01*	*−1.63*	*−2.88*	*−6.63*
1	0.05	−0.04	*−0.15*	*−0.30*	*−0.51*	*−0.83*	*−1.35*	*−2.40*	*−5.55*
0	**0.06**	−0.01	*−0.10*	*−0.22*	*−0.39*	*−0.65*	*−1.07*	*−0.92*	*−4.47*

(*continued overleaf*)

TABLE 2. (*continued*)

	P_D								
η	10	20	30	40	50	60	70	80	90
$(CH{=}CH)_2{-}CH{=}CH_2$									
−1	**0.08**	0.02	−0.05	*−0.14*	*−0.27*	*−0.46*	*−0.79*	*−1.44*	*−3.39*
−2	**0.09**	0.05	0.00	*−0.06*	*−0.15*	*−0.28*	*−0.51*	*−0.96*	*−2.31*
−3	**0.10**	**0.08**	**0.06**	0.02	−0.03	*−0.11*	*−0.23*	*−0.48*	*−1.23*
−4	**0.12**	**0.11**	**0.11**	**0.10**	**0.09**	**0.07**	0.05	0.00	*−0.15*
−5	**0.13**	**0.14**	**0.16**	**0.18**	**0.21**	**0.25**	**0.33**	**0.48**	**0.93**
−6	**0.14**	**0.17**	**0.21**	**0.26**	**0.33**	**0.43**	**0.61**	**0.96**	**2.01**
$H_2C{=}C{-}CH{=}CH{-}CH{=}CH_2$									
6	0.00	*−0.11*	*−0.25*	*−0.44*	*−0.70*	*−1.09*	*−1.75*	*−3.07*	*−7.02*
5	0.01	*−0.09*	*−0.21*	*−0.38*	*−0.62*	*−0.97*	*−1.56*	*−2.73*	*−6.26*
4	0.02	*−0.07*	*−0.18*	*−0.32*	*−0.53*	*−0.84*	*−1.36*	*−2.39*	*−5.49*
3	0.03	−0.04	*−0.14*	*−0.27*	*−0.44*	*−0.71*	*−1.16*	*−2.05*	*−4.72*
2	0.04	−0.02	*−0.10*	*−0.21*	*−0.36*	*−0.58*	*−0.96*	*−1.71*	*−3.96*
1	0.05	0.00	*−0.07*	*−0.15*	*−0.28*	*−0.46*	*−0.76*	*−1.37*	*−3.20*
0	**0.06**	0.02	−0.03	*−0.10*	*−0.19*	*−0.33*	*−0.56*	*−1.03*	*−2.43*
−1	**0.07**	0.04	0.01	−0.04	*−0.10*	*−0.20*	*−0.36*	*−0.69*	*−1.66*
−2	**0.08**	**0.06**	0.04	0.02	−0.02	*−0.07*	*−0.17*	*−0.35*	*−0.90*
−3	**0.09**	**0.08**	**0.08**	**0.07**	**0.07**	0.05	0.03	−0.01	*−0.14*
−4	**0.10**	**0.11**	**0.12**	**0.13**	**0.15**	**0.18**	**0.23**	**0.33**	**0.63**
−5	**0.11**	**0.13**	**0.15**	**0.19**	**0.24**	**0.31**	**0.43**	**0.67**	**1.40**
−6	**0.12**	**0.15**	**0.19**	**0.24**	**0.32**	**0.43**	**0.63**	**1.01**	**2.16**
$(CH{=}CH)_3Ph$									
6	*−0.08*	*−0.27*	*−0.51*	*−0.83*	*−1.28*	*−1.96*	*−3.08*	*−5.33*	*−12.0*
5	*−0.06*	*−0.23*	*−0.44*	*−0.73*	*−1.13*	*−1.73*	*−2.73*	*−4.73*	*−10.7*
4	−0.05	*−0.19*	*−0.38*	*−0.63*	*−0.98*	*−1.50*	*−2.38*	*−4.13*	*−9.38*
3	−0.03	*−0.16*	*−0.32*	*−0.53*	*−0.83*	*−1.28*	*−2.03*	*−3.53*	*−8.03*
2	−0.01	*−0.12*	*−0.25*	*−0.43*	*−0.68*	*−1.06*	*−1.68*	*−2.93*	*−6.68*
1	0.00	*−0.08*	*−0.19*	*−0.33*	*−0.53*	*−0.83*	*−1.33*	*−2.33*	*−5.33*
0	0.02	*−0.04*	*−0.12*	*−0.23*	*−0.38*	*−0.60*	*−0.98*	*−1.73*	*−3.98*
−1	0.04	0.00	*−0.06*	*−0.13*	*−0.23*	*−0.38*	*−0.63*	*−1.13*	*−2.63*
−2	0.05	0.03	0.01	−0.03	*−0.08*	*−0.15*	*−0.28*	*−0.53*	*−1.28*
−3	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**	**0.07**
−4	**0.09**	**0.11**	**0.13**	**0.17**	**0.22**	**0.30**	**0.42**	**0.67**	**1.42**
−5	**0.10**	**0.15**	**0.20**	**0.27**	**0.37**	**0.52**	**0.77**	**1.27**	**2.77**
−6	**0.12**	**0.18**	**0.26**	**0.37**	**0.52**	**0.75**	**1.12**	**1.87**	**4.12**
$(CH{=}CH)_3{-}CH{=}CH_2$									
6	*−0.09*	*−0.28*	*−0.52*	*−0.85*	*−1.30*	*−1.98*	*−3.11*	*−5.38*	*−12.1*
5	*−0.07*	*−0.24*	*−0.46*	*−0.75*	*−1.16*	*−1.76*	*−2.76*	*−4.78*	*−10.8*
4	*−0.06*	*−0.21*	*−0.39*	*−0.65*	*−1.00*	*−1.53*	*−2.41*	*−4.18*	*−9.48*
3	*−0.04*	*−0.17*	*−0.33*	*−0.55*	*−0.85*	*−1.31*	*−2.06*	*−3.58*	*−8.13*
2	−0.02	*−0.13*	*−0.27*	*−0.45*	*−0.70*	*−1.08*	*−1.71*	*−2.98*	*−6.78*
1	−0.01	*−0.09*	*−0.20*	*−0.35*	*−0.55*	*−0.86*	*−1.36*	*−2.38*	*−5.43*
0	0.01	*−0.06*	*−0.14*	*−0.25*	*−0.40*	*−0.63*	*−1.01*	*−1.78*	*−4.08*
−1	0.03	−0.02	*−0.07*	*−0.15*	*−0.25*	*−0.41*	*−0.66*	*−1.18*	*−2.73*
−2	0.04	0.02	−0.01	−0.05	*−0.10*	*−0.18*	*−0.31*	*−0.58*	*−1.38*
−3	**0.06**	**0.06**	**0.06**	0.05	0.05	0.05	0.04	0.02	−0.03
−4	**0.08**	**0.10**	**0.12**	**0.15**	**0.20**	**0.27**	**0.39**	**0.62**	**1.32**
−5	**0.09**	**0.13**	**0.18**	**0.25**	**0.35**	**0.50**	**0.74**	**1.22**	**2.67**
−6	**0.11**	**0.17**	**0.25**	**0.35**	**0.50**	**0.72**	**1.09**	**1.82**	**4.02**

TABLE 2. (*continued*)

	P_D								
η	10	20	30	40	50	60	70	80	90
CH=C(CH=CH$_2$)$_2$									
6	−0.03	*−0.25*	*−0.54*	*−0.92*	*−1.45*	*−2.25*	*−3.58*	*−6.25*	*−14.2*
5	−0.01	*−0.21*	*−0.46*	*−0.80*	*−1.28*	*−2.00*	*−3.19*	*−5.57*	*−12.7*
4	0.01	*−0.16*	*−0.39*	*−0.69*	*−1.11*	*−1.74*	*−2.79*	*−4.89*	*−11.1*
3	0.03	*−0.12*	*−0.32*	*−0.58*	*−0.94*	*−1.48*	*−2.39*	*−4.21*	*−9.66*
2	0.05	*−0.08*	*−0.24*	*−0.46*	*−0.77*	*−1.23*	*−2.00*	*−3.53*	*−8.13*
1	**0.07**	−0.04	*−0.17*	*−0.35*	*−0.60*	*−0.98*	*−1.60*	*−2.85*	*−6.60*
0	**0.09**	0.01	*−0.10*	*−0.24*	*−0.43*	*−0.72*	*−1.20*	*−2.17*	*−5.07*
−1	**0.10**	0.05	−0.03	*−0.12*	*−0.26*	*−0.46*	*−0.81*	*−1.49*	*−3.54*
−2	**0.12**	**0.09**	0.05	−0.01	*−0.09*	*−0.21*	*−0.41*	*−0.81*	*−2.01*
−3	**0.14**	**0.13**	**0.12**	**0.10**	**0.08**	0.05	−0.01	*−0.13*	*−0.48*
−4	**0.16**	**0.18**	**0.19**	**0.22**	**0.25**	**0.30**	**0.38**	**0.55**	**1.05**
−5	**0.18**	**0.22**	**0.27**	**0.33**	**0.42**	**0.56**	**0.78**	**1.23**	**2.58**
−6	**0.20**	**0.26**	**0.34**	**0.44**	**0.59**	**0.81**	**1.18**	**1.91**	**4.11**
CH=C=CH$_2$									
6	0.04	−0.05	*−0.17*	*−0.33*	*−0.56*	*−0.90*	*−1.47*	*−2.60*	*−6.00*
5	**0.06**	−0.02	*−0.12*	*−0.26*	*−0.46*	*−0.74*	*−1.21*	*−2.16*	*−5.01*
4	**0.07**	0.00	*−0.08*	*−0.19*	*−0.34*	*−0.57*	*−0.95*	*−1.72*	*−4.02*
3	**0.08**	0.03	−0.03	*−0.11*	*−0.23*	*−0.40*	*−0.70*	*−1.28*	*−3.03*
2	**0.09**	**0.06**	0.02	−0.04	*−0.12*	*−0.24*	*−0.44*	*−0.84*	*−2.04*
1	**0.11**	**0.09**	**0.06**	0.03	−0.01	*−0.07*	*−0.18*	*−0.40*	*−1.05*
0	**0.12**	**0.12**	**0.11**	**0.11**	**0.10**	**0.09**	**0.07**	0.04	*−0.06*
−1	**0.13**	**0.14**	**0.16**	**0.18**	**0.21**	**0.26**	**0.33**	**0.48**	**0.93**
−2	**0.14**	**0.17**	**0.21**	**0.25**	**0.32**	**0.42**	**0.59**	**0.92**	**1.92**
−3	**0.15**	**0.20**	**0.25**	**0.33**	**0.43**	**0.59**	**0.84**	**1.36**	**2.91**
−4	**0.17**	**0.23**	**0.30**	**0.40**	**0.54**	**0.75**	**1.10**	**1.80**	**3.90**
−5	**0.18**	**0.25**	**0.35**	**0.47**	**0.65**	**0.91**	**1.36**	**2.24**	**4.89**
−6	**0.19**	**0.28**	**0.39**	**0.55**	**0.76**	**1.08**	**1.61**	**2.68**	**5.88**
C≡C−C≡CH									
6	**0.33**	**0.25**	**0.15**	0.02	*−0.17*	*−0.46*	*−0.92*	*−1.85*	*−4.66*
5	**0.34**	**0.27**	**0.19**	**0.08**	*−0.07*	*−0.30*	*−0.68*	*−1.45*	*−3.75*
4	**0.35**	**0.30**	**0.24**	**0.15**	0.03	*−0.15*	*−0.45*	*−1.05*	*−2.85*
3	**0.36**	**0.33**	**0.28**	**0.22**	**0.13**	0.00	*−0.22*	*−0.65*	*−1.95*
2	**0.37**	**0.36**	**0.32**	**0.28**	**0.22**	**0.15**	0.02	*−0.25*	*−1.05*
1	**0.38**	**0.38**	**0.36**	**0.35**	**0.33**	**0.30**	**0.25**	**0.15**	*−0.15*
0	**0.39**	**0.40**	**0.41**	**0.42**	**0.43**	**0.45**	**0.48**	**0.55**	**0.75**
−1	**0.41**	**0.43**	**0.45**	**0.48**	**0.53**	**0.60**	**0.72**	**0.95**	**1.65**
−2	**0.42**	**0.45**	**0.49**	**0.55**	**0.63**	**0.75**	**0.95**	**1.35**	**2.55**
−3	**0.43**	**0.48**	**0.54**	**0.62**	**0.73**	**0.90**	**1.18**	**1.75**	**3.45**
−4	**0.44**	**0.50**	**0.58**	**0.68**	**0.83**	**1.05**	**1.42**	**2.15**	**4.35**
−5	**0.45**	**0.53**	**0.62**	**0.75**	**0.93**	**1.20**	**1.65**	**2.55**	**5.25**
−6	**0.46**	**0.55**	**0.66**	**0.82**	**1.03**	**1.35**	**1.88**	**2.95**	**6.15**
C$_6$H$_4$Ph-4									
6	0.03	*−0.09*	*−0.25*	*−0.46*	*−0.76*	*−1.21*	*−1.95*	*−3.43*	*−7.88*
5	0.04	*−0.06*	*−0.20*	*−0.38*	*−0.64*	*−1.03*	*−1.67*	*−2.95*	*−6.80*
4	**0.06**	−0.03	*−0.15*	*−0.30*	*−0.52*	*−0.85*	*−1.39*	*−2.47*	*−5.72*
3	**0.07**	0.00	*−0.10*	*−0.22*	*−0.40*	*−0.66*	*−1.11*	*−1.99*	*−4.64*
2	**0.08**	0.03	−0.05	*−0.14*	*−0.28*	*−0.49*	*−0.83*	*−1.51*	*−3.56*
1	**0.10**	**0.06**	0.01	*−0.06*	*−0.16*	*−0.31*	*−0.55*	*−1.03*	*−2.48*
0	**0.11**	**0.09**	**0.06**	0.02	−0.04	*−0.13*	*−0.27*	*−0.55*	*−1.40*

(*continued overleaf*)

TABLE 2. (*continued*)

	P_D								
η	10	20	30	40	50	60	70	80	90
C_6H_4Ph-4									
−1	**0.12**	**0.12**	**0.11**	**0.10**	**0.08**	0.05	0.01	*−0.07*	*−0.32*
−2	**0.14**	**0.15**	**0.16**	**0.18**	**0.20**	**0.23**	**0.29**	**0.41**	**0.76**
−3	**0.15**	**0.18**	**0.21**	**0.26**	**0.32**	**0.41**	**0.57**	**0.89**	**1.84**
−4	**0.16**	**0.21**	**0.26**	**0.34**	**0.44**	**0.60**	**0.85**	**1.37**	**2.92**
−5	**0.18**	**0.24**	**0.31**	**0.42**	**0.56**	**0.77**	**1.13**	**1.85**	**4.00**
−6	**0.19**	**0.27**	**0.37**	**0.50**	**0.68**	**0.95**	**1.41**	**2.33**	**5.08**
C≡CPh									
6	**0.21**	**0.06**	*−0.14*	*−0.40*	*−0.76*	*−1.31*	*−2.21*	*−4.03*	*−9.48*
5	**0.22**	**0.09**	*−0.08*	*−0.30*	*−0.62*	*−1.09*	*−1.89*	*−3.47*	*−8.22*
4	**0.24**	**0.13**	−0.02	*−0.21*	*−0.48*	*−0.89*	*−1.56*	*−2.91*	*−6.96*
3	**0.26**	**0.16**	0.04	*−0.12*	*−0.34*	*−0.67*	*−1.23*	*−2.35*	*−5.70*
2	**0.27**	**0.20**	**0.10**	−0.02	*−0.20*	*−0.46*	*−0.91*	*−1.79*	*−4.44*
1	**0.29**	**0.23**	**0.16**	**0.07**	*−0.06*	*−0.25*	*−0.58*	*−1.23*	*−3.18*
0	**0.30**	**0.27**	**0.22**	**0.16**	**0.08**	−0.04	*−0.25*	*−0.67*	*−1.92*
−1	**0.32**	**0.30**	**0.28**	**0.26**	**0.22**	**0.17**	**0.07**	*−0.11*	*−0.66*
−2	**0.33**	**0.34**	**0.34**	**0.35**	**0.36**	**0.38**	**0.40**	**0.45**	**0.60**
−3	**0.35**	**0.37**	**0.40**	**0.44**	**0.50**	**0.59**	**0.73**	**1.01**	**1.86**
−4	**0.36**	**0.41**	**0.46**	**0.54**	**0.64**	**0.80**	**1.05**	**1.57**	**3.12**
−5	**0.38**	**0.44**	**0.52**	**0.63**	**0.78**	**1.01**	**1.38**	**2.13**	**4.38**
−6	**0.40**	**0.48**	**0.58**	**0.72**	**0.92**	**1.22**	**1.71**	**2.69**	**5.64**
CH=CHPh									
6	0.01	*−0.13*	*−0.32*	*−0.57*	*−0.92*	*−1.44*	*−2.32*	*−4.07*	*−9.32*
5	0.03	*−0.10*	*−0.27*	*−0.49*	*−0.80*	*−1.27*	*−2.04*	*−3.59*	*−8.24*
4	0.04	*−0.07*	*−0.22*	*−0.41*	*−0.68*	*−1.09*	*−1.76*	*−3.11*	*−7.16*
3	0.05	−0.04	*−0.17*	*−0.33*	*−0.56*	*−0.91*	*−1.48*	*−2.63*	*−6.08*
2	**0.07**	−0.01	*−0.11*	*−0.25*	*−0.44*	*−0.73*	*−1.20*	*−2.15*	*−5.00*
1	**0.08**	0.02	*−0.06*	*−0.17*	*−0.32*	*−0.55*	*−0.92*	*−1.67*	*−3.92*
0	**0.09**	0.05	−0.01	*−0.09*	*−0.20*	*−0.37*	*−0.64*	*−1.19*	*−2.84*
−1	**0.11**	**0.08**	0.04	−0.01	*−0.08*	*−0.19*	*−0.36*	*−0.71*	*−1.76*
−2	**0.12**	**0.11**	**0.09**	**0.07**	0.04	−0.01	*−0.08*	*−0.23*	*−0.68*
−3	**0.13**	**0.14**	**0.14**	**0.15**	**0.16**	**0.17**	**0.20**	**0.25**	**0.40**
−4	**0.15**	**0.17**	**0.19**	**0.23**	**0.28**	**0.35**	**0.48**	**0.73**	**1.48**
−5	**0.16**	**0.20**	**0.25**	**0.31**	**0.40**	**0.53**	**0.76**	**1.21**	**2.56**
−6	**0.17**	**0.23**	**0.30**	**0.39**	**0.52**	**0.71**	**1.04**	**1.69**	**3.64**

[a]Values in boldface are electron accepting, values in italics are electron donating, and values in ordinary type face show no significant electrical effect.

type of phenomenon studied, the medium and the reagent if any. These are the factors that control the values of P_D and η, which in turn determine the contributions of σ_l, σ_d and σ_e.

a. Conjugated alternating multiply doubly bonded substituents. Values are available for the 1-(1,3-butadienyl), 1-(4-phenyl-1,3-butadienyl) and 1-(1,3,5-hexatrienyl) groups. The substituent constants for the 1,3-butadienyl group were used successfully in the correlation of ionization potentials for 1-substituted 1,3-butadienes. Additional values were estimated for the 2-(1,3-butadienyl), 1-(6-phenyl-1,3,5-hexatrienyl), 1-(1,3,5,7-octatetraenyl) and 2-(1,3,5-hexatrienyl) groups from equations 24a, 26a and 27a. With the exception of the 2-(1,3-butadienyl) group which is of the AM type, all of the conjugated alternating groups appear to be of the LD type. This is in contrast to the behavior of aryl groups which are generally of the LA type.

TABLE 3. Values of P_{EA}, P_0 and P_{ED}

X	P_{EA}	P_0	P_{ED}	Group type
Alternating Dienes and Polyenes				
Conjugated				
CH=CH−CH=CH_2	37	11	52	LD
H_2C=C−CH=CH_2	45	11	44	AM
CH=CH−CH=CHPh	30	12	58	LD
(CH=CH)$_2$CH=CH_2	27	13	61	LD
H_2C=C−CH=CH−CH=CH_2	32	16	52	LD
(CH=CH)$_3$Ph	26	9	59	LD
(CH=CH)$_3$CH=CH_2	27	12	61	LD
Cross-conjugated				
CH=C(CH=CH_2)$_2$	32	11	57	LD
Adjacent				
CH=C=CH_2	59	9	32	LA
Vinyl				
CH=CH_2	53	9	38	LA
CH=CHPh	39	10	50	LD
Ethynyl				
C≡CH	74	4	22	LA
C≡C−C≡CH	80	3	17	PA
C≡CPh	62	3	35	LA
Aryl				
Ph	53	9	39	LA
C_6H_4Ph-4	50	9	41	LA
1-Naph	48	9	49	AM
2-Naph	50	9	40	LA
Other groups				
Me	3	32	65	LD
Et	10	32	57	LD
i-Pr	10	32	57	LD
t-Bu	7	29	64	LD
c-Pr	23	22	55	LD
CF_3	100	0	0	EA
CHO	89	3	8	PA
Ac	89	3	8	PA
$CONH_2$	90	3	8	PA
CO_2Me	90	2	9	PA
CO_2Et	92	3	5	PA
CN	96	0	4	PA
NH_2	25	9	66	LD
NHAc	51	5	44	LA
NMe_2	37	7	56	LD
NO_2	95	1	4	PA
N_3	65	3	32	LA
PMe_2	39	7	54	LD
$POMe_2$	95	2	3	PA
$PO(OMe)_2$	100	0	0	EA
OH	33	9	58	LD
OMe	34	7	59	LD
OEt	32	9	59	LD
OAc	58	9	33	LA
OPh	47	7	46	AM

(*continued overleaf*)

TABLE 3. (*continued*)

X	P_{EA}	P_0	P_{ED}	Group type
SH	48	7	45	AM
SMe	52	6	42	LA
SAc	79	3	18	PA
SEt	48	8	44	AM
SPh	56	4	39	LA
SOMe	92	1	7	PA
SOPh	87	3	10	PA
SO_2Me	97	0	3	PA
SO_2Ph	89	1	10	PA
SeMe	50	7	44	LA
F	53	3	44	LA
Cl	61	7	32	LA
Br	62	6	32	LA
I	70	3	27	LA
H	0	100	0	AM

b. Cross-conjugated alternating multiply doubly bonded substituents. No data are available for these substituents. Values were estimated for the 1-(2-vinyl-1,3-butadienyl) group from equations 24a, 26a and 27a assuming additivity. It seems to be of the LD type. This resembles the behavior of the ethynyl groups.

c. Adjacent multiply doubly bonded substituents. The only group of this type for which substituent constants are available is the allenyl group. The parameters for this group have been used successfully in the correlation of vertical ionization potentials of substituted allenes (see Section VI.C.3 below). This group is of the LA type.

C. Estimation of Electrical Effect Parameters for Dienyl and Polyenyl Substituents

It is often necessary to estimate values of electrical effect parameters for groups for which no measured values are available[27]. The equations available for the estimation of σ_1 values for *trans*-vinylene (CH=CHZ) and vinylidene ($CZ{=}CH_2$) groups are:

$$\sigma_{1X} = 0.291\sigma_{lZ} + 0.174\sigma_{dZ} - 0.279\sigma_{eZ} + 0.0903 \tag{23}$$

and

$$\sigma_{1_{M^1Z^1M^2Z^2}} = 0.292\sigma_{lZ^2} + 0.175\sigma_{dZ^2} + 0.0814\chi_{M^1} + 0.205\chi_{M^2} + 0.394\sigma_{lZ^1} + 0.206\sigma_{dZ^1} + 0.201n_x - 0.803 \tag{24}$$

The equations for the estimation of σ_d for *trans*-vinylene and vinylidene groups are:

$$\sigma_{dX} = 0.239\sigma_{lZ} + 0.500\sigma_{dZ} + 2.19\sigma_{eZ} - 0.0640 \tag{25}$$

and

$$\sigma_{d,M^1Z^1M^2Z^2} = 0.473\sigma_{lZ^2} + 0.272\sigma_{dZ^2} + 2.19\sigma_{eZ^2} + 0.229\chi_{M^1} + 0.432\chi_{M^2} + 0.148\sigma_{dZ^1} + 0.877\sigma_{eZ^1} - 1.77 \tag{26}$$

The only equation available for the estimation of σ_e constants is:

$$\sigma_{eM^1Z^1M^2Z^2} = 0.169\sigma_{lZ^2} - 0.0540\sigma_{dZ^2} + 0.422\sigma_{eZ^2} + 0.0694\chi_{M^1} + 0.0878\sigma_{lZ^1} - 0.269 \quad (27)$$

Equations 24, 26 and 27 apply to $M^1Z^1{=}M^2Z^2$ and $M^1{\equiv}M^2Z^2$ groups. They may be used to calculate substituent constants for both *trans*-vinylene and vinylidene groups. For these groups the value of χ_{M^1} and χ_{M^2}, the Allred–Rochow[28] electronegativity of carbon is 2.50; and the value of n_π, the number of bonds in the $M^1{-}M^2$ bond, is 1. Thus, equations 24, 26 and 27 simplify to:

$$\sigma_{l_{M^1Z^1M^2Z^2}} = 0.292\sigma_{lZ^2} + 0.175\sigma_{dZ^2} + 0.394\sigma_{lZ^1} + 0.206\sigma_{dZ^1} + 0.114 \quad (24a)$$

$$\sigma_{d_{M^1Z^1M^2Z^2}} = 0.473\sigma_{lZ^2} + 0.272\sigma_{dZ^2} + 2.19\sigma_{eZ^2} + 0.148\sigma_{dZ^1} + 0.877\sigma_{eZ^1} - 0.118 \quad (26a)$$

$$\sigma_{e_{M^1Z^1M^2Z^2}} = 0.169\sigma_{lZ^2} + 0.0540\sigma_{dZ^2} + 0.422\sigma_{eZ^2} + 0.0878\sigma_{lZ^1} - 0.0955 \quad (27a)$$

Values of σ_l, σ_d and σ_e for alternating dienyl substituents of the type $(CH{=}CH)_nX$ can be calculated by the following procedure:

1. Values of σ_l, σ_d and σ_e for the appropriate substituted vinylene or vinylidene group are calculated.

2. Taking the *trans*-vinylene or vinylidene group as Z, the values of σ_l, σ_d and σ_e for the appropriate dienyl group can be calculated from the estimation equations 24a, 26a and 27a given above.

Estimated values of σ_D parameters may be calculated from the equations[25]:

$$\sigma_{RX} = 0.934\sigma_{dX} + 0.308\sigma_{eX} - 0.0129 \quad (28)$$

$$\sigma_{RX}{}^{+} = 1.05\sigma_{dX} + 2.14\sigma_{eX} - 0.0731 \quad (29)$$

$$\sigma_{RX}{}^{-} = 1.13\sigma_{dX} - 1.58\sigma_{eX} + 0.00272 \quad (30)$$

$$\sigma_{RX}{}^{\bullet} = 1.15\sigma_{dX} + 3.81\sigma_{eX} - 0.0262 \quad (31)$$

$$\sigma_{RX}{}^{\ddot{\bullet}} = 1.01\sigma_{dX} - 3.01\sigma_{eX} - 0.00491 \quad (32)$$

$$\sigma_{RX}{}^{\circ} = 0.770\sigma_{dX} - 0.288\sigma_{eX} - 0.0394 \quad (33)$$

Values of these parameters are reported in Table 4. Estimated values of Hammett σ constants can be calculated from the relationships[25]:

$$\sigma_{mX} = 1.02\sigma_{lX} + 0.385\sigma_{dX} + 0.661\sigma_{eX} + 0.0152 \quad (34)$$

$$\sigma_{pX} = 1.02\sigma_{lX} + 0.989\sigma_{dX} + 0.837\sigma_{eX} + 0.0132 \quad (35)$$

$$\sigma_{pX}{}^{\circ} = 1.06\sigma_{lX} + 0.796\sigma_{dX} + 0.278\sigma_{eX} - 0.00289 \quad (36)$$

$$\sigma_{pX}{}^{+} = 1.10\sigma_{lX} + 0.610\sigma_{dX} + 2.76\sigma_{eX} + 0.0394 \quad (37)$$

$$\sigma_{pX}{}^{-} = 1.35\sigma_{lX} + 1.36\sigma_{dX} - 1.28\sigma_{eX} + 0.0176 \quad (38)$$

Table 5 reports values of the Hammett substituent constants.

TABLE 4. Values of σ_D^a

X	$\sigma_R^{\ominus}$	σ_R^{-}	σ_R^{0}	σ_R	σ_R^{+}	$\sigma_R^{\oplus}$
Alternating Dienes and Polyenes						
Conjugated						
CH=CH−CH=CH_2	*−0.02*	*−0.23*	*−0.29*	*−0.38*	*−0.57*	*−0.91*
H_2C=C−CH=CH_2	*0.01*	*−0.13*	*−0.20*	*−0.26*	*−0.51*	*−0.63*
CH=CH−CH=CHPh	*−0.13*	*−0.35*	*−0.37*	*−0.49*	*−0.53*	*−1.04*
$(CH=CH)_2$CH=CH_2	*−0.16*	*−0.38*	*−0.40*	*−0.51*	*−0.72*	*−1.07*
H_2C=C−CH=CH−CH=CH_2	*−0.03*	*−0.18*	*−0.23*	*−0.30*	*−0.55*	*−0.67*
$(CH=CH)_3$Ph	*−0.01*	*−0.27*	*−0.34*	*−0.48*	*−0.87*	*−1.12*
$(CH=CH)_3$CH=CH_2	*−0.02*	*−0.28*	*−0.35*	*−0.49*	*−0.88*	*−1.15*
Cross-conjugated						
CH=C$(CH=CH_2)_2$	*−0.08*	*−0.39*	*−0.44*	*−0.61*	*−1.05*	*−1.34*
Adjacent						
CH=C=CH_2	*0.31*	*0.15*	*−0.02*	*−0.05*	*−0.18*	*−0.47*
Vinyl						
CH=CH_2	0.45	−0.08	−0.15	−0.15	−0.15	−0.56
CH=CHPh	*0.02*	−0.23	−0.30	−0.30	−0.30	−1.01
Ethynyl						
C≡CH	0.28	0.13	−0.04	−0.04	−0.12	−0.45
C≡C−C≡CH	*0.34*	0.19	*0.02*	*0.01*	−0.17	*−0.36*
C≡CPh	*0.16*	−0.14	−0.21	−0.21	−0.21	−1.03
Aryl						
Ph	0.28	−0.04	−0.11	−0.11	−0.17	−0.69
C_6H_4Ph-4	*0.18*	*0.00*	*−0.14*	*−0.20*	*−0.36*	*−0.68*
1-Naph	*0.12*	*−0.07*	*−0.18*	*−0.26*	*−0.57*	*−0.75*
2-Naph	*0.19*	*0.01*	*−0.13*	*−0.20*	*−0.50*	*−0.67*
Other groups						
Me	−0.03	−0.09	−0.16	−0.16	−0.16	−0.25
Et	−0.01	−0.07	−0.14	−0.14	−0.14	−0.28
i-Pr	*−0.04*	−0.09	−0.16	−0.16	−0.16	−0.34
t-Bu	*−0.05*	−0.11	−0.18	−0.18	−0.18	−0.33
c-Pr	0.01	*−0.08*	*−0.15*	−0.19	−0.27	−0.43
CF_3	*0.20*	0.18	0.11	0.11	0.15	0.00
CHO	*0.57*	0.53	0.15	0.15	0.15	−0.04
Ac	0.56	0.41	0.20	0.20	0.06	−0.05
$CONH_2$	*0.28*	0.23	0.08	0.08	0.08	−0.10
CO_2Me	*0.37*	0.30	0.11	0.11	0.11	−0.12
CO_2Et	*0.37*	0.31	0.11	0.11	0.11	*−0.06*
CN	0.26	0.26	0.08	0.08	0.08	−0.10
NH_2	*−0.30*	−0.55	−0.42	−0.80	−1.10	−1.05
NHAc	*−0.09*	−0.28	−0.25	−0.35	−0.47	−0.75
NMe_2	*0.05*	−0.30	−0.44	−0.88	−1.22	−1.38
NO_2	0.41	0.37	0.10	0.10	0.10	−0.08
N_3	*0.08*	*−0.11*	*−0.21*	−0.31	*−0.47*	−0.67
PMe_2	*0.30*	*−0.14*	*−0.35*	*−0.55*	*−1.03*	*−1.63*
$POMe_2$	*0.24*	*0.22*	*0.08*	*0.12*	*0.14*	*0.00*
$PO(OMe)_2$	*0.34*	*0.33*	*0.15*	*0.21*	*0.25*	*0.12*
OH	*−0.45*	−0.45	−0.46	−0.62	−0.64	−0.71
OMe	−0.36	−0.51	−0.44	−0.58	−0.66	−0.83
OEt	*−0.35*	−0.51	−0.44	−0.57	−0.65	−0.86
OAc	*−0.23*	−0.16	*−0.22*	−0.23	−0.26	*−0.32*
OPh	*−0.27*	*−0.44*	−0.42	−0.48	*−0.64*	−0.96
SH	*−0.11*	*−0.29*	*−0.32*	*−0.41*	*−0.56*	−0.81

TABLE 4. (*continued*)

X	$\sigma_R^{\ominus}$	σ_R^{-}	σ_R^{0}	σ_R	σ_R^{+}	$\sigma_R^{\oplus}$
SMe	0.01	−0.24	−0.31	−0.38	−0.55	−0.97
SAc	*0.09*	*0.00*	−0.08	*−0.09*	*−0.13*	*−0.34*
SEt	*−0.04*	−0.10	−0.30	−0.30	*−0.59*	−0.99
SPh	*0.16*	−0.11	−0.24	−0.34	*−0.65*	−1.00
SOMe	0.13	0.05	0.00	0.00	−0.10	−0.70
SOPh	*0.03*	*0.06*	−0.07	−0.07	*−0.21*	−0.81
SO_2Me	0.18	0.35	0.11	0.11	0.11	−0.12
SO_2Ph	*0.32*	*0.22*	0.12	0.12	*−0.16*	−0.42
SeMe	*0.01*	*−0.23*	*−0.31*	*−0.42*	*−0.65*	*−1.02*
F	*−0.61*	−0.58	−0.44	−0.48	−0.37	*−0.25*
Cl	*−0.25*	−0.30	−0.25	−0.25	−0.21	−0.41
Br	−0.21	−0.28	−0.25	−0.25	−0.19	−0.44
I	*−0.06*	−0.18	−0.16	−0.16	−0.16	−0.57
H	0	0	0	0	0	0

[a] Values are from References 24, 25 and 27 unless otherwise noted. Those in italics are estimates.

TABLE 5. Values of Hammett substituent constants[a]

X	σ_m	σ_p^{-}	σ_p^{0}	σ_p	σ_p^{+}
Alternating Dienes and Polyenes					
Conjugated					
$CH{=}CH{-}CH{=}CH_2$	−0.08	−0.17	−0.20	−0.33	−0.76
$H_2C{=}C{-}CH{=}CH_2$	*0.01*	*−0.01*	*−0.07*	*−0.15*	*−0.19*
$CH{=}CH{-}CH{=}CHPh$	−0.12	−0.31	−0.28	−0.43	−0.42
$(CH{=}CH)_2CH{=}CH_2$	−0.14	−0.36	−0.32	−0.47	−0.98
$H_2C{=}C{-}CH{=}CH{-}CH{=}CH_2$	*−0.06*	*−0.13*	*−0.15*	*−0.24*	*−0.27*
$(CH{=}CH)_3Ph$	*−0.19*	*−0.31*	*−0.33*	*−0.49*	*−0.57*
$(CH{=}CH)_3CH{=}CH_2$	*−0.20*	*−0.34*	*−0.35*	*−0.51*	*−0.59*
Cross-conjugated					
$CH{=}C(CH{=}CH_2)_2$	*−0.17*	*−0.35*	*−0.35*	*−0.55*	*−0.62*
Adjacent					
$CH{=}C{=}CH_2$	0.06	0.29	0.08	0.02	−0.16
Vinyl					
$CH{=}CH_2$	0.02	0.21	0.02	−0.05	−0.30
$CH{=}CHPh$	−0.06	0.13	−0.16	−0.28	−0.68
Ethynyl					
$C{\equiv}CH$	0.24	0.50	0.26	0.21	0.05
$C{\equiv}C{-}C{\equiv}CH$	0.36	0.72	0.41	0.37	0.26
$C{\equiv}CPh$	0.16	0.39	0.11	−0.01	−0.39
Aryl					
Ph	0.01	0.08	0.00	−0.08	−0.51
C_6H_4Ph-4	0.00	0.11	−0.03	−0.12	−0.42
1-Naph	*−0.02*	*0.05*	*−0.07*	*−0.17*	*−0.28*
2-Naph	*0.01*	*0.13*	*−0.03*	*−0.11*	*−0.25*
Other groups					
Me	−0.06	−0.15	−0.15	−0.17	−0.31
Et	−0.06	−0.09	−0.12	−0.15	−0.28
i-Pr	*−0.04*	*−0.12*	*−0.12*	−0.15	−0.28
t-Bu	0.00	*−0.15*	*−0.14*	−0.19	−0.26
c-Pr	−0.08	−0.09	−0.15	−0.22	−0.46

(*continued overleaf*)

TABLE 5. (*continued*)

X	σ_m	σ_p^-	σ_p^0	σ_p	σ_p^+
CF_3	0.46	0.74	0.52	0.53	0.61
CHO	0.36	0.91	0.50	0.45	0.53
Ac	0.38	0.82	0.46	0.50	0.51
$CONH_2$	0.31	0.62	0.37	0.37	0.39
CO_2Me	0.36	0.74	0.46	0.44	0.49
CO_2Et	0.35	0.74	0.46	0.44	0.49
CN	0.61	1.02	0.69	0.65	0.66
NH_2	−0.21	−0.51	*−0.40*	−0.63	−1.30
NHAc	0.11	0.03	0.00	−0.12	−0.46
NMe_2	−0.22	−0.35	−0.44	−0.67	−1.50
NO_2	0.74	1.29	0.82	0.77	0.79
N_3	0.27	0.38	0.20	0.08	−0.25
PMe_2	−0.25	−0.18	−0.37	−0.61	−1.40
$POMe_2$	0.35	0.65	0.42	0.43	0.50
$PO(OMe)_2$	0.46	0.87	0.56	0.59	0.73
OH	0.13	*−0.24*	−0.10	−0.38	−0.61
OMe	0.11	−0.25	−0.12	−0.28	−0.78
OEt	*0.07*	*−0.27*	−0.16	*−0.29*	*−0.73*
OAc	0.31	0.20	0.21	0.16	0.06
OPh	*0.23*	*−0.04*	*−0.01*	*−0.08*	*−0.57*
SH	*0.07*	*−0.04*	*−0.06*	*−0.19*	*−0.58*
SMe	0.09	0.04	−0.02	−0.17	−0.60
SAc	0.34	0.50	0.33	0.28	0.18
SEt	*0.16*	*−0.01*	*−0.07*	*−0.04*	*−0.63*
SPh	*0.23*	0.18	*0.01*	*−0.15*	*−0.64*
SOMe	0.47	0.74	0.47	0.54	0.21
SOPh	*0.50*	*0.75*	*0.51*	*0.44*	*0.44*
SO_2Me	0.63	1.13	0.71	0.70	0.75
SO_2Ph	*0.62*	0.95	*0.68*	*0.68*	*0.48*
SeMe	0.05	0.03	−0.06	−0.21	−0.68
F	0.34	0.03	0.17	0.06	−0.07
Cl	0.37	0.28	0.27	0.22	0.11
Br	0.34	0.30	0.26	0.22	0.15
I	0.35	0.35	0.27	0.24	0.13
H	0	0	0	0	0

[a]Values are from the references cited in Table 4. Those in italics are estimates.

IV. STERIC EFFECTS

A. Introduction

The concept of steric effects was introduced by Kehrmann[30] over a century ago. Meyer[31] and Sudborough and Lloyd[32] shortly thereafter presented kinetic results supporting the steric effect explanation of rate retardation in the esterification of 2-substituted and 2,6-disubstituted benzoic and 3-*cis*-substituted acrylic acids. Major early reviews of steric effects are given by Stewart[33], Wittig[34] and somewhat later by Wheland[35] and in a volume edited by Newman[36].

B. The Nature of Steric Effects

1. Primary steric effects

Primary steric effects are due to repulsions between electrons in valence orbitals on adjacent atoms which are not bonded to each other. They are believed to result from the

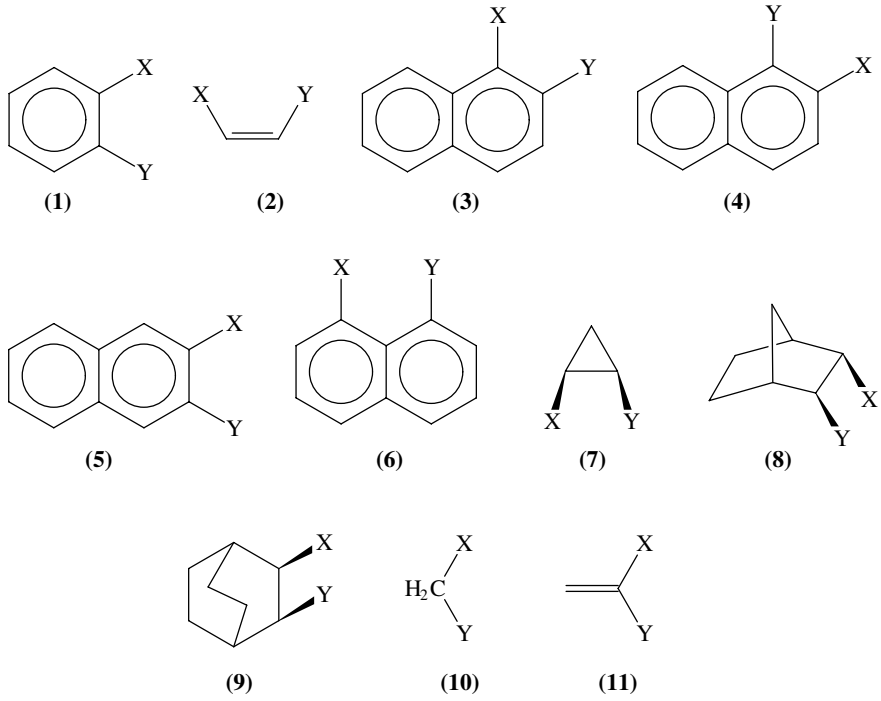
interpenetration of occupied orbitals on one atom by electrons on the other resulting in a violation of the Pauli exclusion principle. *All steric interactions raise the energy of the system in which they occur*. Their effect on chemical reactivity is to either decrease or increase a rate or equilibrium constant depending on whether steric repulsions are greater in the reactant or in the product (equilibria) or transition state (rate).

2. Secondary steric effects

Secondary steric effects on chemical reactivity can result from the shielding of an active site from the attack of a reagent, from solvation, or both. They may also be due to a steric effect on the reacting conformation of a chemical species that determines its concentration.

3. Direct steric effects

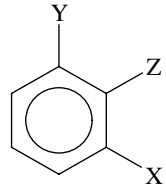
These effects can occur when the active site at which a measurable phenomenon occurs is in close proximity to the substituent. Among the many systems exhibiting direct steric effects are *ortho*-substituted benzenes, **1**, *cis*-substituted ethylenes, **2**, and the *ortho*- (1,2-, 2,1- and 2,3-) and peri- (1,8-) substituted naphthalenes, **3**, **4**, **5** and **6**, respectively. Other examples are *cis*-1,2-disubstituted cyclopropanes, *cis*-2,3-disubstituted norbornanes and *cis*-2,3-disubstituted [2.2.2]-bicyclooctanes, **7**, **8** and **9**, respectively. Some systems generally do not show steric effects. Vicinally substituted systems such as disubstituted methanes, **10**, and 1,1-disubstituted ethenes, **11**, are examples, 2,3-Disubstituted heteroarenes with five-membered rings such as thiophenes and selenophenes



are also generally free of steric effects. This is probably due to the larger XCC angle in these systems as compared with benzenoid systems.

4. Indirect steric effects

These effects are observed when the steric effect of the variable substituent is relayed by a constant substituent between it and the active site as in **12** where Y is the active site, Z is the constant substituent and X is the variable substituent. This is a buttressing effect.



(12)

5. The directed nature of steric effects

There is a regrettable tendency to regard steric effects as being related to 'bulk'. Unfortunately, the word bulk is invariably used without a precise definition of its meaning. The latest form of this verbal handwaving is the use of the phrase steric bulk. Presumably, this is intended to imply size in some vague ill-defined way. Steric effects are vector quantities. This is easily shown by considering, for example, the ratio r of the steric parameter for any five-carbon alkyl group to that for 1-pentyl (Pe). Values of r are: 1-Pe, 1; 2-Pe, 1.54; 3-Pe, 2.22; CH_2Bu-s; 1.47; CH_2Bu-i, 1.00; CH_2Bu-t, 1.97; CMe_2Pr, 2.40; CH-iPrMe, 1.90. All of these groups have the same volume and therefore the same bulk, but they differ in steric effect. In order to account for this it is necessary to consider what happens when a nonsymmetric substituent is in contact with an active site. Taking as an example the simple case of a spherical active site Y in contact with a nonsymmetric substituent, $CZ^LZ^MZ^S$, where the superscripts, L, M and S represent the largest, the medium-sized and the smallest Z groups, respectively, there are three possible conformations of this system. They are shown in top views in Figure 1. As all steric repulsions raise the energy of the system, the preferred conformation will be the one that results in the lowest energy increase. This is the conformation which presents the smallest face to the active site, conformation **A**. This is the basis of the minimum steric interaction (MSI) principle which states: *a nonsymmetric substituent prefers that conformation which minimizes steric interactions*. The directed nature of steric effects results in a conclusion of vital importance: that in general *the volume of a substituent is not an acceptable measure of its steric effect*[37–39]. Although there are still some workers who are unable to comprehend this point, it is nevertheless true that group volumes are not useful as steric parameters. They are actually measures of group polarizability. In short, for a range of different substituent shapes in a data set *steric effects are not directly related to bulk, polarizability is*.

C. The Monoparametric Model of Steric Effects

Stewart[33], who proposed a parallel between the rate of esterification of 2-substituted benzoic acids and the molecular weights of the substituents (the nitro group strongly deviating from this relationship) was the first to attempt to relate the steric effect of a

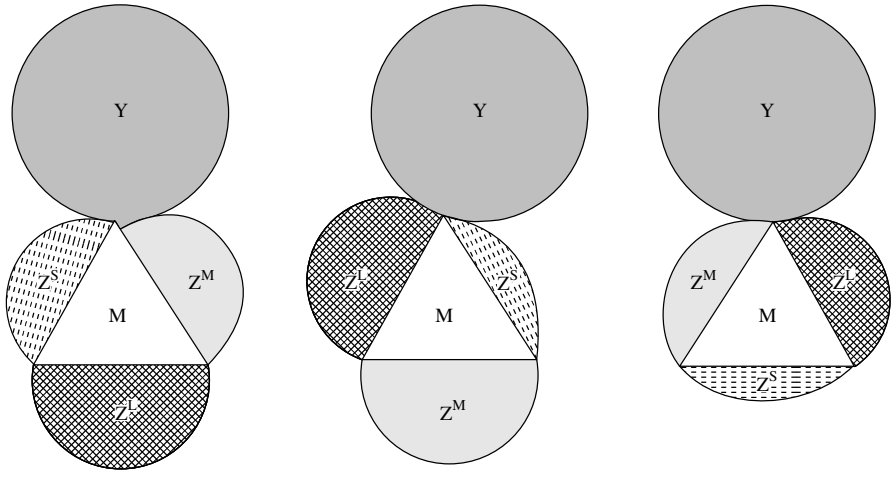


FIGURE 1. Possible conformations of a spherical active site Y adjacent to a tetrahedral substituent $MZ^LZ^MZ^S$ where L, M and S designate the largest, medium-sized and smallest groups, respectively. Conformation **A** has the lowest energy, conformation **C** the highest

group to some property that might at least in part be a measure of size. Kindler[40] made the first attempt at defining a set of steric parameters. These parameters were later shown to be a function of electrical effects. The first successful parameterization of the steric effect is due to Taft[41], who defined the steric parameter E_s for aliphatic systems by the expression:

$$E_{s,X} \equiv \delta \log \frac{k_X}{k_{Me}} \tag{39}$$

where k_X and k_{Me} are the rate constants for the acid-catalyzed hydrolysis of the corresponding alkyl esters XCO_2Alk and $MeCO_2Alk$, respectively. The value of δ is taken as 1.000 for this purpose; $E_{So,X}$ parameters intended to represent the steric effects of substituents in the *ortho* position of a benzene derivative were defined for a few groups from the rates of acid-catalyzed hydrolysis of 2-substituted alkyl benzoates. These parameters are a mix of electrical and steric effects with the former predominating, and are therefore of no use as steric parameters.

The original Taft $E_{S,X}$ values suffered from several deficiencies:

1. Their validity as measures of steric effects was unproven.
2. They were determined from average values of rate constants obtained under varying experimental conditions, often in different laboratories.
3. They were available only for those groups in which the atom bonded to G or Y (the first atom of the substituent) is an sp^3 hybridized carbon atom, and for hydrogen. Values were therefore unavailable for many if not most of the substituents generally encountered.
4. The use of the methyl group as the reference substituent meant that they were not compatible with electrical effect substituent constants for which the reference substituent is hydrogen.

The first problem was resolved when it was shown that the E_S values for symmetric groups are a linear function of van der Waals radii[42]. The latter have long been held to be an effective measure of atomic size. The second and third problems were solved by

Charton, who proposed the use of the van der Waals radius as a steric parameter[43] and developed a method for the calculation of group van der Waals radii for tetracoordinate symmetric top substituents MZ_3 such as the methyl and trifluoromethyl groups[44]. In later work the hydrogen atom was chosen as the reference substituent and the steric parameter υ was defined as:

$$\upsilon_X \equiv r_{VX} - r_{VH} = r_{VX} - 1.20 \tag{40}$$

where r_{VX} and r_{VH} are the van der Waals radii of the X and H groups in Angstrom units[45]. Expressing r_V in these units is preferable to the use of picometers because the coefficient of the steric parameter is then comparable in magnitude to the coefficients of the electrical effect parameters. Whenever possible, υ parameters are obtained directly from van der Waals radii or calculated from them. Recently, an equation has been derived which makes possible the calculation of υ values for nonsymmetric tetrahedral groups of the types $MZ_2^SZ^L$ and $MZ^SZ^MZ^L$ in which the Z groups are symmetric. These are considered to be primary values. For the greater number of substituents however, υ parameters must be calculated from the regression equations obtained for correlations of rate constants with primary values. The values obtained in this manner are considered to be secondary υ values. All other measures of atomic size are a linear function of van der Waals radii. There is therefore no reason for preferring one measure of atomic size over another. As values of υ were developed for a wide range of substituent types with central atoms including oxygen, nitrogen, sulfur and phosphorus as well as carbon, these parameters provide the widest structural range of substituents for which a measure of the steric effect is available.

1. Steric classification of substituents

Substituents may be divided into three categories based on the degree of conformational dependence of their steric effects:

1. No conformational dependence (NCD). Groups of this type include monatomic substituents such as hydrogen and the halogens: cylindrical substituents such as the ethynyl and cyano groups, and tetracoordinate symmetric top substituents such as the methyl, trifluoromethyl and silyl groups.

2. Minimal conformational dependence (MCD). Among these groups are:

a. Nonsymmetric substituents with the structure MH_n $(lp)_{3-n}$, such as the hydroxyl and amino groups (lp is a lone pair)

b. Nonsymmetric substituents with the structure $MZ_2^SZ^L$, where S stands for small and L for large.

3. Strong conformational dependence (SCD). These groups have the structures:

a. $MZ_2^LZ^S$ and $MZ^LZ^MZ^S$, where the superscript M indicates medium.

b. Planar π-bonded groups MZ^LZ^S, where M and either or both Z's are sp^2 hybridized, such as phenyl, acetyl, nitro ($X_{p\pi}$ groups). (Figure 2).

c. Quasi-planar π-bonded groups such as dimethylamino and cyclopropyl.

The steric parameter for NCD groups can be obtained directly from van der Waals radii or calculated from them. The values for MCD groups are often obtainable from van der Waals radii, although in some cases they must be derived as secondary values from regression equations obtained by correlating rate constants with known values of the steric parameter. Steric parameters for SCD groups of the nonsymmetric type are usually obtainable only from regression equations. In the case of planar π-bonded groups the maximum and minimum values of the steric parameter are available from the van der Waals radii. These groups are sufficiently common and important to require a more detailed discussion.

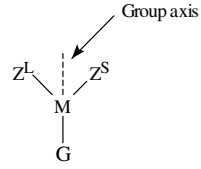


FIGURE 2. Planar π-bonded ($X_{p\pi}$) group. Superscripts L and S designate the larger and smaller, respectively of the Z groups attached to the central M atom. The bond order of the MZ^L and/or the MZ^S bonds is not less than 1.5. The MG bond is collinear with the group axis

2. Planar π-bonded groups

These $X_{p\pi}$ groups represent an especially difficult problem because their delocalized electrical effect depends on the steric effect when they are bonded to planar π-bonded skeletal groups, $G_{p\pi}$. An approach to the problem has been developed[45,46]. The σ_d and σ_e electrical effect parameters are a function of the dihedral angle formed by $X_{p\pi}$ and $G_{p\pi}$. The relationship generally used has the form:

$$P = P_0 \cos^2 \theta \tag{41}$$

where P is the property of interest, P_0 is its value when the dihedral angle is zero and θ is the dihedral angle. Thus:

$$\sigma_{dX,\theta} = \sigma_{dX,0} \cos^2 \theta \tag{42}$$

and:

$$\sigma_{eX,\theta} = \sigma_{eX,0} \cos^2 \theta \tag{43}$$

where $\sigma_{dX,0}$ and $\sigma_{eX,0}$ are the values of σ_d and σ_e when the substituent and skeletal group are coplanar ($\theta = 0$). The steric parameter does not depend on equation 41. The effective value of υ, which is derived from the geometry of the system, is given by the expression:

$$\upsilon = d' \cos\theta + r_{VZ^S} - 1.20 \tag{44}$$

where Z^S is the smaller of the two Z groups attached to the central atom, M of the $X_{p\pi}$ group and d' is the distance between the center of Z^S and the perpendicular to the line joining that center with the group axis. There is no simple *a priori* way to determine θ. It could conceivably be estimated by molecular mechanics calculations, but there is some reason to believe that θ is a function of the medium. Alternatively, the $X_{p\pi}$ group can be included in the data set by means of an iteration procedure. The method requires an initial correlation of the data set with all $X_{p\pi}$ and other SCD groups excluded. This constitutes the basis set. The correlation equation used for this purpose is the LDRS equation which takes the form:

$$Q_X = L\sigma_{IX} + D\sigma_{dX} + R\sigma_{eX} + S\upsilon + h \tag{45}$$

The correlation is then repeated for each $X_{p\pi}$ group using υ values increasing incrementally by some convenient amount from the minimum, which represents the half-thickness of the group, to the maximum, which occurs when $X_{p\pi}$ is nearly perpendicular to $G_{p\pi}$. The proper value of θ is that which:

1. Results in the best fit of the data to the correlation equation. The best fit is indicated by the minimal value of the S_{est} and S^0 statistics, and the maximal value of the F and $100R^2$ statistics. The statistics used in this work are described in the appendix.
2. Has the L, D, R, S and h values that are in best agreement with those of the basis set.

D. Multiparametric Models of Steric Effects

In some cases a simple monoparametric model of the steric effect is insufficient. Examples are, when the active site is itself large and nonsymmetric, or alternatively when the phenomenon studied is some form of bioactivity in which binding to a receptor is the key step. The failure of the monoparametric model is due to the fact that a single steric parameter cannot account for the variation of the steric effect at various points in the substituent. The use of a multiparametric model of steric effects that can represent the steric effect at different segments of the substituent is required. Five multiparametric models are available; that of Verloop and coworkers[48], the simple branching model, the expanded branching model, the segmental model and the composite model. The Verloop model suffers from the fact that its parameters measure maximum and minimum distances perpendicular to the group axis. These maxima and minima may occur at any point in the group skeleton (the longest chain in the group). The steric effect, however, may be very large at one segment of the chain and negligible at others. If a data set is large, as it must be if a multiparametric model is to be used, the likelihood that the maximum and minimum distances of all groups are located at the same segment and that it is this segment at which the steric effect is important is very small. The Verloop model will therefore not be discussed further.

1. The branching equations

The simple branching model[45,47] for the steric effect is given by the expression:

$$S\psi = \sum_{i=1}^{m} a_i n_i + a_\mathrm{b} n_\mathrm{b} \tag{46}$$

where $S\psi$ represents the steric effect parameterization, the a_i and a_b are coefficients, n_i is the number of branches attached to the i-th atom, and n_b is the number of bonds between the first and last atoms of the group skeleton. It follows that n_b is a measure of group length. Unfortunately, it is frequently highly collinear in group polarizability, which greatly limits its utility. For saturated cyclic substituents it is necessary to determine values of n_i from an appropriate regression equation. For planar π-bonded groups n_i is taken to be 1 for each atom in the group skeleton. For other groups n_i is obtained simply by counting branches. The model makes the assumption that all of the branches attached to a skeleton atom are equivalent. This is at best only a rough approximation. Distinguishing between branches results in an improved model called the expanded branching equation:

$$S\psi = \sum_{i=1}^{m} \sum_{j=1}^{3} a_{ij} n_{ij} + a_\mathrm{b} n_\mathrm{b} \tag{47}$$

which allows for the difference in steric effect that results from the order of branching[45,47]. This difference follows from the MSI principle. The first branch has the smallest steric effect because a conformation in which it is rotated out of the way of the active site is preferred. In this conformation the active site is in contact with two hydrogen atoms. The preferred conformation in the case of a second branch has the larger of the two branches directed out of the way. The smaller branch and a hydrogen atom are in contact with the active site. When there are three branches, the largest will be directed out of the way and the other two will be in contact with the active site.

The problem with the expanded branching method is that it requires a large number of parameters. Data sets large enough to permit its use are seldom seen.

2. The segmental model

As both branching methods have problems associated with them, the segmental method[47] is often the simplest and most effective of the multiparametric models. In this model each atom of the group skeleton together with the atoms attached to it constitutes a segment of the substituent. Applying the MSI principle, the segment is considered to have that conformation which presents its smallest face to the active site. The segment is assigned the υ value of the group which it most resembles. Values of the segmental steric parameters υ_i, where i designates the segment number, are given in Table 6. Numbering starts from the first atom of the group skeleton which is the atom that is attached to the rest of the system. The segmental model is given by the expression:

$$S\psi = \sum_{i=1}^{m} S_i \upsilon_i \tag{48}$$

TABLE 6. Values of segmental and simple steric parameters[a]

X	υ_1	υ_2	υ_3	υ
Alternating Dienes and Polyenes				
Conjugated				
CH=CH−CH=CH_2	*0.57*	*0.57*	*0.57*	*0.57*
H_2C=C−CH=CH_2	*0.57*	*0.57*	*0.57*	*0.57*
CH=CH−CH=CHPh	*0.57*	*0.57*	*0.57*	*0.57*
$(CH=CH)_2$CH=CH_2	*0.57*	*0.57*	*0.57*	*0.57*
H_2C=C−CH=CH−CH=CH_2	*0.57*	*0.57*	*0.57*	*0.57*
$(CH=CH)_3$Ph	*0.57*	*0.57*	*0.57*	*0.57*
$(CH=CH)_3$CH=CH_2	*0.57*	*0.57*	*0.57*	*0.57*
Cross-conjugated				
CH=C$(CH=CH_2)_2$	*0.57*	*0.57*	*0.57*	*0.57*
Adjacent				
CH=C=CH_2	*0.57*	0.58	*0.57*	*0.57*
Vinyl				
CH=CH_2	*0.57*	*0.57*	0	
CH=CHPh	*0.57*	*0.57*	*0.57*	
Ethynyl				
C≡CH	0.58	0.58	0	0.58
C≡C−C≡CH	0.58	0.58	0.58	0.58
C≡CPh	0.58	0.58	*0.57*	0.58
Aryl				
Ph	*0.57*	*0.57*	*0.57*	*0.57*
C_6H_4Ph-4	*0.57*	*0.57*	*0.57*	*0.57*
1-Naph	*0.57*	*0.57*	*0.57*	*0.57*
2-Naph	*0.57*	*0.57*	*0.57*	*0.57*
Other groups				
Me	0.52	0		0.52
Et	0.52	0.52	0	0.56
i-Pr	0.76	0.52	0	0.76
t-Bu	1.24	0.52	0	1.24
c-Pr				0.64
CF_3	0.90	0.27	0	0.90
CHO	*0.50*	0.32		*0.50*

(*continued overleaf*)

TABLE 6. (*continued*)

X	υ_1	υ_2	υ_2	υ_2
Ac	*0.50*	0.32	0	*0.50*
$CONH_2$	*0.50*	0.32	0	*0.50*
CO_2Me	*0.50*	0.32	0.52	*0.50*
CO_2Et	*0.50*	0.32	0.52	*0.50*
CN	0.40	0.40	0	0.40
NH_2	0.35	0		0.35
NHAc	0.35	*0.50*	0.32	0.50
NMe_2	0.35	0.52	0	0.52
NO_2	0.35	0.32		0.35
N_3	0.35	0.35	0.35	0.35
PMe_2	1.09	0.52	0	0.84
$POMe_2$	1.39	0.52	0	1.22
$PO(OMe)_2$	1.29	0.32	0.52	1.04
OH	0.32	0		0.32
OMe	0.32	0.52	0	0.36
OEt	0.32	0.52	0.52	0.48
OAc	0.32	*0.52*	0.32	0.50
OPh	0.52	*0.57*	*0.57*	0.57
SH	0.60	0		0.60
SMe	0.60	0.52	0	0.64
SAc	0.60	*0.50*	*0.32*	1.09
SEt	0.60	0.52	0.52	0.94
SPh	0.60	*0.57*	*0.57*	1.00
SOMe	0.74	0.52	0	0.76
SOPh	0.74	*0.57*	*0.57*	1.10
SO_2Me	1.03	0.52	0	1.13
SO_2Ph	1.03	*0.57*	*0.57*	
SeMe	0.70	0.52	0	0.74
F	0.27			0.27
Cl	0.55			0.55
Br	0.65			0.65
I	0.78			0.78
H	0			0

[a] Values are from References 24, 25, 27, 47 and 75. Those in italics are half thicknesses of planar π-bonded groups.

When only steric effects are present:

$$Q_X = S\psi_X \tag{49}$$

In the general case electrical effects are also present and the general form of the LDRS equation:

$$Q_X = L\sigma_{DX} + D\sigma_{dX} + R\sigma_{eX} + S\psi_X + h \tag{50}$$

is required.

3. The composite model

The composite model is a combination of the monoparametric υ model with the simple branching model. This method has proven useful in modelling amino acid, peptide and protein properties[49]. It is an improvement over the simple branching model and requires only one additional parameter.

V. INTERMOLECULAR FORCES

A. Introduction

Inter- and intramolecular forces (imf) are of vital importance in the quantitative description of structural effects on bioactivities and chemical properties. They can make a significant contribution to chemical reactivities and some physical properties as well. Types of intermolecular forces and their present parameterization are listed in Table 7[50].

B. Parameterization of Intermolecular Forces

1. Hydrogen bonding

Hydrogen bonding requires two parameters for its description, one to account for the hydrogen atom donating capacity of a substituent and another to account for its hydrogen atom accepting capacity. A simple approach is to use of n_H, the number of OH and/or NH bonds in the substituent, and n_n, the number of lone pairs on oxygen and/or nitrogen atoms, as parameters[49,52]. The use of these parameters is based on the argument that if one of the phases involved in the phenomenon studied includes a protonic solvent, particularly water, then all of the hydrogen bonds that the substituent is capable of forming will indeed form. For such a system, hydrogen bond parameters defined from equilibria in highly dilute solution in an 'inert' solvent are unlikely to represent a suitable model. This parameterization accounts only for the number of hydrogen-donor and hydrogen-acceptor sites in a group. It does not take into account differences in hydrogen bond energy. A more sophisticated parameterization than that described above would be to use the hydrogen bond energy for each type of hydrogen bond formed[50]. Thus for each substituent the parameter E_{hbX}, would be given by the equation:

$$E_{hbX} = \sum_{i=1}^{m} n_{hbi} E_{hbi} \tag{51}$$

where E_{hbX} is the hydrogen bonding parameter, E_{hbi} is the energy of the i-th type of hydrogen bond formed by the substituent X and n_{hbi} is the number of such hydrogen bonds. The validity of this parameterization is as yet untested. In any event, the site number parameterization suffers from the fact that though it accounts for the number of

TABLE 7. Intermolecular forces and the quantities upon which they depend[50]

Intermolecular force	Quantity
molecule–molecule	
Hydrogen bonding (hb)	E_{hb}, n_H, n_n
Dipole–dipole (dd)	dipole moment
Dipole–induced dipole (di)	dipole moment, polarizability
Induced dipole–induced dipole (ii)	polarizability
Charge transfer (ct)	ionization potential, electron affinity
ion–molecule	
ion–dipole (Id)	ionic charge, dipole moment
ion–induced dipole (Ii)	ionic charge, polarizability

Abbreviations are in parentheses. The dd interactions are also known as Keesom interactions; di interactions are also known as Debye interactions; ii interactions are also known as London or dispersion interactions. Collectively, dd, di and ii interactions are known as van der Waals interactions. Charge transfer interactions are also known as donor–acceptor interactions.

hydrogen bonds formed, it does not differentiate between their energies and can therefore be only an approximation. A recent definition of a scale of hydrogen-bond acceptor values from 1-octanol–water partition coefficients of substituted alkanes shows that the site number method strongly overestimates the hydrogen acceptor capability of the nitro group and seriously underestimates that of the methylsulfoxy group[51]. Much remains to be done in properly parameterizing hydrogen bonding.

2. van der Waals interactions

These interactions (dd, di, ii) are a function of dipole moment and polarizability. It has been shown that the dipole moment cannot be replaced entirely by the use of electrical effect substituent constants as parameters[52]. This is because the dipole moment has no sign. Either an overall electron donor group or an overall electron acceptor group may have the same value of μ. It has also been shown that the bond moment rather than the molecular dipole moment is the parameter of choice. The dipole moments of MeX and PhX were taken as measures of the bond moments of substituents bonded to sp^3- and sp^2-hybridized carbon atoms, respectively, of a skeletal group. Application to substituents bonded to sp-hybridized carbon atoms should require a set of dipole moments for substituted ethynes.

The polarizability parameter used in this work, α, is given by the expression:

$$\alpha \equiv \frac{MR_X - MR_H}{100} = \frac{MR_X}{100} - 0.0103 \tag{52}$$

where MR_X and MR_H are the group molar refractivities of X and H, respectively[49,52]. The factor 1/100 is introduced to scale the α parameter so that its coefficients in the regression equation are roughly comparable to those obtained for the other parameters used. There are many other polarizability parameters including parachor, group molar volumes of various kinds, van der Waals volumes and accessible surface areas, any of which will do as well because they are all highly collinear in each other[53]. Proposing other polarizability parameters has been a cottage industry in the past.

Values of α can be estimated by additivity from the values for fragments or from group molar refractivities calculated from the equation:

$$MR_X = 0.320n_c + 0.682n_b - 0.0825n_n + 0.991 \tag{53}$$

where n_c, n_b and n_n are the number of core, bonding and nonbonding electrons, respectively, in the group X[53].

3. Charge transfer interactions

These interactions can be roughly parameterized by the indicator variables n_A and n_D, where n_A takes the value 1 when the substituent is a charge transfer acceptor and 0 when it is not; n_D takes the value 1 when the substituent is a charge transfer donor and 0 when it is not. An alternative parameterization makes use of the first ionization potential of MeX (ip_{MeX}) as the electron donor parameter and the electron affinity of MeX as the electron acceptor parameter. Usually, the indicator variables n_A and n_D are sufficient. This parameterization accounts for charge transfer interactions directly involving the substituent. If the substituent is attached to a π-bonded skeletal group, then the skeletal group is capable of charge transfer interaction the extent of which is modified by the substituent. This is accounted for by the electrical effect parameters of the substituent.

4. The intermolecular force (IMF) equation

A general relationship for the quantitative description of intermolecular forces, called the intermolecular force (IMF) equation, is:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + M\mu_X + A\alpha_X + H_1 n_{HX} + H_2 n_{nX} + Ii_X + B_{DX} n_{DX} + B_{AX} n_{AX} + S\psi_X + B^0 \quad (54)$$

Some values of the IMF parameters for diene and polyene substituents are presented in Table 8.

TABLE 8. Values of intermolecular force parameters[a]

X	μ_{Ph}	μ_{Me}	α	n_H	n_n	i
Alternating Dienes and Polyenes						
Conjugated						
CH=CH−CH=CH_2	*0*	0585	0.190	0	0	0
H_2C=C−CH=CH_2	*0*	0.26	0.190	0	0	0
CH=CH−CH=CHPh	*0*	*0.6*	0.423	0	0	0
$(CH=CH)_2CH=CH_2$	*0*	*0.6*	0.270	0	0	0
H_2C=C−CH=CH−CH=CH_2	*0*	*0.3*	0.270	0	0	0
$(CH=CH)_3$Ph	*0*	*0.6*	0.513	0	0	0
$(CH=CH)_3CH=CH_2$	*0*	*0.6*	0.360	0	0	0
Cross-conjugated						
CH=C$(CH=CH_2)_2$	*0*	*0.6*	0.270	0	0	0
Adjacent						
CH=C=CH_2			0.138	0	0	0
Vinyl						
CH=CH_2	0.13	0.364	0.100	0	0	0
CH=CHPh	0	0.72	0.331	0	0	0
Ethynyl						
C≡CH	0.71	0.7809	0.085	0	0	0
C≡C−C≡CH			0.170	0	0	0
C≡CPh	0		0.322	0	0	0
Aryl						
Ph	0	0.37	0.243	0	1	0
C_6H_4Ph-4	*0*	*0.37*	0.476	0	1	0
1-Naph	*0*	0.223	0.404	0	1	0
2-Naph	*0*	0.44	0.404	0	1	0
Other groups						
Me	0.37	0	0.046	0	0	0
Et	0.37	0	0.093	0	0	0
i-Pr	0.37	0	0.140	0	0	0
t-Bu	0.52	0	0.186	0	0	0
c-Pr	0.48	0.139	0.125	0	0	0
CF_3	2.86	2.321	0.040	0	0	0
CHO	2.92	2.69	0.059	0	2	0
Ac	2.88	2.93	0.102	0	2	0
$CONH_2$	3.42	3.72	0.088	2	3	0
CO_2Me	1.92	1.706	0.118	0	4	0
CO_2Et	1.849	1.84	0.164	0	4	0
CN	4.14	3.9185	0.053	0	0	0

(*continued overleaf*)

TABLE 8. (*continued*)

X	μ_{Ph}	μ_{Me}	α	n_H	n_n	i
NH_2	1.49	1.296	0.044	2	1	1
NHAc	3.75	3.71	0.212	1	3	0
NMe_2	1.60	0.612	0.145	0	1	1
NO_2	4.26	3.56	0.063	0	4	0
N_3	1.56	2.17	0.092	0	1	0
PMe_2	1.31	1.192	0.202	0	0	0
$POMe_2$	4.39	4.29	0.189	0	2	0
$PO(OMe)_2$			0.208	0	6	0
OH	1.40	1.77	0.018	1	2	0/1
OMe	1.36	1.31	0.068	0	2	0
OEt	1.38	1.22	0.114	0	2	0
OAc	1.69	1.706	0.114	0	4	0
OPh	1.13	1.17	0.267	0	2	0
SH	1.21	1.52	0.082	0	0	0/1
SMe	1.29	*1.06*	0.128	0	0	0
SAc			0.174	0	2	0
SEt			0.174	0	0	0
SPh	1.37	1.50	0.333	0	1	0
SOMe	3.98	3.96	0.127	0	2	0
SOPh	4.02		0.320	0	2	0
SO_2Me	4.73		0.125	0	4	0
SO_2Ph	5.00	4.73	0.322	0	4	0
SeMe	1.31		0.160	0	0	0
F	1.66	1.8549	−0.001	0	0	0
Cl	1.70	1.895	0.050	0	0	0
Br	1.70	1.84	0.079	0	0	0
I	1.71	1.618	0.129	0	0	0
H	0	0	0	0	0	0

[a] Values are from References 24, 25, 27, 51 and 53. Those in italics are estimates. μ_{ph} and μ_{Me} parameterize the bond moments of the X-C(sp^2) and X-C(sp^3) bonds, respectively i values reported as 0/1 take the value 1 when bonded to sp^2-hybridized carbon and 0 when bonded to sp^3-hybridized carbon. Dipole moments for alternating dienyl and polyenyl groups are assumed to be approximately equal to those for the 1- and 2-(1,3-butadienyl) groups.

VI. APPLICATIONS

A. Introduction

Examples of the application of correlation analysis to diene and polyene data sets are considered below. Both data sets in which the diene or polyene is directly substituted and those in which a phenylene lies between the substituent and diene or polyene group have been considered. In that best of all possible worlds known only to Voltaire's Dr. Pangloss, all data sets have a sufficient number of substituents and cover a wide enough range of substituent electronic demand, steric effect and intermolecular forces to provide a clear, reliable description of structural effects on the property of interest. In the real world this is not often the case. We will therefore try to demonstrate how the maximum amount of information can be extracted from small data sets.

The choice of correlation equations. In choosing a correlation equation there are several factors that must be considered. They include the number of data points in the set to be studied, the experimental conditions, the type of data to be correlated and the possibility of steric effects.

a. *The number of data points*. The number of data points, n, and the number of independent variables, N_v, determine the number of degrees of freedom, N_{DF}. Thus:

$$N_{DF} = n - N_V - 1 \tag{55}$$

In order to obtain reliable models (minimize the probability of chance correlations) it is necessary to consider the ratio $R_{DF/V}$:

$$R_{DF/V} = \frac{N_{DF}}{N_V} \tag{56}$$

The minimum value of $R_{DF/V}$ required for a reliable model depends on the quality of the determination of the data to be correlated. The smaller the experimental error in the data, the smaller the value of $R_{DF/V}$ required for dependable results. Experience indicates that in the case of chemical reactivity data $R_{DF/V}$ should be not less than 3. For bioactivity studies $R_{DF/V}$ depends heavily on the type of data; for rate and equilibrium constants obtained from enzyme kinetics a value of not less than 3 is reasonable while for toxicity studies on mammals at least 7 is required.

b. *Steric effects*. If substituent and active site are proximal, then steric effects may occur. In that event it is necessary to include a steric effect parameterization in the correlation equation. The choice of parameterization depends on the number of data points in the set. If N_{DF} is sufficiently large, then the segmental method is a good choice of parameterization. If this is not the case, then it is best to use a monoparametric method.

c. *Intermolecular forces*. If intermolecular forces are likely to be significant, as is the case with bioactivity data and many types of chemical properties, then it is necessary to use the intermolecular force equation or some relationship derived from it. If N_{DF} is too small, it may be necessary to use composite parameters such as log P in order to get a reliable model.

d. *Small chemical reactivity data sets*. Chemical reactivity data sets which involve only electrical effects are best modelled by the LDR equation. Although data sets are often encountered which are too small to give reliable results with the LDR equation, it is still possible to extract from them useful information regarding structural effects. There are two ways to handle this problem. The best approach is to combine two or more small data sets into a single large data set. This can be done if all of the data sets to be combined have been studied under experimental conditions such that all but one are kept constant and the variation in that one can be parameterized. Consider, for example, the case in which the data are rate constants that have been determined at various temperatures. Addition to the correlation equation of the term $T\tau$, where

$$\tau \equiv \frac{100}{t} \tag{57}$$

and t is the absolute temperature, makes possible the combination of rate constants at different temperatures into a single data set. Thus, the LDR equation becomes the LDRT equation:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + T\tau_X + h \tag{58}$$

If the data sets were studied in aqueous organic solvents, they can be combined into a single large set by the addition of the term $F\phi$ where ϕ is the mole fraction of organic solvent in the medium. Thus, the LDR equation becomes the LDRF equation:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + F\phi_X + h \tag{59}$$

In general, if a number of data sets are available that have the same skeletal group and active site but vary in one of the experimental conditions, they can be combined into a

single larger data set by parameterizing the variable condition. Taking the LDR equation as the example once more gives the relationship:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + \Sigma P_i\zeta_{iX} + h \tag{60}$$

where $\Sigma P_i\zeta_{iX}$ is the parameterization of the variable condition. This approach can be extended to data sets involving chemical and physical properties and bioactivities.

e. *The use of composite variables*. When faced with small data sets, the alternative to combining them is to decrease the number of independent variables. This can be done by replacing two or more pure parameters with composite parameters of an appropriate composition. Consider, for example, a chemical reactivity data set of five members ($n = 5$). The problem is to determine the magnitude of the electrical effect (L, C or ρ), the composition of the electrical effect (P_D) and the electronic demand of the reactivity (η) without assuming prior knowledge. This can be done by the following procedure:

1.(a) If the substituent is attached to an sp^2- or sp-hybridized carbon atom of the skeletal group that is directly conjugated with the reaction site, then the data set is correlated with the CR equation using the σ_{c50} constants.

(b) The data set is correlated with the LD equation in the form:

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + h \tag{61}$$

If further correlations are necessary, the appropriate parameters can be chosen on the basis of the approximate η and P_D values obtained in the first two correlations.

2. If the substituent is attached to an sp^2-hybridized carbon atom that is not directly conjugated with the reaction site, then it is correlated with the Hammett equation using the σ_m constants.

3. If the substituent is bonded to an sp^3-hybridized carbon atom, it is correlated with the L equation:

$$Q_X = L\sigma_{lX} + h \tag{62}$$

The final regression equation obtained will give a reasonable model of the electrical effect on the chemical reactivity in the data set of interest.

B. Conjugated Alternating Dienes and Polyenes

1. Chemical reactivity (QSRR)

Two types of chemical reactivity of data sets can be distinguished: those in which the diene or polyene system acts simply as a skeletal group, and those in which it acts in whole or in part as a reaction site.

a. *Diene and polyene skeletal groups*. Molko and Grand[54] have reported pK_a values for *trans*,*trans*- and *cis*,*trans*-4′-substituted-5-phenyl-2,4-pentadienoic acids in 50% v/v aqueous ethanol at 25 °C. The pK_a values are: X, pK_a EE, pK_a ZE: H, 5.81, 6.17; Cl, 5.73, 6.06; OMe, 5.96, 6.27; Me, 5.90, 6.21; NMe_2, 6.10, 6.43. The data were correlated with the CR equation using the σ_{c50} substituent constants and with the LD equation using the σ_d constants. The best regression equations are for the *trans*,*trans* acids:

$$pK_{aX} = -0.518\ (\pm 0.0201)\sigma_{lX} - 0.563\ (\pm 0.0149)\sigma_{dX} + 5.81\ (\pm 0.00561) \tag{63}$$

$100R^2$, 99.87; A$100R^2$, 99.82; F, 755.68; S_{est}, 0.00730; S^0, 0.0575; n, 5; P_D, 52.0 (±1.83); η, 0.

For the *Z*,*E* acids:

$$pK_{aX} = -0.527\ (\pm 0.0419)\sigma_{c50X} + 6.15\ (\pm 0.0113) \tag{64}$$

$100R^2$, 98.14; F, 158.5; S_{est}, 0.0215; S^0, 0.176; n, 5; P_D, 50; η, 0.

Yanovskaya and coworkers[55] have reported rate constants for the alkaline hydrolysis of ethyl *trans,trans*-4′-substituted 5-phenyl-2,4-pentadienoates in 60% aqueous dioxan giving the values: X, log k; H, −2.60; Cl, −2.23; Br, −2.31; NO_2, −1.83; OMe, −2.61; NMe_2, −3.00. Correlation with the CR equation gave as the best regression equation:

$$\log k_X = 0.724\ (\pm 0.0453)\sigma_{c50X} + 1.12\ (\pm 0.253)\sigma_{eX} - 2.37\ (\pm 0.0246) \qquad (65)$$

$100R^2$, 99.34; A$100R^2$, 99.17; F, 224.7; S_{est}, 0.0412; S^0, 0.115; n, 6; P_D, 50; η, 1.55 (±0.0150).

The value of η is in accord with the attack of a nucleophile on the carbonyl carbon atom to form a negatively charged tetrahedral intermediate in the rate-determining step.

Doyle and coworkers[56] have reported polarographic half-wave potentials in aqueous ethanol for 1- and 2-substituted perfluoro-1,3-cyclohexadienes. The $E_{0.5}$ values are: X, $E_{0.5}$ (1-X), $E_{0.5}$ (2-X): H, −1.24, −1.22; CF_3, −0.87, —; OMe, —, −1.39; OEt, —, −1.40; Me, −1.42, −1.37; F, −1.19, −1.19. Correlation with the CR equation gave as the best regression equations for the 1-substituted compounds:

$$E_{0.5,X} = 0.772\ (\pm 0.0785)\sigma_{c50,X} - 1.26\ (\pm 0.0217) \qquad (66)$$

$100R^2$, 97.98; F, 96.87; S_{est}, 0.0399; S^0, 0.201; n, 4; P_D, 50; η, 0
and for the 2-substituted compounds:

$$E_{0.5,X} = 0.667\ (\pm 0.0832)\sigma_{c50,X} - 1.23\ (\pm 0.0150) \qquad (67)$$

$100R^2$, 95.54; F, 64.21; S_{est}, 0.0246; S^0, 0.273; n, 5; P_D, 50; η, 0.

There is no significant difference between the values of C for 1- and for 2-substitution; the values of P_D and η are the same.

b. *Diene and polyene reactions at the double bonds*. Tidwell and coworkers[57] have reported second-order rate constants for the acid-catalyzed hydration of 2-substituted 1,3-butadienes at 25 °C; their values are: X, k_2: *c*-Pr, 122,000; Me, 3.19; Cl, 0.201; H, 0.396; OEt, 60,000,000.

Correlation with the LD and CR equations gave as the best regression equation:

$$k_{2X} = -8.85\ (\pm 1.27)\sigma_{c60,X} - 50.3\ (\pm 9.33)\sigma_{eX} - 0.673\ (\pm 0.218) \qquad (68)$$

$100R^2$, 99.66; A$100R^2$, 99.55; F, 292.5; S_{est}, 0.299; S^0, 0.0923; n, 5; P_D, 60; η, 3.79 (±0.447).

The large values of P_D and η and the negative sign of C are in accord with a large electron deficiency in the transition state; the large value of C suggests a directly substituted active site.

The Diels-Alder reaction ($4\pi + 2\pi$ cycloaddition) is by far the best studied reaction of dienes from both theoretical and experimental viewpoints. Frontier molecular orbital theory predicts three types of Diels-Alder reaction. Structural effects on rate constants show the existence of two types of reaction:

1. Donor (electron-rich) diene and acceptor (electron-poor) ene (dienophile), designated D_dE_a.

2. Acceptor diene and donor ene, designated D_aE_d.

The great majority of the reactions studied are of the D_dE_a type. Thus, DeWitt and coworkers[58] have reported relative rate constants (k_X/k_H) for the reaction of 4′-substituted 1-phenyl-1,3-butadienes with maleic anhydride in dioxan at 25 °C, 35 °C, and 45 °C. Their data are: X, $k_r(25)$, $k_r(35)$, $k_r(45)$: H, 1, 1, 1; Me, 1.11, 1.29, 1.37; Cl, 0.580, 0.632; 0.636; OMe, 2.65, 2.33, 2.40; NO_2, 0.275, 0.300, 0.280.

Writing the LDRT equation for log (k_X/k_H) gives:

$$\log k_{rX} = \log k_X/k_H = \log k_X - \log k_H \tag{69}$$

$$\log k_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + T\tau + h \tag{70}$$

$$\log k_H = L\sigma_{lH} + D\sigma_{dH} + R\sigma_{eH} + T\tau + h \tag{71}$$

$$\log k_X - \log k_H = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + T\tau + h - L\sigma_{lH} - D\sigma_{dH} - R\sigma_{eH} - T\tau - h \tag{72}$$

As $\sigma_{lH} = \sigma_{dH} = \sigma_{eH} = 0$, equation 72 simplifies to:

$$\log k_{rX} = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} \tag{73}$$

which is a form of the LDR equation. Relative rate constants are independent of temperature. All of the data were therefore combined into a single data set and correlated with the LDR equation giving as the best regression equation:

$$k_{rX} = -0.856\ (\pm 0.0711)\sigma_{lX} - 0.866\ (\pm 0.0608)\sigma_{dX} - 3.07\ (\pm 0.626)\sigma_{eX} - 0.0579\ (\pm 0.0266) \tag{74}$$

$100R^2$, 97.55; A$100R^2$, 97.14; F, 145.9; S_{est}, 0.0573; S^0, 0.183; n, 15; P_D, 50.4 (±4.47); η, 3.55 (±0.679).

That this is an example of the D_dE_a type of reaction is shown by the negative signs of L and D.

Sauer, Sustmann and coworkers[59] have reported second-order rate constants for the reaction of *trans*-1-substituted 1,3-butadienes with tetracyanoethylene (TCNE) in dichloromethane at 20 °C; their values are: X, $\log k_2 + 6$: OMe, 7.935, vinyl, 5.456; Ph, 5.814; Me, 5.243; H, 3.228. The data were correlated with the CR equation; the best regression equation is:

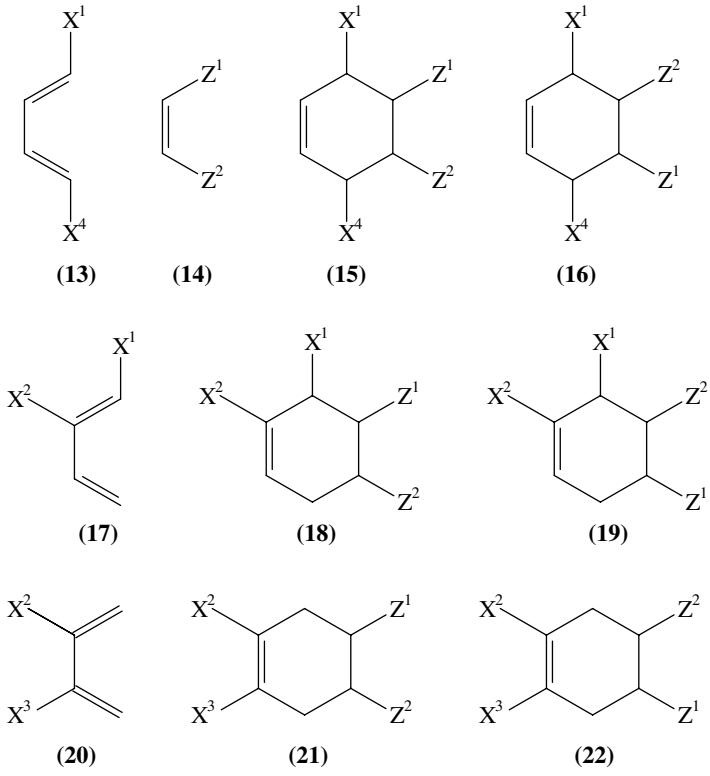
$$\log 10^6 k_2X = -6.70\ (\pm 0.0258)\sigma_{c60,X} - 18.1\ (\pm 0.107)\sigma_{eX} + 3.227\ (\pm 0.0101) \tag{75}$$

$100R^2$, 99.998; A$100R^2$, 99.997; F, 43239; S_{est}, 0.0114; S^0, 0.00760; n, 5; P_D, 60; η, 1.80 (±0.0811).

The excellent fit of the data in this case is undoubtedly fortuitous. The reaction is of the D_dE_a type. The large value of C is due to the substituent being directly attached to the reaction site.

If both diene and ene are nonsymmetric, it is possible to obtain two products from this type of cycloaddition. Consider the reaction of the diene **13** with the ene **14**. The possible product types are **15** and **16**. Reaction of the diene **17** with the ene **14** can give as product types **18** and **19** while that of the diene **20** with **14** as product types can give **21** and **22**. Both products are not always obtained. Thus, Kresze and coworkers[60] have determined rate constants for the reaction of 4′-substituted 1-phenyl-1,3-butadienes with 4-chloronitrosobenzene in benzene at temperatures from 15 °C to 35 °C. Their values are: X, k(15), k(20), k(25), k(30), k(35): NO_2, 0.94, —, 1.94, —, 3.98; Cl, 1.12, 1.60, 2.22, 3.17, 4.29; H, 1.47, 2.11, 3.08, 4.32, 5.73; Me, 1.52, 2.32, 3.20, 4.19, 5.68; OMe, 2.21, 3.19, 4.46, 6.27, 8.48. In this case the diene is **17** with X^1 equal to substituted phenyl and X^4 equal to H, while in the ene which is the N=O group Z^1 is 4-chlorophenyl and there is no Z^2. The only product formed was **16**. The data were correlated with the LDRT equation; the best regression equation was:

$$\log k_X = -0.365\ (\pm 0.0414)\sigma_{lX} - 0.311\ (\pm 0.0381)\sigma_{dX} - 2.02\ (\pm 0.371)\sigma_{eX} - 26.8\ (\pm 1.11) + 9.408\ (\pm 0.372) \tag{76}$$



(13) **(14)** **(15)** **(16)**

(17) **(18)** **(19)**

(20) **(21)** **(22)**

$100R^2$, 97.66; A$100R^2$, 97.29; F, 187.5; S_{est}, 0.0423; S^0, 0.173; n, 23; P_D, 46.0 (±6.81); η, 6.49 (±0.891).

Again, the reaction is of the D_dE_a type. The electronic demand is very large; its sign indicates the need to stabilize an electron-deficient carbon atom.

In a later paper Kresze and coworkers[61] reported partial rate factors for the reaction of methyl 4′-substituted 5-phenyl-2,4-dienoates with nitrosobenzene (the ene is the N=O group) in benzene at temperatures ranging from 20 °C to 40 °C to form product types **15** and **16** with X^1 equal to substituted phenyl, X^4 equal to carbomethoxy, Z^1 equal to phenyl and no Z^2. Their partial rate factors are: X, $k_{\mathbf{15}}(20)$, $k_{\mathbf{15}}(25)$, $k_{\mathbf{15}}(30)$, $k_{\mathbf{15}}(35)$, $k_{\mathbf{15}}(40)$, $k_{\mathbf{16}}(20)$, $k_{\mathbf{16}}(25)$, $k_{\mathbf{16}}(30)$, $k_{\mathbf{16}}(35)$, $k_{\mathbf{16}}(40)$: NMe_2, 0.84, 1.53, 2.03, 3.81, 4.85, 1.66, 3.18, 4.35, 8.51, 11.22; OMe, 0.48, 0.82, 1.44, 1.87, 3.05, 1.68, 2.90, 5.06, 6.60, 10.8; Me, 0.37, 0.63, 1.13, 1.57, 2.38, 1.59, 2.72, 4.84, 6.71, 10.2; H, 0.34, 0.58, 1.05, 1.47, 2.22, 1.42, 2.44, 4.44, 6.22, 9.41; Cl, 0.37, 0.55, 0.81, 1.48, 1.92, 1.18, 1.78, 2.62, 4.78, 6.20; CN, 0.62, 0.89, 1.23, 2.16, 3.21, 0.95, 1.48, 2.17, 4.07, 6.40.

The data were correlated with the LDRT equation. The best regression equation obtained for the $\log k_{\mathbf{15}}$ values is:

$$\log k_{\mathbf{15},X} = -0.363\ (\pm 0.0395)\sigma_{lX} - 0.222\ (\pm 0.0310)\sigma_{dX} - 37.2\ (\pm 1.13)\tau + 12.9\ (\pm 0.373) \quad (77)$$

$100R^2$, 97.94; A$100R^2$, 97.79; F, 412.7; S_{est}, 0.0473; S^0, 0.154; n, 30; P_D, 37.9 (± 6.2); η, 0

while that for the $\log k_{\mathbf{16}}$ values, obtained by excluding the points for the cyano group, is:

$$\log k_{\mathbf{16},X} = -0.196\ (\pm 0.0727)\sigma_{lX} - 0.250\ (\pm 0.0922)\sigma_{dX} - 1.06\ (\pm 0.228)\sigma_{eX} - 36.2\ (\pm 1.06)\tau + 11.9\ (\pm 0.360) \quad (78)$$

$100R^2$, 98.60; A$100R^2$, 98.40; F, 352.6; S_{est}, 0.0416; S^0, 0.132; n, 25; P_D, 56.1 (±25.4); η, 4.24 (± ?); r_{de}, 0.812.

Both reactions are of the D_dE_a type. Equations 76 and 78 are in accord with a transition state in which the C−O bond is almost completely formed while the C−N bond formation is much less advanced. This is indicated by the large positive values of η which are evidence of a large electron deficiency at the carbon atom of the diene to which the substituted phenyl group is attached. The lack of a significant dependence on σ_e in equation 77 is in accord with this transition state, as in this case the substituted phenyl group is bonded to the carbon atom which forms a bond with the oxygen atom of the nitroso group. The P_D and η values are in fairly good agreement with each other.

Craig and coworkers[62] have reported rate constants for the reaction of 2-substituted 1,3-butadienes with maleic anhydride in benzene at 25 °C; their values are: X, k: Cl, 0.019; H, 0.19; Me, 0.57; Et, 1.15; *i*-Pr, 2.2; *t*-Bu, 5.6; OMe, 1.9. As the Diels-Alder reaction proceeds through the s-*cis* conformation of the diene, and substituents in the 2- and 3-positions can affect the fraction of the diene in this conformation, steric effects must be considered. The data set was correlated therefore with the CRS equation:

$$Q_X = C\sigma_{cX} + R\sigma_{eX} + S\upsilon_X + h \quad (79)$$

The best regression obtained is:

$$\log k_X = -4.83\ (\pm 0.762)\sigma_{c50,X} + 0.696\ (\pm 0.288)\upsilon_X - 1.01\ (\pm 0.190) \quad (80)$$

$100R^2$, 93.21; A$100R^2$, 91.86; F, 22.47; S_{est}, 0.263; S^0, 0.345; n, 7; P_D, 50; η, 0.

The sign of C shows that the reaction is of the D_dE_a type. As expected, steric effects are significant.

2. Chemical properties (QSCR)

As an example of chemical properties we consider the boiling points of 1-substituted 1,3-butadienes, 1-substituted 4-methyl-1,3-butadienes and 2-substituted 1,3-butadienes[63]. The data points available are for the 1-substituted, the 1-substituted 4-methyl- and the 2-substituted compounds: X, bp(1-X), bp(1-X-4-Me), bp(2-X): H, 268.75, 315.15, 268.75; Me, 315.15, 355.15, 307.15; Et, 346.15, 381.15, —; OMe, 364.65, —, 348.15; OEt, 383.15, —, 368.15; Cl, 341.15, —, 332.55; F, —, —, 285.15; I, —, —, 385.15; CHO, —, 446.65, —; CO_2Me, —, 453.15, —; CO_2Et, —, 468.15, —; CN, 409.65, —, —; CH=CHMe, —, 420.65, —; Vinyl, 371.65, —, —; C_2H, 356.55, —, —. The model for chemical properties is the IMF equation. As the only interactions expected to be significant in these data sets are dipole–dipole, dipole-induced–dipole and induced-dipole–induced-dipole forces, we have dropped from the IMF equation all terms other than μ_{PhX}, which represents the X−C(sp^2) bond moment, and the polarizability parameter α. The resulting correlation equation is:

$$bp_X = M\mu_X + A\alpha_X + h \quad (81)$$

Correlation of the boiling points of 2-substituted 1,3-butadienes with equation 81 gave, as the best regression equation:

$$bp_X = 14.0\ (\pm 5.92)\mu_X + 703\ (\pm 81.4)\alpha_X + 269.27\ (\pm 7.20) \quad (82)$$

$100R^2$, 96.90; A$100R^2$, 96.27; F, 62.42; S_{est}, 8.97; S^0, 0.233; n, 7.

The boiling points of the 1-substituted and 1-substituted 4-methyl-1,3-butadienes were combined into a single data set by introducing the variable n_{Me}, which takes the value 1 when there is a 4-methyl group and 0 when there is not. Thus the correlation equation is:

$$bp_X = M\mu_X + A\alpha_X + B_{Me}n_{Me} + h \tag{83}$$

The best regression obtained is:

$$bp_X = 24.9\ (\pm 6.04)\mu_X + 715\ (\pm 67.3)\alpha_X + 40.7\ (\pm 5.50)n_{Me} + 274.38\ (\pm 5.88) \tag{84}$$

$100R^2$, 96.97; A$100R^2$, 96.50; F, 128.1; S_{est}, 10.6; S^0, 0.201; n, 16.

The IMF equation in the form of equations 81 and 83 represents boiling points effectively.

3. Physical properties (QSPR)

Ionization potentials (IP) of 1- and 2-substituted 1,3-butadienes and of 1,4-disubstituted 1,3-butadienes[64] were correlated with the LDRA, CR and CRA equations, respectively. The choice of correlation equation was made on the basis of the number of data points in the set. The values of the ionization potential were: 1-X, IP: H, 9.03; Me, 8.61; Et, 8.51; *i*-Pr, 8.47; *t*-Bu, 8.43; vinyl, 8.29; Ph, 8.16; OMe, 8.62; CH=CH−CH=CH_2, 7.79; CH=CHMe, 7.96; C_2H, 9.20. 2-X, IP; OMe, 8.62; Ph, 8.15; Cl, 8.828; Me, 8.845; H, 9.03. 1-X, 4-X, IP; OMe, OMe, 7.67; Ph, Ph, 8.09; vinyl, vinyl, 7.79; Me, Me, 8.18; Me, Et, 8.18; Me, vinyl, 7.96.

The best regression equations are for the 1-substituted 1,3-butadienes:

$$IP_{1X} = 2.94\ (\pm 0.259)\sigma_{1X} + 2.21\ (\pm 0.162)\sigma_{dX} + 7.58\ (\pm 0.598)\sigma_{ex} + 9.08\ (\pm 0.0474) \tag{85}$$

$100R^2$, 97.89; A$100R^2$, 97.36; F, 108.1; S_{est}, 0.0730; S^0, 0.182; n, 11; P_D, 42.9 (±4.06); η, 3.43 (±0.0976).

For the 2-substituted 1,3-butadienes:

$$IP_{2X} = -0.383\ (\pm 0.0910)\sigma_{c50,X} + 7.20\ (\pm 0.314)\sigma_{eX} + 9.00\ (\pm 0.0189) \tag{86}$$

$100R^2$, 91.49; A$100R^2$, 89.78; F, 21.49; S_{est}, 0.139; S^0, 0.386; n, 5; P_D, 50; η, −18.8 (± ?).

For the 1,4-disubstituted 1,3-butadienes:

$$IP_{1X,4X} = 1.51\ (\pm 0.242)\sigma_{c50X} + 6.13\ (\pm 0.867)\sigma_{eX} + 1.21\ (\pm 0.512)\alpha_X + 8.94\ (\pm 0.0995) \tag{87}$$

$100R^2$, 96.73; A$100R^2$, 95.09; F, 29.55; S_{est}, 0.113; S^0, 0.276; n, 7; P_D, 50; η, 4.06 (± ?).

Landesberg and Katz[65] have reported three sets of carbonyl stretching frequencies of 4′-substituted 1-phenyl-1,3-butadiene iron tricarbonyl complexes. Their values are: X, $\nu_{CO}(1)$, $\nu_{CO}(2)$, $\nu_{CO}(3)$: NH_2, 2047, 1980, 1973; OMe, 2048, 1983, 1975; H, 2049, 1986, 1979; NHAc, 2050, 1986, 1979, Br, 2052, 1989, 1981; Ac, 2053, 1990, 1982; CN, 2055, 1993, 1984. The data were correlated with the CR and LD equations. The best regression equations obtained are for $\nu_{CO}(1)$:

$$\nu_{CO,X}(1) = 9.27\ (\pm 1.27)\sigma_{lX} + 5.60\ (\pm 0.685)\sigma_{dX} + 2049\ (\pm 0.484) \tag{88}$$

$100R^2$, 97.41; A$100R^2$, 96.90; F, 75.34; S_{est}, 0.570; S^0, 0.213; n, 7; P_D, 37.7 (±5.88); η, 0.

For ν_{CO} (2):

$$\nu_{CO}(2) = 11.6\ (\pm 3.05)\sigma_{lX} + 9.51\ (\pm 1.64)\sigma_{dX} + 1985\ (\pm 1.16) \quad (89)$$

$100R^2$, 93.71; A$100R^2$, 92.45; F, 29.79; S_{est}, 1.37; S^0, 0.332; n, 7; P_D, 45.0 ($\pm$10.7); η, 0.

For ν_{CO} (3):

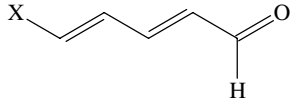
$$\nu_{CO}(3) = 8.43\ (\pm 3.12)\sigma_{lX} + 8.86\ (\pm 1.67)\sigma_{dX} + 1978\ (\pm 1.19) \quad (90)$$

$100R^2$, 91.49; A$100R^2$, 89.78; F, 21.49; S_{est}, 1.39; S^0, 0.386; n, 7; P_D, 51.2 ($\pm$14.3); η, 0.

Yanovskaya and coworkers[55] have reported ν_{CO} for 5-substituted 2,4-pentadienals, **23**, and 7-substituted 2,4,6-heptatrienals, **24**, in chloroform. Their values are: X, ν_{CO} **(23)**, ν_{CO} **(24)**: Me, 1680, 1678; CO_2Et, 1689, 1682; CN, 1692, 1687; NMe_2, 1584, 1640; Ph, 1675, 1675; CH=CHMe, 1678, —; CH=CHCN, 1687, 1678; CH=CHPh, 1675, —. The data were correlated with the CRA equation. The best regression equations were for **23**:

$$\nu_{CO,X} = 14.1\ (\pm 6.74)\sigma_{c75,X} + 415\ (\pm 98.1)\sigma_{eX} + 129\ (\pm 46.8)\alpha_X + 1696\ (\pm 10.8) \quad (91)$$

$100R^2$, 94.72; A$100R^2$, 92.61; F, 23.93; S_{est}, 10.7; S^0, 0.325; n, 8; P_D, 75, η, 9.81.



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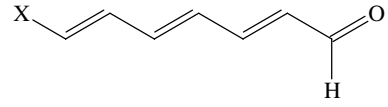


(24)

For **24**:

$$\nu_{CO,X} = 8.86\ (\pm 2.91)\sigma_{c75,X} + 114\ (\pm 39.2)\sigma_{eX} + 1680\ (\pm 4.24) \quad (92)$$

$100R^2$, 96.35; A$100R^2$, 95.44; F, 39.65; S_{est}, 4.15; S^0, 0.270; n, 6; P_D, 75; η, 4.28 ($\pm$0.450).

Kajimoto and Fueno[66] have reported ^{13}C chemical shifts for 2-substituted 1,3-butadienes at each carbon atom of the dienyl moiety. Their values are: X, δ^1, δ^2, δ^3, δ^4: OEt, −24.5, 15.3, −7.5, 19.3; Me, −4.4, −0.5, −9.0, 14.5; Ph, −1.3, −5.0^u, −9.3^u, 10.6; H, 11.7, −8.8, −8.8, 11.7; CO_2Me, 6.1, −16.3, −6.9, 3.1; CN, 29.5, −21.3, −4.6, 1.1. Values labelled u are uncertain. The data sets were correlated with the CR and LD equations. The best regression equations are for the δ^1 values:

$$\Delta\delta^1_X = 61.5\ (\pm 16.8)\sigma_{dX} + 8.28\ (\pm 4.20) \quad (93)$$

$100R^2$, 77.10; F, 13.47; S_{est}, 9.62; S^0, 0.586; n, 6; P_D, 100; η, 0.

For δ^2 values:

$$\Delta\delta^2_X = -11.3\ (\pm 4.25)\sigma_{lX} - 46.7\ (\pm 3.68)\sigma_{dX} - 7.82\ (\pm 1.33) \quad (94)$$

$100R^2$, 98.48; A$100R^2$, 98.10; F, 97.13; S_{est}, 2.05; S^0, 0.174; n, 6; P_D, 80.5 ($\pm$10.0); η, 0.

For δ^3:

$$\Delta\delta^3_X = 7.60\ (\pm 1.22)\sigma_{lX} - 9.31\ (\pm 0.359) \quad (95)$$

$100R^2$, 90.68; F, 38.94; S_{est}, 0.606; S^0, 0.374; n, 6; P_D, 0; η, 0.

For δ^4:

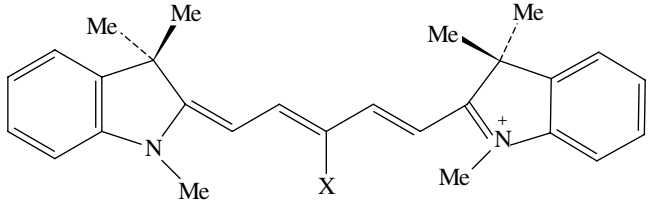
$$\Delta\delta_X^4 = -13.4\ (\pm 1.95)\sigma_{lX} - 21.5\ (\pm 1.69)\sigma_{dX} + 11.0\ (\pm 0.611) \tag{96}$$

$100R^2$, 98.87; A$100R^2$, 98.59; F, 131.0; S_{est}, 0.945; S^0, 0.150; n, 6; P_D, 61.7 ($\pm$6.67); η, 0.

^{13}C chemical shifts in $CDCl_3$ of the 12-substituted indocyanines **25** were reported by Grahn and Reichardt[67]. Their values for C^2 are: X, $\Delta\delta^2$: H, 0; OMe, -0.23; *c*-Pr, 0.26; *c*-Bu, -0.16; *c*-Hx, -0.02; Me, 0.08; Ph, 0.27; F, 0.08; Cl, 1.51; Br, 1.71; I, 1.78; N_2Ph, 4.18; CHO, 4.75; CN, 3.25; NO_2, 6.14. Correlation of the set with the LDRA equation gave equation 97 as the best regression equation:

$$\Delta\delta_X^2 = 4.52\ (\pm 0.941)\sigma_{lX} + 5.85\ (\pm 0.923)\sigma_{dX} + 1.16\ (\pm 0.372) \tag{97}$$

$100R^2$, 85.77; A$100R^2$, 84.68; F, 36.17; S_{est}, 0.842; S^0, 0.422; n, 15; P_D, 56.4 ($\pm$11.4); η, 0.



(25)

C. Adjacent Dienes and Polyenes

1. Chemical reactivity (QSRR)

Battioni and coworkers[68] have reported rate constants for the reaction of 4′-substituted 6,6-diphenyl-3,4,5-hexatrien-2-one with diazomethane in dimethylformamide at 29.7 °C. The values are: X, 10^5 k (s^{-1}): OMe, 3.76; Me, 5.05; H, 7.36; Br, 11.6; NO_2, 66.6. The triene is a 50:50 mixture of *cis* and *trans* isomers. The data set was correlated with the CR equation. The best regression equation is:

$$k_X = 1.13\ (\pm 0.0172)\sigma_{c50,X} + 0.860\ (\pm 0.00708) \tag{98}$$

$100r^2$, 99.93; F, 4285; S_{est}, 0.0150; S^0, 0.0341; n, 5; P_D, 50; η, 0.

2. Chemical properties (QSCR)

Boiling points of 1-substituted 1,2-propadienes[63,69] were correlated with the MA equation. The values used are: X, bp: H, 238.65; Me, 283.95; Et, 318.05; Pr, 349.15; CH_2Br, 383.15; CH_2Cl, 361.15; CH_2I, 403.15; CH_2OMe, 361.15; $SiMe_3$, 364.15. The best regression equation is:

$$bp_X = 14.0\ (\pm 5.92)\mu_X + 703\ (\pm 81.4)\alpha_X + 269.27\ (\pm 7.20) \tag{99}$$

$100R^2$, 96.90; A$100R^2$, 96.27; F, 62.42; S_{est}, 8.97; S^0, 0.233; n, 9.

3. Physical properties (QSPR)

The application of correlation analysis to physical properties of alkenes and cumulenes was reviewed by Runge[70]. Vertical ionization potentials of 1-substituted 1,2-propadienes were correlated with the LDRA equation. The values are: X, IP(v): H, 10.07; Me, 9.33, Et, 9.22; CO_2Me, 10.02; CN, 10.35; OMe, 8.75; Cl, 9.57; Br, 9.46; Ph, 8.29; CH=C=CH_2, 8.53; CH_2C_2H, 9.65; CMe=CH_2, 8.54; E−CH=CHMe, 8.32. The best regression equation is:

$$\mathrm{IP}(\nu)_X = 1.13\ (\pm 0.306)\sigma_{lX} + 2.06\ (\pm 0.330)\sigma_{dX} + 8.18\ (\pm 1.86)\sigma_{eX} - 2.89\ (\pm 1.39)\alpha_X + 10.02\ (\pm 0.147) \quad (100)$$

$100R^2$, 93.40; A$100R^2$, 91.42; F, 31.85; S_{est}, 0.208; S^0, 0.320; n, 14; P_D, 64.6 (±13.8); η, 3.97 (±0.638); $r_{e\alpha}$, 0.705.

Runge and Firl[71] have reported ^{13}C chemical shifts for 1-substituted allenes. Their values are: X, δ^1, δ^2, δ^3: H, 73.5, 212.6, 73.5; Me, 84.2, 209.4, 73.4; Et, 91.6, 208.8, 74.7; *i*-Pr, 99.8, 207.8, 76.2; *t*-Bu, 102.1, 207.0, 77.0; Ph, 94.0, 209.6, 78.8; OMe, 123.0, 201.1, 91.4; OEt, 121.7, 202.3, 89.6; SMe, 88.5, 206.9, 80.9; Cl, 88.7, 202.4, 84.8; Br, 71.9, 206.9, 83.1; F, 128.5, 199.1, 92.6; CO_2H, 88.1, 217.7, 80.0; CN, 67.4, 218.6, 80.7. Correlation with the LDRA equation gave as the best regression equation for C^1 on exclusion of the values for Br and CO_2H:

$$\delta^1_X = -82.4\ (\pm 9.78)\sigma_{dX} + 219\ (\pm 63.2)\sigma_{eX} + 135\ (\pm 41.2)\alpha_X + 75.1\ (\pm 4.13) \quad (101)$$

$100R^2$, 90.55; A$100R^2$, 88.44; F, 25.54; S_{est}, 6.94; S^0, 0.377; n, 12; P_D, 100; η, −2.66; $r_{e\alpha}$, 0.712.

For C^2:

$$\delta^2_X = 2.89\ (\pm 1.28)\sigma_{lX} + 23.7\ (\pm 1.13)\sigma_{dX} - 46.0\ (\pm 7.88)\sigma_{eX} - 20.8\ (\pm 5.53)\alpha_X + 212\ (\pm 0.596) \quad (102)$$

$100R^2$, 98.20; A$100R^2$, 97.66; F, 122.9; S_{est}, 0.888; S^0, 0.167; n, 14; P_D, 89.1 (±7.10); η, −1.94 (±0.319); $r_{e\alpha}$, 0.697.

Although a statistically significant correlation was obtained for δ^3, it must be fortuitous as L and D had opposite signs.

D. Cross-conjugated Alternating Dienes and Polyenes

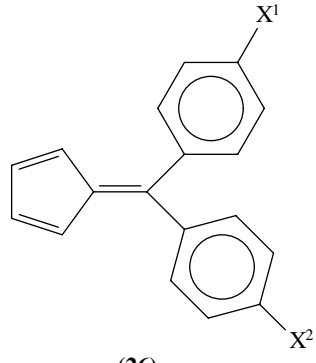
1. Chemical reactivity (QSRR)

Norton and Knoblich[72] have reported $E_{0.5}$ versus the standard calomel electrode in 75% aqueous dioxan at 25 °C for 6,6-di(4′-substituted-phenyl)-pentafulvenes **26**. Their values are: X^1, X^2, $-E_{0.5}$: Cl, Cl, 1.47; Cl, H, 1.51; Br, H, 1.51; F, F, 1.53; F, H, 1.54; H, H, 1.55; Me, H, 1.58; Me, Me, 1.60; OMe, H, 1.60; OMe, OMe, 1.63. The data set was correlated with the LDR equation in the form:

$$Q_X = L\Sigma\sigma_{lX} + D\Sigma\sigma_{dX} + R\Sigma\sigma_{eX} + h \quad (103)$$

on the assumption that the substituent effects are approximately additive. The best regression equation obtained is:

$$E_{0.5,X} = 0.199\ (\pm 0.00691)\Sigma\sigma_{lX} + 0.193\ (\pm 0.00712)\Sigma\sigma_{dX} - 0.0945\ (\pm 0.0316)\Sigma\sigma_{eX} - 1.55\ (\pm 0.00229) \quad (104)$$



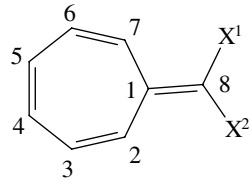
(26)

$100R^2$, 99.57; A$100R^2$, 99.45; F, 466.6; S_{est}, 0.00399; S^0, 0.0843; n, 10; P_D, 49.2 (±2.20); η, −0.490 (±0.163); r_{ld}, 0.731.

2. Physical properties (QSPR)

Bönzli and Neuenschwander[73] have reported ^{13}C and ^{1}H chemical shifts for 8,8-disubstituted heptafulvenes, **27**. In some cases the substituents are segments of a ring. Values of the ^{13}C shifts are: X^1, X^2, δ^2, δ^3, δ^4, δ^5, δ^7, δ^8: CN, H, 133.02, 132.99, 133.54, 132.37, 156.72, 87.22; Ph, H, 128.78, 131.80, 131.49, 127.05, 139.1, 125.83; OMe, H, 126.38, 129.82, 131.71, 124.55, 122.51, 144.75; $COCF_3$, CN, 142.84, 141.58, 140.46, 142.65, 165.20, 88.19; CN, CN, 138.65, 137.42, 137.42, 138.65, 163.70, 70.10; $CO(CH_2)_4CO$, 142.93, 140.60, 140.60, 142.93, 158.94, 114.52; Cl, Cl, 130.15, 132.35, 132.35, 130.15, 135.94, 113.15; H, H, 126.90, 130.80, 130.80, 126.90, 146.60, 111.90; Ph, Ph, 127.48, 132.00, 132.00, 127.48, 136.61, 135.62, $(CH_2)_4$, 125.36, 131.00, 131.00, 125.36, 129.37, 139.73; NMe_2, $OSiMe_3$, 122.82, 130.61, 131.61, 123.63, 107.48; 148.76; NMe_2, NMe_2, 120.80, 130.80, 130.80, 120.80, 105.70, 157.50. The data sets were correlated with the LDRA equation in the form:

$$Q_X = L\Sigma\sigma_{lX} + D\Sigma\sigma_{dX} + R\Sigma\sigma_{eX} + \Sigma\alpha_X + h \tag{105}$$



(27)

The best regression equations are for C^2:

$$\delta^2_X = 8.07\ (\pm1.35)\Sigma\sigma_{lX} + 10.8\ (\pm1.17)\Sigma\sigma_{dX} - 10.8\ (\pm2.32)\Sigma\sigma_{eX} + 128\ (\pm0.983) \tag{106}$$

$100R^2$, 96.26; A$100R^2$, 95.43; F, 68.62; S_{est}, 1.68; S^0, 0.237; n, 12; P_D, 57.2 (±8.22); η, −1.00 (±0.419); r_{de}, 0.597.

For C^3:

$$\delta_X^3 = 4.66\ (\pm 1.11)\Sigma\sigma_{lX} + 6.07\ (\pm 0.961)\Sigma\sigma_{dX} - 14.1\ (\pm 3.85)\Sigma\sigma_{eX} + 131\ (\pm 0.811) \quad (107)$$

$100R^2$, 91.53; A$100R^2$, 89.65; F, 28.81; S_{est}, 1.38; S^0, 0.356; n, 12; P_D, 57.0 (±11.8); η, −2.32 (±0.517); r_{de}, 0.597.

For C^4:

$$\delta_X^4 = 4.46\ (\pm 1.13)\Sigma\sigma_{lX} + 5.25\ (\pm 0.974)\Sigma\sigma_{dX} - 11.9\ (\pm 3.90)\Sigma\sigma_{eX} + 131\ (\pm 0.821) \quad (108)$$

$100R^2$, 89.48; A$100R^2$, 87.14; F, 22.68; S_{est}, 1.40; S^0, 0.397; n, 12; P_D, 54.1 (±13.0); η, −2.27 (±0.611); r_{de}, 0.597.

For C^5:

$$\delta_X^5 = 8.55\ (\pm 1.39)\Sigma\sigma_{lX} + 10.7\ (\pm 1.20)\Sigma\sigma_{dX} - 12.7\ (\pm 4.80)\Sigma\sigma_{eX} + 127\ (\pm 1.01) \quad (109)$$

$100R^2$, 96.08; A$100R^2$, 95.21; F, 65.45; S_{est}, 1.40; S^0, 0.242; n, 12; P_D, 55.6 (±8.16); η, −1.18 (±0.427); r_{de}, 0.597.

For C^7:

$$\delta_X^7 = 11.2\ (\pm 3.25)\Sigma\sigma_{lX} + 31.4\ (\pm 2.26)\Sigma\sigma_{dX} + 141\ (\pm 2.16) \quad (110)$$

$100R^2$, 96.71; A$100R^2$, 96.38; F, 132.4; S_{est}, 4.07; S^0, 0.209; n, 12; P_D, 73.8 (±8.68); η, 0; r_{de}, 0.597.

For C^8:

$$\delta_X^8 = -30.9\ (\pm 8.96)\Sigma\sigma_{lX} - 26.1\ (\pm 6.47)\Sigma\sigma_{dX} + 47.5\ (\pm 24.1)\Sigma\sigma_{eX} + 119\ (\pm 7.58) \quad (111)$$

$100R^2$, 87.79; A$100R^2$, 85.08; F, 19.17; S_{est}, 11.2; S^0, 0.428; n, 12; P_D, 45.8 (±14.4); η, 0; r_{de}, 0.597.

C^1 and C^6 chemical shifts were not well modelled by equation 105. The 1 and 6, 2 and 5, and 3 and 4 positions of heptafulvene are equivalent to each other when groups in position 8 are the same. Results for these positions are comparable, as expected in view of the fact that for seven of the twelve compounds in the data set $X^1 = X^2$. The cyclic 8,8 substituents $CO(CH_2)_4CO$ and $(CH_2)_4$ were assumed equivalent to two Ac and two Et groups, respectively, in the parameterization of the substituents.

The values of the ^1H chemical shifts are: X^1, X^2, δ^1, δ^2, δ^3: CN, H, 6.73, 6.36, 6.29; Ph, H, 6.40, 5.77, 5.85; OMe, H, 5.74, 5.13, 5.23; $COCF_3$, CN, 9.43, 7.41, 7.88; CN, CN, 7.37, 7.28, 7.16; $CO(CH_2)_4CO$, 9.62, 7.67, 7.55; Cl, Cl, 6.30, 6.20, 6.15; H, H, 5.97, 5.48, 5.65; Ph, Ph, 6.14, 5.62, 5.88; $(CH_2)_4$, 5.82, 5.51, 5.70; NMe_2, $OSiMe_3$, 5.44, 5.11, 5.31; NMe_2, NMe_2, 4.84, 4.37, 4.71. Correlation with equation 105 gave for H^1:

$$\delta_X^{1H} = 1.15\ (\pm 0.521)\Sigma\sigma_{lX} + 2.38\ (\pm 0.450)\Sigma\sigma_{dX} - 3.56\ (\pm 1.80)\Sigma\sigma_{eX} + 6.16\ (\pm 0.379) \quad (112)$$

$100R^2$, 86.19; A$100R^2$, 83.12; F, 16.64; S_{est}, 0.647; S^0, 0.455; n, 12; P_D, 67.4 (±18.3); η, −1.50 (±0.703); r_{de}, 0.597.

For H^2:

$$\delta_X^{2H} = 1.35\ (\pm 0.188)\Sigma\sigma_{lX} + 1.41\ (\pm 0.136)\Sigma\sigma_{dX} + 1.03\ (\pm 0.505)\Sigma\alpha_X + 5.52\ (\pm 0.159) \quad (113)$$

$100R^2$, 96.64; A$100R^2$, 95.90; F, 76.81; S_{est}, 0.235; S^0, 0.224; n, 12; P_D, 51.0 (±6.32); η, 0; r_{de}, 0.597.

For H^3:

$$\delta_X^{3H} = 1.14\ (\pm 0.171)\Sigma\sigma_{lX} + 1.27\ (\pm 0.124)\Sigma\sigma_{dX} + 1.24\ (\pm 0.460)\Sigma\alpha_X + 5.62\ (\pm 0.145) \quad (114)$$

$100R^2$, 96.36; A$100R^2$, 95.55; F, 70.65; S_{est}, 0.214; S^0, 0.234; n, 12; P_D, 52.8 (±6.89); η, 0; r_{de}, 0.597.

VII. CONCLUSION

Methods have been presented, with examples, for obtaining quantitative structure–property relationships for alternating conjugated and cross-conjugated dienes and polyenes, and for adjacent dienes and polyenes. The examples include chemical reactivities, chemical properties and physical properties. A method of estimating electrical effect substituent constants for dienyl and polyenyl substituents has been described. The nature of these substituents has been discussed, but unfortunately the discussion is very largely based on estimated values. A full understanding of structural effects on dienyl and polyenyl systems awaits much further experimental study. It would be particularly useful to have more chemical reactivity studies on their substituent effects, and it would be especially helpful if chemical reactivity studies on the transmission of electrical effects in adjacent multiply doubly bonded systems were available. Only further experimental work will show how valid our estimates and predictions are.

VIII. APPENDIX (GLOSSARY)

This appendix is an updated and slightly modified version of one we have published elsewhere[50].

General

X A variable substituent.
Y An active site. The atom or group of atoms at which a measurable phenomenon occurs.
G A skeletal group to which X and Y may be attached.

Parameter An independent variable.
Pure parameter A parameter which represents a single effect.
Composite parameter A parameter which represents two or more effects.
Modified composite parameter A composite parameter whose composition has been altered by some mathematical operation.
Monoparametric equation A relationship in which the effect of structure on a property is represented by a single generally composite parameter. Examples are the Hammett and Taft equations.
Diparametric equation A relationship in which the effect of structure on a property is represented by two parameters, one of which is generally composite. Examples discussed in this work include the LD, CR and MYT equations. Other examples are the Taft, Ehrenson and Brownlee DSP (dual substituent parameter), Yukawa–Tsuno YT and the Swain, Unger, Rosenquist and Swain SURS equations. The DSP equation is a special case of the LDR equation with the intercept set equal to zero. It is inconvenient to use and has no advantages. The SURS equation uses composite parameters which are of poorer quality than

those used with the LDR and DSP equations. The MYT equation has all the advantages of the YT equation and gives results which are easier to interpret.

Multiparametric equation An equation which uses three or more parameters any of which may be either pure or composite.

Electrical effect parameterization

σ_1 The localized (field) electrical effect parameter. It is identical to σ_I. Though other localized electrical effect parameters such as σ_I^q and σ_F have been proposed, there is no advantage to their use. The σ^* parameter has sometimes been used as a localized electrical effect parameter; such use is generally incorrect. The available evidence is strongly in favour of an electric field model for transmission of the effect.

σ_d The intrinsic delocalized (resonance) electrical effect parameter. It represents the delocalized electrical effect in a system with zero electronic demand.

σ_e The electronic demand sensitivity parameter. It adjusts the delocalized effect of a group to meet the electronic demand of the system.

σ_D A composite delocalized electrical effect parameter which is a function of σ_d and σ_e. Examples of σ_D constants are the $\sigma_R{}^+$ and $\sigma_R{}^-$ constants. The $\sigma_{R,k}$ constants, where k designates the value of the electronic demand η, are also examples of σ_D constants.

σ_R A composite delocalized electrical effect parameter of the σ_D type with η equal to 0.380. It is derived from 4-substituted benzoic acid pK_a values.

$\sigma_R{}^\circ$ A composite delocalized electrical effect parameter of the σ_D type with η equal to -0.376. It is derived from 4-substituted phenylacetic acid pK_a values.

$\sigma_R{}^+$ A composite delocalized electrical effect parameter of the σ_D type with η equal to 2.04. It is derived from rate constants for the solvolysis of 4-substituted cumyl chlorides.

$\sigma_R{}^\oplus$ A composite delocalized electrical effect parameter of the σ_D type with η equal to 3.31. It is derived from ionization potentials of the lowest-energy π orbital in substituted benzenes.

$\sigma_R{}^\ominus$ A composite delocalized electrical effect parameter of the σ_D type with η equal to -2.98. It is derived from pK_a values of substituted nitriles.

$\sigma_R{}^-$ A composite delocalized electrical effect parameter of the σ_D type with η equal to -1.40. It is derived from pK_a values of substituted anilinium ions.

$\sigma_{k'/k}$ A composite parameter which is a function of σ_1, σ_d and σ_e. Its composition is determined by the values of k and k'. The Hammett σ_m and σ_p constants are of this type.

$\sigma_{Ck'}$ A composite constant that is a function of σ_1 and σ_d; its composition is determined by the value of k'.

$\sigma^\blacklozenge$ An electrical effect modified composite parameter.

σ Any electrical effect parameter.

η The electronic demand of a system or of a composite electrical effect parameter that is a function of both σ_d and σ_e. It is represented in subscripts as k. It is a descriptor of the nature of the electrical effect. It is given by R/D, where R and D are the coefficients of σ_e and σ_d, respectively.

P_D The percent delocalized effect. It too is a descriptor of the nature of the electrical effect. It is represented in subscripts as k'.

LDR equation A triparametric model of the electrical effect.

P_{EA} The percent of the $\sigma_{k'/k}$ values in a substituent matrix which exhibit an electron acceptor electrical effect.

P_{ED} The percent of the $\sigma_{k'/k}$ values in a substituent matrix which exhibit an electron donor electrical effect.

P_0 The percent of the $\sigma_{k'/k}$ values in a substituent matrix which do not exhibit a significant electrical effect.

Steric effect parameterization

r_v The van der Waals radius. A useful measure of group size. The internuclear distance of two nonbonded atoms in contact is equal to the sum of their van der Waals radii.

υ A composite steric parameter based on van der Waals radii. For groups whose steric effect is at most minimally dependent on conformation, it represents the steric effect due to the first atom of the longest chain in the group and the branches attached to that atom. The only alternative monoparametric method for describing steric effects is that of Taft which uses the E_s parameter. This was originally developed only for alkyl and substituted alkyl groups and for hydrogen. Kutter and Hansch[74] have estimated E_s values for other groups from the υ values using a method which, in many cases, disregards the MSI principle. It is best to avoid their use.

Simple branching equation (SB) A topological method for describing steric effects which takes into account the order of branching by using as parameters n_i, the number of atoms other than H that are bonded to the i-th atoms of the substituent.

n_i The number of branches on the i-th atoms of a substituent. These are the steric parameters used in the SB equation.

Expanded branching equation (XB) A topological method for describing steric effects which takes into account the order of branching by using as parameters n_{ij}, the number of j-th branching atoms bonded to the i-th atoms of the substituent.

n_{ij} The number of j-th branches on the i-th atoms of a substituent. These are the steric parameters used in the XB model of steric effects.

n_b The number of bonds in the longest chain of a substituent. It is a steric parameter which serves as a measure of the length of a group along the group axis.

Segmental equation A steric effect model that separately parameterizes each segment of a substituent. It requires fewer parameters than the XB equation and is generally more effective than the SB equation.

υ_i A steric parameter based on van der Waals radii that is a measure of the steric effect of the i-th segment of a substituent. The i-th segment consists of the i-th atom of the longest chain in the substituent and the groups attached to it. The MSI principle is assumed to apply and the segment is assigned the conformation that gives it the smallest possible steric effect.

MSI principle The principle of minimal steric interaction which states that the preferred conformation of a group is that which results in the smallest possible steric effect.

Intermolecular force parameterization

α A polarizability parameter defined as the difference between the group molar refractivities for the group X and for H divided by 100. Many other polarizability

parameters, such as the van der Waals volume, the group molar volume and the parachor, can be used in its place. All of these polarizability parameters are very highly linear in each other.

n_H A hydrogen-bonding parameter which represents the lone-pair acceptor (proton donor) capability of a group. It is defined as the number of OH and/or NH bonds in the group.

n_n A hydrogen-bonding parameter which represents the lone-pair donor (proton acceptor) capability of the group. It is defined as the number of lone pairs on O and/or N atoms in the group.

i A parameter which represents ion–dipole and ion–induced dipole interactions. It is defined as one for ionic groups and 0 for nonionic groups.

n_D A charge transfer donor parameter which takes the values 1 when the substituent can act as a charge transfer donor and 0 when it cannot.

n_A A charge transfer acceptor parameter which takes the values 1 when the substituent can act as a charge transfer acceptor and 0 when it cannot.

IMF equation A multiparametric equation which models phenomena that are a function of the difference in intermolecular forces between an initial and a final state.

Statistics

Correlation equation An equation with which a data set is correlated by simple (one parameter) or multiple (two or more parameters) linear regression analysis.

Regression equation The equation obtained by the correlation of a data set with a correlation equation.

n The number of data points in a data set.

Degrees of freedom (DF) Defined as the number of data points (n) minus the number of parameters (N_p), plus 1 [$DF = n - (N_p + 1)$].

F statistic A statistic which is used as a measure of the goodness of fit of a data set to a correlation equation. The larger the value of F, the better the fit. Confidence levels can be assigned by comparing the F value calculated with the values in an F table for the N_p and DF values of the data set.

$100R^2$ A statistic which represents the percent of the variance of the data accounted for by the regression equation. It is a measure of the goodness of fit.

S_{est} The standard error of the estimate. It is a measure of the error to be expected in predicting a value of the dependent variable from the appropriate parameter values.

S^0 Defined as the ratio of S_{est} to the root-mean-square of the data. It is a measure of the goodness of fit. The smaller the value of S^0, the better the fit.

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