# 3

BONDING WEAKER
THAN COVALENT

In the first two chapters we discussed the structure of molecules each of which is an aggregate of atoms in a distinct three-dimensional arrangement held together by bonds with energies on the order of 50 to 100 kcal/mol (200 to 400 kJ/mol). There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, called van der Waals forces, are caused by electrostatic attractions such as those between dipole and dipole, induced dipole and induced dipole, etc, and are responsible for liquefaction of gases at sufficiently low temperatures. The bonding discussed in this chapter has energies of the order of 2 to 10 kcal/mol (9 to 40 kJ/mol), intermediate between the two extremes, and produces clusters of molecules. We will also discuss compounds in which portions of molecules are held together without any attractive forces at all.

HYDROGEN BONDING

A *hydrogen bond* is a bond between a functional group A—H and an atom or group of atoms B in the same or a different molecule.[1] With exceptions to be noted later, hydrogen bonds are formed only when A is oxygen, nitrogen, or fluorine and when B is oxygen, nitrogen, or fluorine. The oxygen may be singly or doubly bonded and the nitrogen singly, doubly, or triply bonded. The bonds are usually represented by dotted lines, as shown in the following examples:
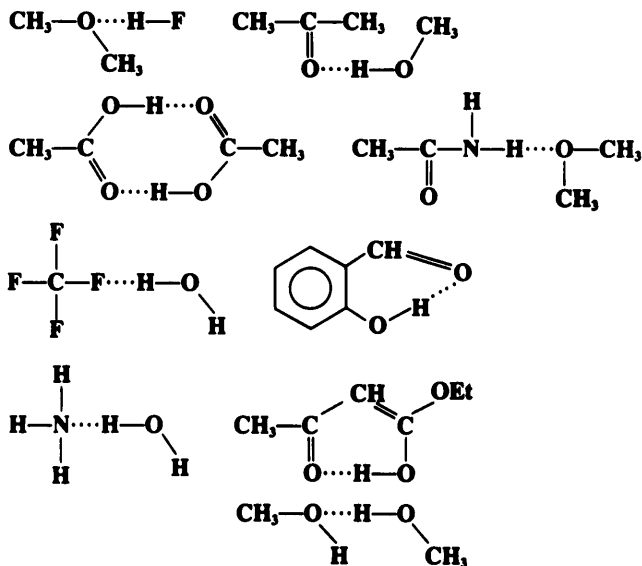
[1]For a treatise, see Schuster; Zundel; Sandorfy *The Hydrogen Bond*; 3 vols., North Holland Publishing Co.: Amsterdam, 1976. For a monograph, see Joesten; Schaad *Hydrogen Bonding*; Marcel Dekker: New York, 1974. For

Hydrogen bonds can exist in the solid and liquid phases and in solution. Even in the gas phase, compounds that form particularly strong hydrogen bonds may still be associated.[2] Acetic acid, for example, exists in the gas phase as a dimer, as shown above, except at very low pressures.[3] In solution and in the liquid phase, hydrogen bonds rapidly form and break. The mean lifetime of the $NH_3\cdots H_2O$ bond is 2×10^{-12} sec.[4] Except for a few very strong hydrogen bonds,[5] such as the $FH\cdots F^-$ bond (which has an energy of about 50 kcal/mol or 210 kJ/mol), the strongest hydrogen bonds are the $FH\cdots F$ bond and the bonds connecting one carboxylic acid with another. The energies of these bonds are in the range of 6 to 8 kcal/mol or 25 to 30 kJ/mol (for carboxylic acids, this refers to the energy of each bond). Other $OH\cdots O$ and $NH\cdots N$ bonds have energies of 3 to 6 kcal/mol (12 to 25 kJ/mol). To a first approximation, the strength of hydrogen bonds increases with increasing acidity of A—H and basicity of B, but the parallel is far from exact.[6] A quantitative measure of the strengths of hydrogen bonds has been established, involving the use of an α scale to represent hydrogen-bond donor acidities and a β scale for hydrogen-bond acceptor basicities.[7] The use of the β scale, along with another parameter, ξ, allows hydrogen bond basicities to be related to proton transfer basicities (pK values).[8]

When two compounds whose molecules form hydrogen bonds with each other are both dissolved in water, the hydrogen bond between the two molecules is usually greatly weakened or completely removed,[9] because the molecules generally form hydrogen bonds with the water molecules rather than with each other, especially since the water molecules are present in such great numbers.

Many studies have been made of the geometry of hydrogen bonds,[10] and the evidence shows that in most (though not all) cases the hydrogen is on or near the straight line formed by A and B.[11] This is true both in the solid state (where x-ray crystallography and neutron diffraction have been used to determine structures),[12] and in solution.[13] It is significant that the vast majority of intramolecular hydrogen bonding occurs where *six-membered rings* (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable, while five-membered rings, where linearity is usually not

reviews, see Meot-Ner *Mol. Struct. Energ.* **1987**, *4*, 71-103; Deakyne *Mol. Struct. Energ.* **1987**, *4*, 105-141; Joesten *J. Chem. Educ.* **1982**, *59*, 362-366; Gur'yanova; Gol'dshtein; Perepelkova *Russ. Chem. Rev.* **1976**, *45*, 792-806; Pimentel; McClellan *Annu. Rev. Phys. Chem.* **1971**, *22*, 347-385; Kollman; Allen *Chem. Rev.* **1972**, *72*, 283-303; Huggins *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 147-151 [*Angew. Chem. 83*, 163-168]; Rochester, in Patai *The Chemistry of the Hydroxyl Group*, pt. 1; Wiley: New York, 1971, 327-392, pp. 328-369. See also Hamilton; Ibers *Hydrogen Bonding in Solids*; W.A. Benjamin: New York, 1968.

[2]For a review of energies of hydrogen bonds in the gas phase, see Curtiss; Blander *Chem. Rev.* **1988**, *88*, 827-841.

[3]For a review of hydrogen bonding in carboxylic acids and acid derivatives, see Hadži; Detoni, in Patai *The Chemistry of Acid Derivatives*, pt. 1; Wiley: New York, 1979, pp. 213-266.

[4]Emerson; Grunwald; Kaplan; Kromhout *J. Am. Chem. Soc.* **1960**, *82*, 6307.

[5]For a review of very strong hydrogen bonding, see Emsley *Chem. Soc. Rev.* **1980**, *9*, 91-124.

[6]For reviews of the relationship between hydrogen bond strength and acid–base properties, see Pogorelyi; Vishnyakova *Russ. Chem. Rev.* **1984**, *53*, 1154-1167; Epshtein *Russ. Chem. Rev.* **1979**, *48*, 854-867.

[7]For reviews, see Abraham; Doherty; Kamlet; Taft *Chem. Br.* **1986**, 551-554; Kamlet; Abboud; Taft *Prog. Phys. Org. Chem.* **1981**, *13*, 485-630. For a comprehensive table and α and β values, see Kamlet; Abboud; Abraham; Taft *J. Org. Chem.* **1983**, *48*, 2877. For a criticism of the β scale, see Laurence; Nicolet; Helbert *J. Chem. Soc., Perkin Trans. 2* **1986**, 1081. See also Nicolet; Laurence; Luçon *J. Chem. Soc., Perkin Trans. 2* **1987**, 483; Abboud; Roussel; Gentric; Sraidi; Lauransan; Guihéneuf; Kamlet; Taft *J. Org. Chem.* **1988**, *53*, 1545; Abraham; Grellier; Prior; Morris; Taylor *J. Chem. Soc., Perkin Trans. 2* **1990**, 521.

[8]Kamlet; Gal; Maria; Taft *J. Chem. Soc., Perkin Trans. 2* **1985**, 1583.

[9]Stahl; Jencks *J. Am. Chem. Soc.* **1986**, *108*, 4196.

[10]For reviews, see Etter *Acc. Chem. Res.* **1990**, *23*, 120-126; Taylor; Kennard *Acc. Chem. Res.* **1984**, *17*, 320-326.

[11]See Stewart *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985, pp. 148-153.

[12]A statisical analysis of x-ray crystallographic data has shown that most hydrogen bonds in crystals are nonlinear by about 10 to 15°: Kroon; Kanters; van Duijneveldt-van de Rijdt; van Duijneveldt; Vliegenthart *J. Mol. Struct.* **1975**, *24*, 109. See also Ceccarelli; Jeffrey; Taylor *J. Mol. Struct.* **1981**, *70*, 255; Taylor; Kennard; Versichel *J. Am. Chem. Soc.* **1983**, *105*, 5761; **1984**, *106*, 244.

[13]For reviews of a different aspect of hydrogen bond geometry: the angle between $A—H\cdots B$ and the rest of the molecule, see Legon; Millen *Chem. Soc. Rev.* **1987**, *16*, 467-498, *Acc. Chem. Res.* **1987**, *20*, 39-46.

favored (though it is known), are much rarer. Except for the special case of FH····F⁻ bonds (see p. 78), the hydrogen is not equidistant between A and B. For example, in ice the O—H distance is 0.97 Å, while the H····O distance is 1.79 Å.[14]

In certain cases x-ray crystallography has shown that a single H—A can form simultaneous hydrogen bonds with two B atoms (*bifurcated* or *three-center hydrogen bonds*). An example is an adduct (**1**) formed from pentane-2,4-dione (in its enol form) and diethylamine, in

1   **2**   **3**
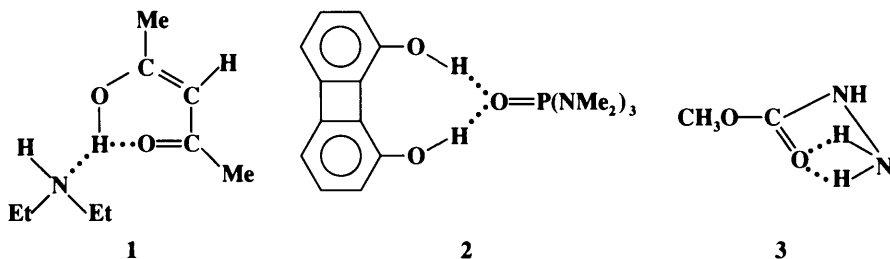
which the O—H hydrogen simultaneously bonds[15] to an O and an N (the N—H hydrogen forms a hydrogen bond with the O of another pentane-2,4-dione molecule).[16] On the other hand, in the adduct (**2**) formed from 1,8-biphenylenediol and HMPA, the B atom (in this case oxygen) forms simultaneous hydrogen bonds with two A—H hydrogens.[17] Another such case is found in methyl hydrazine carboxylate **3**.[18]

Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but the most important way is by the effect of the hydrogen bond on ir[19] and other spectra. The ir frequencies of groups such as O—H or C=O are shifted when the group is hydrogen bonded. Hydrogen bonding always moves the peak toward lower frequencies, for both the A—H and the B groups, though the shift is greater for the former. For example, a free OH group of an alcohol or phenol absorbs at about 3590 to 3650 cm⁻¹, while a hydrogen-bonded OH group is found about 50 to 100 cm⁻¹ lower.[20] In many cases, in dilute solution, there is partial hydrogen bonding, that is, some OH groups are free and some are hydrogen bonded. In such cases two peaks appear. Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified by an increase in concentration while intramolecular peaks are unaffected. Other types of spectra that have been used for the detection of hydrogen bonding include Raman, electronic,[21] and nmr.[22] Since hydrogen bonding involves a rapid movement of protons from one atom to another, nmr records an average value. Hydrogen bonding can be detected because it usually produces a chemical shift to a lower field. Hydrogen bonding changes with temper-

---

[14]Pimentel; McClellan *The Hydrogen Bond*; W.H. Freeman: San Francisco, 1960, p. 260.

[15]Emsley; Freeman; Parker; Dawes; Hurthouse *J. Chem. Soc., Perkin Trans. 1* **1986,** 471.

[16]For some other three-center hydrogen bonds, see Taylor; Kennard; Versichel *J. Am. Chem. Soc.* **1984,** *106,* 244; Jeffrey; Mitra *J. Am. Chem. Soc.* **1984,** *106,* 5546; Staab; Elbl; Krieger *Tetrahedron Lett.* **1986,** *27,* 5719.

[17]Hine; Ahn; Gallucci; Linden *J. Am. Chem. Soc.* **1984,** *106,* 7980; Hine; Hahn; Miles *J. Org. Chem.* **1986,** *51,* 577.

[18]Caminati; Fantoni; Schäfer; Siam; Van Alsenoy *J. Am. Chem. Soc.* **1986,** *108,* 4364.

[19]For reviews of the use of ir spectra to detect hydrogen bonding, see Symons *Chem. Soc. Rev.* **1983,** *12,* 1-34; Egorochkin; Skobeleva *Russ. Chem. Rev.* **1979,** *48,* 1198-1211; Tichý *Adv. Org. Chem.* **1965,** *5,* 115-298; Ratajczak; Orville-Thomas *J. Mol. Struct.* **1968,** *1,* 449. For a review of studies by ir of the shapes of intramolecular hydrogen-bonded compounds, see Aaron *Top. Stereochem.* **1979,** *11,* 1-52. For a review of the use of rotational spectra to study hydrogen bonding, see Legon *Chem. Soc. Rev.* **1990,** *19,* 197-237.

[20]Tichý, Ref. 19, contains a lengthy table of free and intramolecularly hydrogen-bonding peaks.

[21]For a discussion of the effect of hydrogen bonding on electronic spectra, see Lees; Burawoy *Tetrahedron* **1963,** *19,* 419.

[22]For a review of the use of nmr to detect hydrogen bonding, see Davis; Deb *Adv. Magn. Reson.* **1970,** *4,* 201-270.

ature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with infrared spectra, intramolecular hydrogen bonding can be distinguished from intermolecular by its constancy when the concentration is varied.

Hydrogen bonds are important because of the effects they have on the properties of compounds, among them:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.

2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected. It is interesting to speculate what the effect on the human race would be if ethanol had the same solubility in water as ethane or chloroethane.

3. Hydrogen bonding causes lack of ideality in gas and solution laws.

4. As previously mentioned, hydrogen bonding changes spectral absorption positions.

5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (see p. 71). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.[23] Hydrogen bonding is also important in maintaining the three-dimensional structures of protein and nucleic acid molecules.

Besides oxygen, nitrogen, and fluorine, there is evidence that weaker hydrogen bonding exists in other systems.[24] Although many searches have been made for hydrogen bonding where A is carbon,[25] only three types of C—H bonds have been found that are acidic enough to form weak hydrogen bonds. These are found in terminal alkynes, $RC\equiv CH$,[26] chloroform and some other halogenated alkanes, and HCN. Weak hydrogen bonds are formed by compounds containing S—H bonds.[27] There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds,[28] but Br and I form very weak bonds if at all.[29] However, the *ions* Cl^-, Br^-, and I^- form hydrogen bonds that are much stronger than those of the covalently bonded atoms.[30] As we have already seen, the $FH\cdots F^-$ bond is especially strong. In this case the hydrogen is equidistant from the fluorines.[31] Similarly, a sulfur atom[27] can be the B component in weak hydrogen bonds,[32] but the SH^- ion forms much stronger bonds.[33] Hydrogen bonding has been directly observed (by nmr and ir) between a negatively charged carbon (see Carbanions, Chapter 5) and an

[23]For reviews of the effect of hydrogen bonding on reactivity, see Hibbert; Emsley *Adv. Phys. Org. Chem.* **1990,** *26,* 255-379; Sadekov; Minkin; Lutskii *Russ. Chem. Rev.* **1970,** *39,* 179-195.

[24]For a review, see Pogorelyi *Russ. Chem. Rev.* **1977,** *46,* 316-336.

[25]For a monograph on this subject, see Green *Hydrogen Bonding by C—H Groups;* Wiley: New York, 1974. See also Taylor; Kennard *J. Am. Chem. Soc.* **1982,** *104,* 5063; Harlow; Li; Sammes *J. Chem. Soc., Perkin Trans. 1* **1984,** 547; Nakai; Inoue; Yamamoto; Ōki *Bull. Chem. Soc. Jpn.* **1989,** *62,* 2923; Seiler; Dunitz *Helv. Chim. Acta* **1989,** *72,* 1125.

[26]For a review, see Hopkinson, in Patai *The Chemistry of the Carbon-Carbon Triple Bond,* pt. 1, Wiley: New York, 1978, pp. 75-136. See also DeLaat; Ault *J. Am. Chem. Soc.* **1987,** *109,* 4232.

[27]For reviews of hydrogen bonding in sulfur-containing compounds, see Zuika; Bankovskii *Russ. Chem. Rev.* **1973,** *42,* 22-36; Crampton, in Patai *The Chemistry of the Thiol Group,* pt. 1; Wiley: New York, 1974, pp. 379-396; Ref. 24.

[28]For a review of hydrogen bonding to halogens, see Smith, in Patai *The Chemistry of the Carbon–Halogen Bond,* pt. 1; Wiley: New York, 1973, pp. 265-300. See also Bastiansen; Fernholt; Hedberg; Seip *J. Am. Chem. Soc.* **1985,** *107,* 7836.

[29]West; Powell; Whatley; Lee; Schleyer *J. Am. Chem. Soc.* **1962,** *84,* 3221; Fujimoto; Takeoka; Kozima *Bull. Chem. Soc. Jpn.* **1970,** *43,* 991; Azrak; Wilson *J. Chem. Phys.* **1970,** *52,* 5299.

[30]Allerhand; Schleyer *J. Am. Chem. Soc.* **1963,** *85,* 1233; McDaniel; Vallee *Inorg. Chem.* **1963,** *2,* 996; Fujiwara; Martin *J. Am. Chem. Soc.* **1974,** *96,* 7625; French; Ikuta; Kebarle *Can. J. Chem.* **1982,** *60,* 1907.

[31]A few exceptions have been found, where the presence of an unsymmetrical cation causes the hydrogen to be closer to one fluorine than to the other: Williams; Schneemeyer *J. Am. Chem. Soc.* **1973,** *95,* 5780.

[32]Vogel; Drago *J. Am. Chem. Soc.* **1970,** *92,* 5347; Mukherjee; Palit; De *J. Phys. Chem.* **1970,** *74,* 1389; Schaefer; McKinnon; Sebastian; Peeling; Penner; Veregin *Can. J. Chem.* **1987,** *65,* 908; Marstokk; Møllendal; Uggerrud *Acta Chem. Scand.* **1989,** *43,* 26.

[33]McDaniel; Evans *Inorg. Chem.* **1966,** *5,* 2180; Sabin *J. Chem. Phys.* **1971,** *54,* 4675.

OH group in the same molecule.[34] Another type of molecule in which carbon is the B component are isocyanides, R—$\overset{\oplus}{N}\equiv\overset{\ominus}{C}$, which form rather strong hydrogen bonds.[35] There is evidence that double and triple bonds, aromatic rings,[36] and even cyclopropane rings[37] may be the B component of hydrogen bonds, but these bonds are very weak. An interesting case is that of the *in*-bicyclo[4.4.4]-1-tetradecyl cation **4** (see out–in isomerism, p. 133). Nmr

4   **5**
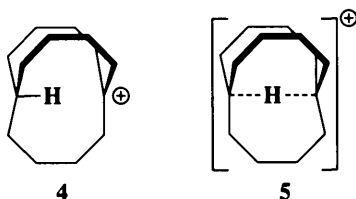
and ir spectra show that the actual structure of this ion is **5**, in which both the A and the B component of the hydrogen bond is a carbon.[38]

Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.[39]

ADDITION COMPOUNDS

When the reaction of two compounds results in a product that contains all the mass of the two compounds, the product is called an *addition compound*. There are several kinds. In the rest of this chapter we will discuss addition compounds in which the molecules of the starting materials remain more or less intact and weak bonds hold two or more molecules together. We can divide them into four broad classes: electron donor-acceptor complexes, complexes formed by crown ethers and similar compounds, inclusion compounds, and catenanes.

Electron Donor–Acceptor (EDA) Complexes[40]

In *EDA complexes*,[41] there is always a donor molecule and an acceptor. The donor may donate an unshared pair (an *n* donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). One test for the presence of an EDA complex is the electronic spectrum. These complexes generally exhibit a spectrum (called a *charge-transfer*

[34]Ahlberg; Davidsson; Johnsson; McEwen; Rönnqvist *Bull. Soc. Chim. Fr.* **1988**, 177.

[35]Ferstandig *J. Am. Chem. Soc.* **1962**, *84*, 3553; Allerhand; Schleyer *J. Am. Chem. Soc.* **1963**, *85*, 866.

[36]For example, see Bakke; Chadwick *Acta Chem. Scand., Ser. B* **1988**, *42*, 223; Atwood; Hamada; Robinson; Orr; Vincent *Nature* **1991**, *349*, 683.

[37]Joris; Schleyer; Gleiter *J. Am. Chem. Soc.* **1968**, *90*, 327; Yoshida; Ishibe; Kusumoto *J. Am. Chem. Soc.* **1969**, *91*, 2279.

[38]McMurry; Lectka; Hodge *J. Am. Chem. Soc.* **1989**, *111*, 8867. See also Sorensen; Whitworth *J. Am. Chem. Soc.* **1990**, *112*, 8135.

[39]Dahlgren; Long *J. Am. Chem. Soc.* **1960**, *82*, 1303; Creswell; Allred *J. Am. Chem. Soc.* **1962**, *84*, 3966; Singh; Rao *Can. J. Chem.* **1966**, *44*, 2611; Cummings; Wood *J. Mol. Struct.* **1974**, *23*, 103.

[40]For monographs, see Foster *Organic Charge-Transfer Complexes*; Academic Press: New York, 1969; Mulliken; Person, *Molecular Complexes*; Wiley: New York, 1969; Rose, *Molecular Complexes*; Pergamon: Elmsford, NY, 1967. For reviews, see Poleshchuk; Maksyutin, *Russ. Chem. Rev.* **1976**, *45*, 1077-1090; Banthorpe *Chem. Rev.* **1970**, *70*, 295-322; Kosower *Prog. Phys. Org. Chem.* **1965**, *3*, 81-163; Foster *Chem. Br.* **1976**, *12*, 18-23.

[41]These have often been called *charge-transfer complexes*, but this term implies that the bonding involves charge transfer, which is not always the case, so that the more neutral name EDA complex is preferable. See Ref. 59.

spectrum) that is not the same as the sum of the spectra of the two individual molecules.[42] Because the first excited state of the complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-uv region and EDA complexes are often colored. Many EDA complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. In most EDA complexes the donor and acceptor molecules are present in an integral ratio, most often 1:1, but complexes with nonintegral ratios are also known. There are several types of acceptor; we will discuss complexes formed by two of them.

1. *Complexes in which the acceptor is a metal ion and the donor an olefin or an aromatic ring* (*n* donors do not give EDA complexes with metal ions but form covalent bonds instead).[43] Many metal ions form complexes, which are often stable solids, with olefins, dienes (usually conjugated, but not always), alkynes, and aromatic rings. The generally accepted picture of the bonding in these complexes,[44] first proposed by Dewar,[45] can be illustrated for the complex in which silver ion is bonded to an olefin. There are two bonds between the metal ion and the olefin. One is a σ bond formed by overlap of the filled π orbital of the olefin with the empty $5s$ orbital of the silver ion, and the other a π bond

$$\begin{array}{c} R_2C \\ \| \; Ag^+ \\ R_2C \end{array}$$

formed by overlap of a filled $4d$ orbital of the silver ion and an empty antibonding π^* orbital of the olefin. The bond is not from the silver ion to one atom but to the whole π center. The net result is that some electron density is transferred from the olefin to the metal ion.[46]

Among the compounds that form complexes with silver and other metals are benzene[47] (represented as in **6**) and cyclooctatetraene. When the metal involved has a coordination number greater than 1, more than one donor molecule participates. In many cases, this extra electron density comes from CO groups, which in these complexes are called carbonyl groups. Thus, benzenechromium tricarbonyl (**7**) is a stable compound.[48] Three arrows are

[42]For examples of EDA complexes that do not show charge-transfer spectra, see Dewar; Thompson *Tetrahedron Suppl.* **1966**, 7, 97; Bentley; Dewar *Tetrahedron Lett.* **1967**, 5043.

[43]For monographs, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed; University Science Books: Mill Valley, CA, 1987; Alper *Transition Metal Organometallics in Organic Synthesis*, 2 vols.; Academic Press: New York, 1976, 1978; King *Transition-Metal Organic Chemistry*; Academic Press: New York, 1969; Green, *Organometallic Compounds*, vol. 2; Methuen: London, 1968; For general reviews, see Churchill; Mason *Adv. Organomet. Chem.* **1967**, 5, 93-135; Cais, in Patai *The Chemistry of Alkenes*, vol. 1; Wiley: New York, 1964, pp. 335-385. Among the many reviews limited to certain classes of complexes are: transition metals–dienes, Nakamura *J. Organomet. Chem.* **1990**, 400, 35-48; metals–cycloalkynes and arynes, Bennett; Schwemlein *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1296-1320 [*Angew. Chem. 101*, 1349-1373]; metals–pentadienyl ions, Powell *Adv. Organomet. Chem.* **1986**, 26, 125-164; complexes of main-group metals, Jutzi *Adv. Organomet. Chem.* **1986**, 26, 217-295; intramolecular complexes, Omae *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 889-902 [*Angew. Chem. 94*, 902-915]; transition metals–olefins and acetylenes, Pettit; Barnes *Fortschr. Chem. Forsch.* **1972**, 28, 85-139; Quinn; Tsai *Adv. Inorg. Chem. Radiochem.* **1969**, 12, 217-373; Pt- and Pd-olefins and acetylenes, Hartley *Chem. Rev.* **1969**, 69, 799-844; silver ion–olefins and aromatics, Beverwijk; van der Kerk; Leusink; Noltes *Organomet. Chem. Rev., Sect. A* **1970**, 5, 215-280; metals–substituted olefins, Jones *Chem. Rev.* **1968**, 68, 785-806; transition metals–allylic compounds, Clarke *J. Organomet. Chem.* **1974**, 80, 155-173; transition metals–arenes, Silverthorn *Adv. Organomet. Chem.* **1976**, 14, 47-137; metals–organosilicon compounds, Haiduc; Popa *Adv. Organomet. Chem.* **1977**, 15, 113-146; metals–carbocations, Pettit; Haynes, in Olah; Schleyer *Carbonium Ions*, vol. 5, Wiley: New York, 1976, pp. 2263-2302; metals–seven- and eight-membered rings, Bennett *Adv. Organomet. Chem.* **1966**, 4, 353-387. For a list of review articles on this subject, see Bruce *Adv. Organomet. Chem.* **1972**, 10, 273-346, pp. 317-321.

[44]For reviews, see Pearson *Metallo-organic Chemistry*; Wiley: New York, 1985; Ittel; Ibers *Adv. Organomet. Chem.* **1976**, 14, 33-61; Hartley *Chem. Rev.* **1973**, 73, 163-190; *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 596-606 [*Angew. Chem. 84*, 657-667].

[45]Dewar *Bull. Soc. Chim. Fr.* **1951**, 18, C79.

[46]For a discussion of how the nature of the metal ion affects the stability of the complex, see p. 263.

[47]For a monograph, see Zeiss; Wheatley; Winkler *Benzenoid-Metal Complexes*; Ronald Press: New York, 1966.

[48]Nicholls; Whiting *J. Chem. Soc.* **1959**, 551. For reviews of arene–transition-metal complexes, see Uemura *Adv. Met.-Org. Chem.* **1991**, 2, 195-245; Silverthorn *Adv. Organomet. Chem.* **1975**, 13, 47-137.

shown, since all three aromatic bonding orbitals contribute some electron density to the metal. Metallocenes (p. 47) may be considered a special case of this type of complex, although the bonding in metallocenes is much stronger.

**6**   **7**   **8**
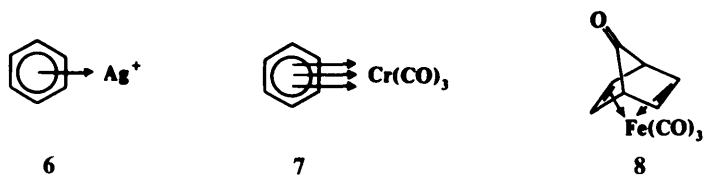
In a number of cases olefins that are too unstable for isolation have been isolated in the form of metal complexes. As example is norbornadienone, which was isolated in the form of its iron–tricarbonyl complex (**8**).[49] The free dienone spontaneously decomposes to carbon monoxide and benzene (see **7-36**).

The donor (or ligand) molecules in these complexes are classified by the prefix *hapto*[50] and/or the descriptor η^n (the Greek letter eta), where n indicates how many atoms the ligand uses to bond with the metal.[51] Thus, ethene is a dihapto or η^2 ligand, and benzene hexahapto or η^6. Ferrocene can be called bis(η^5-cyclopentadienyl)iron(II).This system can be extended to compounds in which only a single σ bond connects the organic group to the metal, e.g., C_6H_5—Li (a monohapto or η^1 ligand), and to complexes in which the organic group is an ion, e.g., π-allyl complexes such as **9**, in which the allyl ligand is trihapto or η^3.

$$CH_2=CH—CH_2—Li$$
allyllithium

9
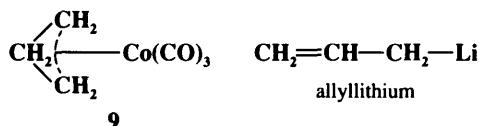
Note that in a compound such as allyllithium, where a σ bond connects the carbon to the metal, the allyl group is referred to as monohapto or η^1.

2. *Complexes in which the acceptor is an organic molecule.* Picric acid, 1,3,5-trinitrobenzene, and similar polynitro compounds are the most important of these.[52] Picric

Picric acid
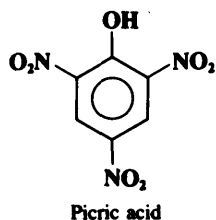
acid forms addition compounds with many aromatic hydrocarbons, aromatic amines, aliphatic amines, olefins, and other compounds. These addition compounds are usually solids with definite melting points and are often used as derivatives of the compounds in question. They are called picrates, though they are not salts of picric acid but addition compounds.

[49]Landesberg; Sieczkowski *J. Am. Chem. Soc.* **1971**, *93*, 972.
[50]For a discussion of how this system originated, see Cotton *J. Organomet. Chem.* **1975**, *100*, 29.
[51]Another prefix used for complexes is μ (mu), which indicates that the ligand bridges two metal atoms.
[52]For a review, see Parini *Russ. Chem. Rev.* **1962**, *31*, 408-417; for a review of complexes in which the acceptor is an organic cation, see Kampar *Russ. Chem. Rev.* **1982**, *51*, 107-118; also see Ref. 40.

Unfortunately, salts of picric acid are also called picrates. Similar complexes are formed between phenols and quinones (quinhydrones).[53] Olefins that contain electron-withdrawing substituents also act as acceptor molecules as do carbon tetrahalides[54] and certain anhydrides.[55] A particularly strong olefin acceptor is tetracyanoethylene.[56]

The bonding in these cases is more difficult to explain than in the previous case, and indeed no really satisfactory explanation is available.[57] The difficulty is that although the donor has a pair of electrons to contribute (both n donors and π donors are found here), the acceptor does not have a vacant orbital. Simple attraction of the dipole-induced-dipole type accounts for some of the bonding[58] but is too weak to explain the bonding in all cases;[59] e.g., nitromethane, with about the same dipole moment as nitrobenzene, forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor–acceptor interaction.

Crown Ether Complexes and Cryptates[60]

Crown ethers are large-ring compounds containing several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (**10**),[61] dicyclohexano-18-crown-6 (**11**), and 15-crown-5 (**12**). These compounds have the property[62] of forming complexes with positive ions, gen-

[53]For a review of quinone complexes, see Foster; Foreman, in Patai *The Chemistry of the Quinonoid Compounds*, pt. 1, Wiley: New York, 1974, pp. 257-333.

[54]See Blackstock; Lorand; Kochi *J. Org. Chem.* **1987**, *52*, 1451.

[55]For a review of anhydrides as acceptors, see Foster, in Patai, Ref. 3, pp. 175-212.

[56]For a review of complexes formed by tetracyanoethylene and other polycyano compounds, see Melby, in Rappoport *The Chemistry of the Cyano Group*, Wiley: New York, 1970, pp. 639-669. See also Fatiadi *Synthesis* **1987**, 959-978.

[57]For reviews, see Bender *Chem. Soc. Rev.* **1986**, *15*, 475-502; Kampar; Neilands *Russ. Chem. Rev.* **1986**, *55*, 334-342; Bent *Chem. Rev.* **1968**, *68*, 587-648.

[58]See, for example, Le Fèvre; Radford; Stiles *J. Chem. Soc. B* **1968**, 1297.

[59]Mulliken; Person *J. Am. Chem. Soc.* **1969**, *91*, 3409.

[60]For a treatise, see Atwood; Davies; MacNicol *Inclusion Compounds*, 3 vols.; Academic Press: New York, 1984. For monographs, see Weber et al. *Crown Ethers and Analogs*; Wiley: New York, 1989; Vögtle *Host Guest Complex Chemistry I, II, and III (Top. Curr. Chem. 98, 101, 121)*; Springer: Berlin, 1981, 1982, 1984; Vögtle; Weber *Host Guest Complex Chemistry/Macrocycles*; Springer: Berlin, 1985 [this book contains nine articles from the *Top. Curr. Chem.* vols. just mentioned]; Hiraoka *Crown Compounds*; Elsevier: New York, 1982; De Jong; Reinhoudt *Stability and Reactivity of Crown-Ether Complexes*; Academic Press: New York, 1981; Izatt; Christensen *Synthetic Multidentate Macrocyclic Compounds*; Academic Press: New York, 1978. For reviews, see McDaniel; Bradshaw; Izatt *Heterocycles* **1990**, *30*, 665-706; Sutherland, *Chem. Soc. Rev.* **1986**, *15*, 63-91; Sutherland in Takeuchi; Marchand *Applications of NMR Spectroscopy to Problems in Stereochemistry and Conformational Analysis*; VCH: New York, 1986; Franke; Vögtle *Top. Curr. Chem.* **1986**, *132*, 135-170; Cram *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, [*Angew. Chem. 98*, 1041-1060]; Vögtle; Löhr; Franke; Worsch *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 727-742 [*Angew. Chem. 97*, 721]; Gutsche *Acc. Chem. Res.* **1983**, *16*, 161-170; Tabushi; Yamamura *Top. Curr. Chem.* **1983**, *113*, 145-182; Stoddart *Prog. Macrocyclic Chem.* **1981**, *2*, 173-250; De Jong; Reinhoudt *Adv. Phys. Org. Chem.* **1980**, *17*, 279-433; Vögtle; Weber, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 59-156; Poonia *Prog. Macrocyclic Chem.* **1979**, *1*, 115-155; Reinhoudt; De Jong *Prog. Macrocyclic Chem.* **1979**, *1*, 157-217; Cram; Cram *Acc. Chem. Res.* **1978**, *11*, 8-14; *Science*, **1974**, *183*, 803-809; Knipe *J. Chem. Educ.* **1976**, *53*, 618-622; Gokel; Durst *Synthesis* **1976**, 168-184, *Aldrichimica Acta* **1976**, *9*, 3-12; Lehn *Struct. Bonding (Berlin)* **1973**, *16*, 1-69; Christensen; Eatough; Izatt *Chem. Rev.* **1974**, *74*, 351-384; Pedersen; Frensdorff *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 16-25 [*Angew. Chem. 84*, 16-26]. For a monograph on the synthesis of crown ethers, see Gokel; Korzeniowski *Macrocyclic Polyether Synthesis*; Springer: New York, 1982. For reviews, see Krakowiak; Bradshaw; Zamecka-Krakowiak *Chem. Rev.* **1989**, *89*, 929-972; Jurczak; Pietraszkiewicz *Top. Curr. Chem.* **1986**, *130*, 183-204; Gokel; Dishong; Schultz; Gatto *Synthesis* **1982**, 997-1012; Bradshaw; Stott *Tetrahedron* **1980**, *36*, 461-510; Laidler; Stoddart, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 3-42. For reviews of acyclic molecules with similar properties, see Vögtle *Chimia* **1979**, *33*, 239-251; Vögtle; Weber *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 753-776 [*Angew. Chem. 91*, 813-837]. For a review of cryptands that hold two positive ions, see Lehn *Pure Appl. Chem.* **1980**, *52*, 2441-2459. The 1987 Nobel Prize in Chemistry was awarded to Charles J. Pedersen, Donald J. Cram, and Jean-Marie Lehn for their work in this area. The three Nobel lectures were published in two journals (respectively, CJP, DJC, J-ML): *Angew. Chem. Int. Ed. Engl.* **1988**, *27* [*Angew. Chem. 100*] pp. 1021-1027 [1053-1059], 1009-1020 [1041-1052], 89-112 [91-116]; and *Chem. Scr.* **1988**, *28*, pp. 229-235, 263-274, 237-262. See also the series *Advances in Supramolecular Chemistry*.

[61]Cook; Caruso; Byrne; Bowers; Speck; Liotta *Tetrahedron Lett.* **1974**, 4029.

[62]Discovered by Pedersen *J. Am. Chem. Soc.* **1967**, *89*, 2495, 7017. For an account of the discovery, see Schroeder; Petersen *Pure Appl. Chem.* **1988**, *60*, 445.
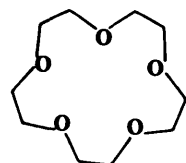
erally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions.[62a] The crown ether is called the *host* and the ion is the *guest*. In most cases the ions are held tightly in the center of the cavity.[63] Each crown ether binds
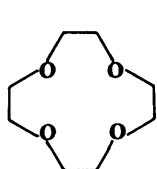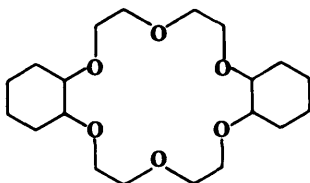
10   **11**   **12**

different ions, depending on the size of the cavity. For example, **10** binds Li^{+}[64] but not K^{+},[65] while **11** binds K^{+} but not Li^{+}.[66] Similarly, **11** binds Hg^{2+} but not Cd^{2+} or Zn^{2+}, and Sr^{2+} but not Ca^{2+}.[67] The complexes can frequently be prepared as well-defined sharp-melting solids.

Apart from their obvious utility in separating mixtures of cations,[68] crown ethers have found much use in organic synthesis (see the discussion on p. 363). Chiral crown ethers have been used for the resolution of racemic mixtures (p. 121). Although crown ethers are most frequently used to complex cations, amines, phenols, and other neutral molecules have also been complexed[69] (see p. 133 for the complexing of anions).[70]

Macrocycles containing nitrogen or sulfur atoms,[71] e.g., **13** and **14**,[72] have similar properties, as do those containing more than one kind of hetero atom, e.g., **15**,[73] **16**,[74] or **17**.[75] Bicyclic molecules like **16** can surround the enclosed ion in three dimensions, binding it even more tightly than the monocyclic crown ethers. Bicyclics and cycles of higher order[76] are called *cryptands* and the complexes formed are called *cryptates* (monocylics are also sometimes called cryptands). The tricyclic cryptand **17** has ten binding sites and a spherical cavity.[75] Another molecule with a spherical cavity (though not a cryptand) is **18**, which

[62a]For a monograph, see Inoue; Gokel *Cation Binding by Macrocycles*; Marcel Dekker: New York, 1990.

[63]For reviews of thermodynamic and kinetic data for this type of interaction, see Izatt; Bradshaw; Nielsen; Lamb; Christensen; Sen *Chem. Rev.* **1985**, *85*, 271-339; Parsonage; Staveley, in Atwood; Davies; MacNicol, Ref. 60, vol. 3, pp. 1-36.

[64]Anet; Krane; Dale; Daasvatn; Kristiansen *Acta Chem. Scand.* **1973**, *27*, 3395.

[65]Certain derivatives of 14-crown-4 and 12-crown-3 show very high selectivity for Li^{+} compared to the other alkali metal ions. See Bartsch; Czech; Kang; Stewart; Walkowiak; Charewicz; Heo; Son *J. Am. Chem. Soc.* **1985**, *107*, 4997; Dale; Eggestad; Fredriksen; Groth *J. Chem. Soc., Chem. Commun.* **1987**, 1391; Dale; Fredriksen *Pure Appl. Chem.* **1989**, *61*, 1587.

[66]Izatt; Nelson; Rytting; Haymore; Christensen *J. Am. Chem. Soc.* **1971**, *93*, 1619.

[67]Kimura; Iwashima; Ishimori; Hamaguchi *Chem. Lett.* **1977**, 563.

[68]Crown ethers have been used to separate isotopes of cations, e.g., ^{44}Ca from ^{40}Ca. For a review, see Heumann *Top. Curr. Chem.* **1985**, *127*, 77-132.

[69]For reviews, see Vögtle; Müller; Watson *Top. Curr. Chem.* **1984**, *125*, 131-164; Weber, *Prog. Macrocycl. Chem.* **1987**, *3*, 337-419; Diederich *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 362-386 [*Angew. Chem. 100*, 372-396].

[70]A neutral molecule (e.g., urea) and a metal ion (e.g., Li^{+}) were made to be joint guests in a macrocyclic host, with the metal ion acting as a bridge that induces a partial charge on the urea nitrogens: van Staveren; van Eerden; van Veggel; Harkema; Reinhoudt *J. Am. Chem. Soc.* **1988**, *110*, 4994. See also Rodrigue; Bovenkamp; Murchie; Buchanan; Fortier *Can. J. Chem.* **1987**, *65*, 2551; Fraser; Fortier; Markiewicz; Rodrigue; Bovenkamp *Can. J. Chem.* **1987**, *65*, 2558.

[71]For reviews of sulfur-containing macroheterocycles, see Voronkov; Knutov *Sulfur Rep.* **1986**, *6*, 137-256, *Russ. Chem. Rev.* **1982**, *51*, 856-871. For a review of those containing S and N, see Reid; Schröder *Chem. Soc. Rev.* **1990**, *19*, 239-269.

[72]For a review of **14** and its derivatives, see Chaudhuri; Wieghardt *Prog. Inorg. Chem.* **1987**, *35*, 329-436.

[73]Dietrich; Lehn; Sauvage *Chem. Commun.* **1970**, 1055.

[74]Newcomb; Gokel; Cram *J. Am. Chem. Soc.* **1974**, *96*, 6810.

[75]Graf; Lehn *J. Am. Chem. Soc.* **1975**, *97*, 5022.

[76]For reviews, see Potvin; Lehn *Prog. Macrocycl. Chem.* **1987**, *3*, 167-239; Kiggen; Vögtle *Prog. Macrocycl. Chem.* **1987**, *3*, 309-336; Dietrich, in Atwood; Davies; MacNicol, Ref. 60, vol. 2, pp. 337-405; Parker *Adv. Inorg. Radiochem.* **1983**, *27*, 1-26; Lehn *Acc. Chem. Res.* **1978**, *11*, 49-57, *Pure Appl. Chem.* **1977**, *49*, 857-870.

13   **14**   **15**   **16**

17   **18**
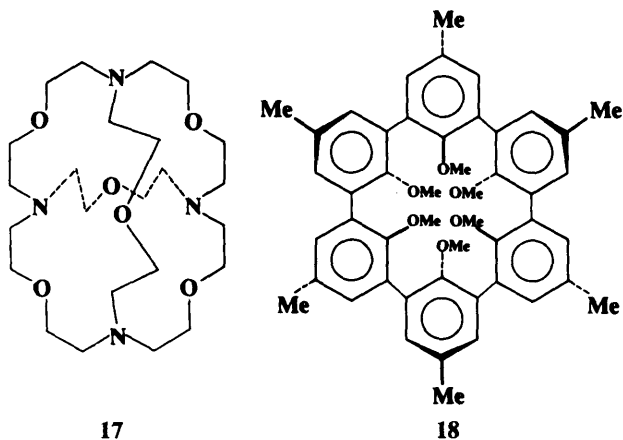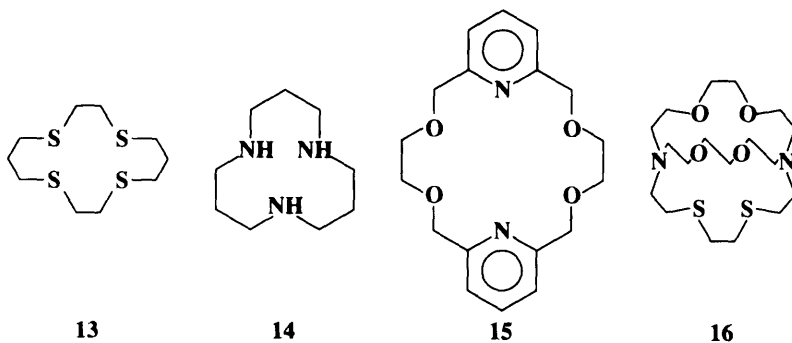
complexes Li$^+$ and Na$^+$ (preferentially Na$^+$), but not K$^+$, Mg^{2+}, or Ca^{2+}.[77] Molecules such as these, whose cavities can be occupied only by spherical entities, have been called *spherands*.[77] Other types are *calixarenes*, e.g., **19**,[78] *cryptophanes*, e.g., **20**,[79] *hemispherands* (an


19   **20**
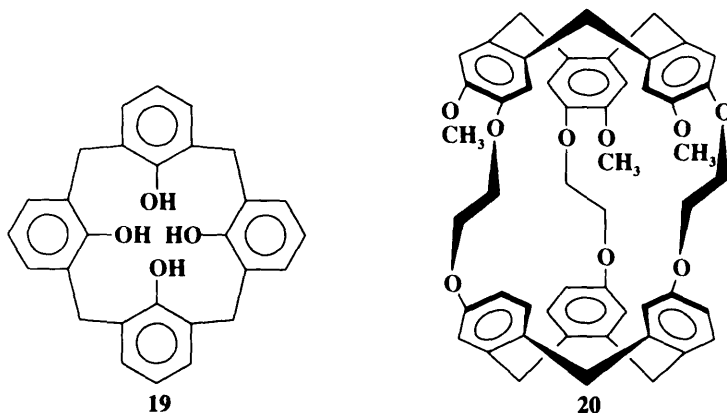
[77]Cram; Dicker *J. Chem. Soc., Chem. Commun.* **1982,** 1219; Cram; Doxsee *J. Org. Chem.* **1986,** *51,* 5068; Cram *CHEMTECH* **1987,** 120, *Chemtracts: Org. Chem.* **1988,** *1,* 89; Paek; Knobler; Maverick; Cram *J. Am. Chem. Soc.* **1989,** *111,* 8662; Bryant; Ho; Knobler; Cram *J. Am. Chem. Soc.* **1990,** *112,* 5837.

[78]For monographs, see Vicens; Böhmer *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Kluwer: Dordrecht, 1991; Gutsche *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. For reviews, see Gusche *Prog. Macrocycl. Chem.* **1987,** *3,* 93-165, *Top. Curr. Chem.* **1984,** *123,* 1-47.

[79]For reviews, see Collet *Tetrahedron* **1987,** *43,* 5725-5759, in Atwood; Davies; MacNicol, Ref. 60, Vol. 1, pp. 97-121.

example is **21**[80]), and *podands*.[81] The last-named are host compounds in which two or more arms come out of a central structure. Examples are **22**[82] and **23**.[83] **23**, also called an *octopus molecule*, binds simple cations such as Na^+, K^+, and Ca^{2+}. *Lariat ethers* are compounds

21

22

23

24
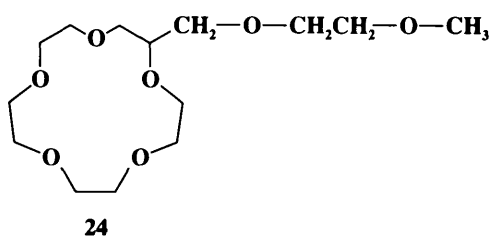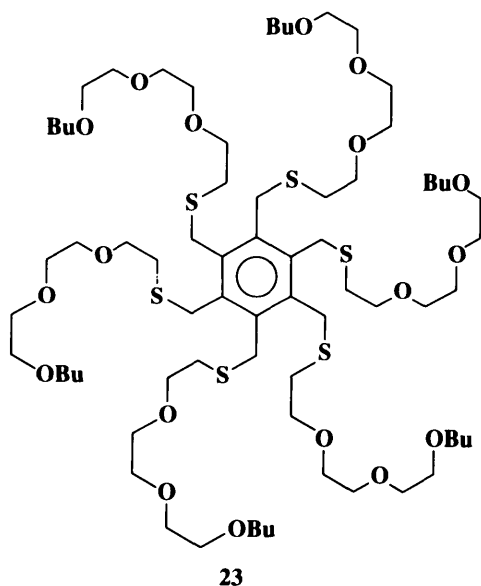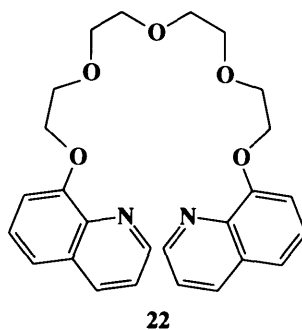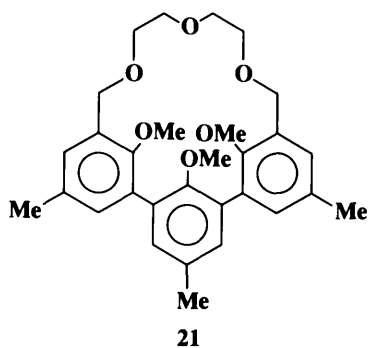
containing a crown ether ring with one or more side chains that can also serve as ligands.[84] An example is **24**.

The bonding in these complexes is the result of ion-dipole attractions between the hetero atoms and the positive ions.

As we have implied, the ability of these host molecules to bind guests is often very specific, enabling the host to pull just one molecule or ion out of a mixture. This is called

[80]Lein; Cram *J. Am. Chem. Soc.* **1985**, *107*, 448.

[81]For reviews, see Kron; Tsvetkov *Russ. Chem. Rev.* **1990**, *59*, 283-298; Menger *Top. Curr. Chem.* **1986**, *136*, 1-15.

[82]Tümmler; Maass; Weber; Wehner; Vögtle *J. Am. Chem. Soc.* **1977**, *99*, 4683.

[83]Vögtle; Weber *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 814 [*Angew. Chem. 13*, 896].

[84]See Gatto; Dishong; Diamond *J. Chem. Soc., Chem. Commun.* **1980**, 1053; Gatto; Gokel *J. Am. Chem. Soc.* **1984**, *106*, 8240; Nakatsuji; Nakamura; Yonetani; Yuya; Okahara *J. Am. Chem. Soc.* **1988**, *110*, 531.

molecular recognition.[85] In general, cryptands, with their well-defined three-dimensional cavities, are better for this than monocyclic crown ethers or ether derivatives. An example is the host **25**, which selectively binds the dication **26** ($n = 5$) rather than **26** ($n = 4$), and **26** ($n = 6$) rather than **26** ($n = 7$).[86] The host **27**, which is water-soluble, forms 1:1 complexes

$$H_3\overset{+}{N}—(CH_2)_n—\overset{+}{N}H_3$$

26

25

27

· 4 H_2O
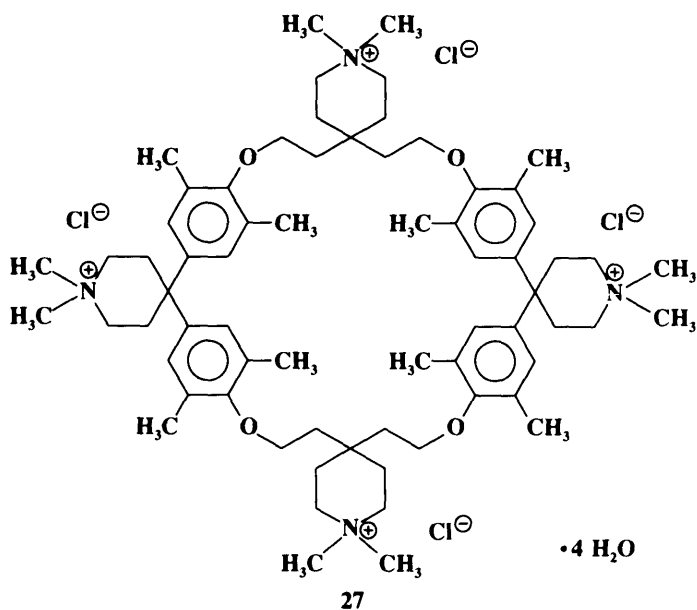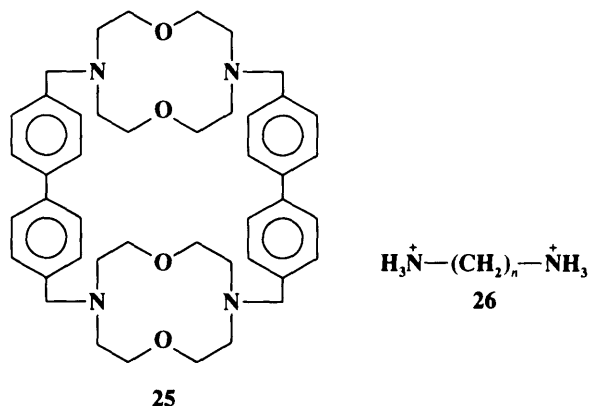
with neutral aromatic hydrocarbons such as pyrene and fluoranthene, and even (though more weakly) with biphenyl and naphthalene, and is able to transport them through an aqueous phase.[87]

[85]For reviews, see Rebek *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 245-255 [*Angew. Chem. 102*, 261-272], *Acc. Chem. Res.* **1990**, *23*, 399-404, *Top. Curr. Chem.* **1988**, *149*, 189-210, *Mol. Struct. Energ.* **1988**, *10*, 219-250; Diederich *J. Chem. Educ.* **1990**, *67*, 813-820; Hamilton *J. Chem. Educ.* **1990**, *67*, 821-828; Raevskii *Russ. Chem. Rev.* **1990**, *59*, 219-233.
[86]Mageswaran; Mageswaran; Sutherland *J. Chem. Soc., Chem. Commun.* **1979**, 722.
[87]Diederich; Dick *J. Am. Chem. Soc.* **1984**, *106*, 8024; Diederich; Griebel *J. Am. Chem. Soc.* **1984**, *106*, 8037. See also Vögtle; Müller; Werner; Losensky *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 901 [*Angew. Chem. 99*, 930].

Of course, it has long been known that molecular recognition is very important in biochemistry. The action of enzymes and various other biological molecules is extremely specific because these molecules also have host cavities that are able to recognize only one or a few particular types of guest molecules. It is only in recent years that organic chemists have been able to synthesize non-natural hosts that can also perform crude (compared to biological molecules) molecular recognition. The macrocycle **28** has been used as a catalyst, for the hydrolysis of acetyl phosphate and the synthesis of pyrophosphate.[88]

28
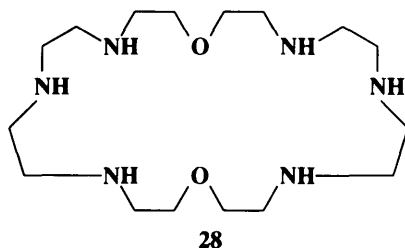
No matter what type of host, the strongest attractions occur when combination with the guest causes the smallest amount of distortion of the host.[89] That is, a fully preorganized host will bind better than a host whose molecular shape must change in order to accomodate the guest.

Inclusion Compounds

This type of addition compound is different from either the EDA complexes or the crown ether type of complexes previously discussed. Here the host forms a crystal lattice which has spaces large enough for the guest to fit into. There is no bonding between the host and the guest except van der Waals forces. There are two main types, depending on the shape of the space.[90] The spaces in *inclusion compounds* are in the shape of long tunnels or channels, while the other type, often called *clathrate*,[91] or *cage compounds* have spaces that are completely enclosed. In both types the guest molecule must fit into the space and potential guests that are too large or too small will not go into the lattice, so that the addition compound will not form.

One important host molecule among the inclusion compounds is urea.[92] Ordinary crystalline urea is tetragonal, but when a guest is present, urea crystallizes in a hexagonal lattice, containing the guest in long channels (Figure 3.1).[93] The hexagonal type of lattice can form only when a guest molecule is present, showing that van der Waals forces between the host and the guest, while small, are essential to the stability of the structure. The diameter of the channel is about 5 Å, and which molecules can be guests is dependent only on their

[88]Hosseini; Lehn *J. Am. Chem. Soc.* **1987,** *109,* 7047. For a discussion, see Mertes; Mertes *Acc. Chem. Res.* **1990,** *23,* 413-418.

[89]See Cram, *Angew. Chem. Int. Ed. Engl.* **1986,** *25,* 1039-1057 [*Angew. Chem. 98,* 1041-1060].

[90]For a treatise that includes both types, see Atwood; Davies; MacNicol, Ref. 60. For reviews, see Weber *Top. Curr. Chem.* **1987,** *140,* 1-20; Gerdil *Top. Curr. Chem.* **1987,** *140,* 71-105; Mak; Wong *Top. Curr. Chem.* **1987,** *140,* 141-164. For a review of channels with helical shapes, see Bishop; Dance *Top. Curr. Chem.* **1988,** *149,* 137-188.

[91]For reviews, see Goldberg *Top. Curr. Chem.* **1988,** *149,* 1-44; Weber; Czugler *Top. Curr. Chem.* **1988,** *149,* 45-135; MacNicol; McKendrick; Wilson *Chem. Soc. Rev.* **1978,** *7,* 65-87.

[92]For a review of urea and thiourea inclusion compounds, see Takemoto; Sonoda, in Atwood; Davies; MacNicol, Ref. 60, vol. 2, pp. 47-67.

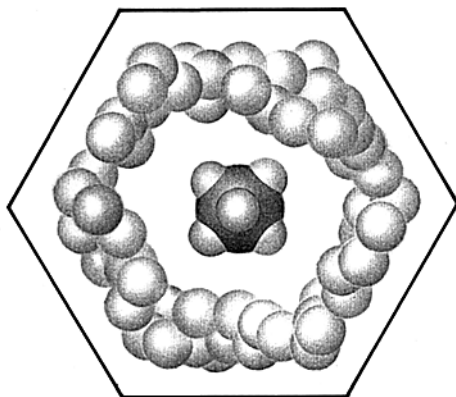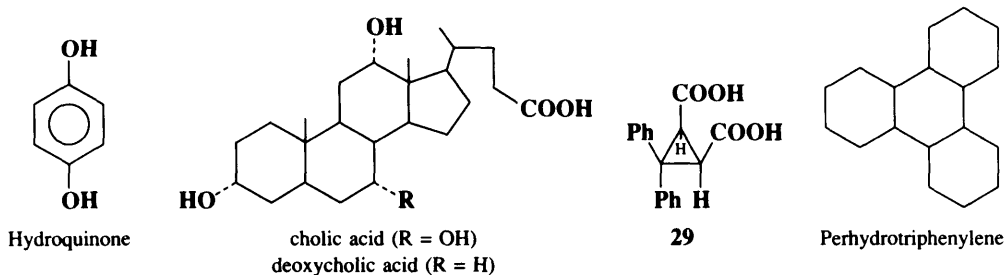[93]This picture is taken from a paper by Montel *Bull. Soc. Chim. Fr.* **1955,** 1013.

FIGURE 3.1 Guest molecule in a urea lattice.[93]

shapes and sizes and not on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate or diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.[94] In these complexes, there is usually no integral molar ratio (though by chance there may be). For example, the octane–urea ratio is 1:6.73.[95] A deuterium quadrupole echo spectroscopy study of a urea complex showed that the urea molecules do not remain rigid, but undergo 180° flips about the $C{=}O$ axis at the rate of more than 10^6 per second at 30°C.[96]

The complexes are solids but are not useful as derivatives, since they melt, with decomposition of the complex, at the melting point of urea. They are useful, however, in separating isomers that would be quite difficult to separate otherwise. Thiourea also forms inclusion compounds though with channels of larger diameter, so that n-alkanes cannot be guests but, for example, 2-bromooctane, cyclohexane, and chloroform readily fit.

The most important host for clathrates is hydroquinone.[97] Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), SO_2, CO_2, and argon (but not neon). In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage and many guest molecules, among them Cl_2, propane, and methyl iodide, can fit. The water clathrates, which are solids, can normally be kept only
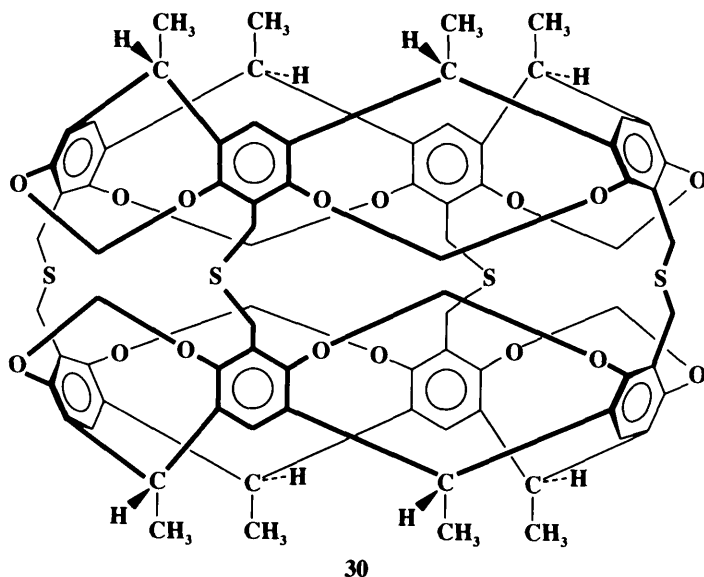
OH

OH

Hydroquinone

OH

COOH

HO

R

cholic acid (R = OH)
deoxycholic acid (R = H)

COOH

Ph

COOH

Ph H

29

Perhydrotriphenylene

[94]Radell; Connolly; Cosgrove *J. Org. Chem.* **1961**, *26*, 2960.
[95]Redlich; Gable; Dunlop; Millar *J. Am. Chem. Soc.* **1950**, *72*, 4153.
[96]Heaton; Vold; Vold *J. Am. Chem. Soc.* **1989**, *111*, 3211.
[97]For a review, see MacNicol, in Atwood; Davies; MacNicol, Ref. 60, vol. 2, pp. 1-45.

30

at low temperatures; at room temperature, they decompose.[98] Another inorganic host is sodium chloride (and some other alkali halides), which can encapsulate organic molecules such as benzene, naphthalene, and diphenylmethane.[99]

Among other hosts[100] for inclusion and/or clathrate compounds are deoxycholic acid,[101] cholic acid,[102] small ring compounds such as **29**,[103] perhydrotriphenylene,[104] and the compound **30**, which has been called a *carcerand*.[105]

Cyclodextrins

There is one type of host that can form both channel and cage complexes. This type is called *cyclodextrins* or *cycloamyloses*.[106] The host molecules are made up of six, seven, or eight glucose units connected in a large ring, called, respectively, α-, β-, or γ-cyclodextrin (Figure 3.2 shows the β or seven-membered ring compound). The three molecules are in the shape of hollow truncated cones (Figure 3.3) with primary OH groups projecting from the narrow

[98]For a monograph on water clathrates, see Berecz; Balla-Achs *Gas Hydrates*; Elsevier: New York, 1983. For reviews, see Jeffrey, in Atwood; Davies, MacNicol, Ref. 60, vol. 1, pp. 135-190; Cady *J. Chem. Educ.* **1983**, *60*, 915-918; Byk; Fomina *Russ. Chem. Rev.* **1968**, *37*, 469-491.

[99]Kirkor; Gebicki; Phillips; Michl *J. Am. Chem. Soc.* **1986**, *108*, 7106.

[100]See also Toda *Pure App. Chem.* **1990**, *62*, 417-422, *Top. Curr. Chem.* **1988**, *149*, 211-238, **1987**, *140*, 43-69; Davies; Finocchiaro; Herbstein, in Atwood; Davies; MacNicol, Ref. 60, vol. 2, pp. 407-453.

[101]For a review, see Giglio, in Atwood; Davies; MacNicol, Ref. 60, vol. 2, pp. 207-229.

[102]See Miki; Masui; Kasei; Miyata; Shibakami; Takemoto *J. Am. Chem. Soc.* **1988**, *110*, 6594.

[103]Weber; Hecker; Csöregh; Czugler *J. Am. Chem. Soc.* **1989**, *111*, 7866.

[104]For a review, see Farina, in Atwood; Davies; MacNicol, Ref. 60, vol. 2, pp. 69-95.

[105]Cram; Karbach; Kim; Baczynskyj; Marti; Sampson; Kalleymeyn *J. Am. Chem. Soc.* **1988**, *110*, 2554; Sherman; Knobler; Cram *J. Am. Chem. Soc.* **1991**, *113*, 2194.

[106]For a monograph, see Bender; Komiyama *Cyclodextrin Chemistry*; Springer: New York, 1978. For reviews, see, in Atwood; Davies; MacNicol, Ref. 60, the reviews, by Saenger, vol. 2, 231-259, Bergeron, vol. 3, 391-443, Tabushi, Vol. 3, 445-471, Breslow, vol. 3, 473-508; Croft; Bartsch *Tetrahedron* **1983**, *39*, 1417-1474; Tabushi; Kuroda *Adv. Catal.* **1983**, *32*, 417-466; Tabushi *Acc. Chem. Res.* **1982**, *15*, 66-72; Saenger *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 344-362 [*Angew. Chem. 92*, 343-361]; Bergeron *J. Chem. Ed.* **1977**, *54*, 204-207; Griffiths; Bender *Adv. Catal.* **1973**, *23*, 209-261.
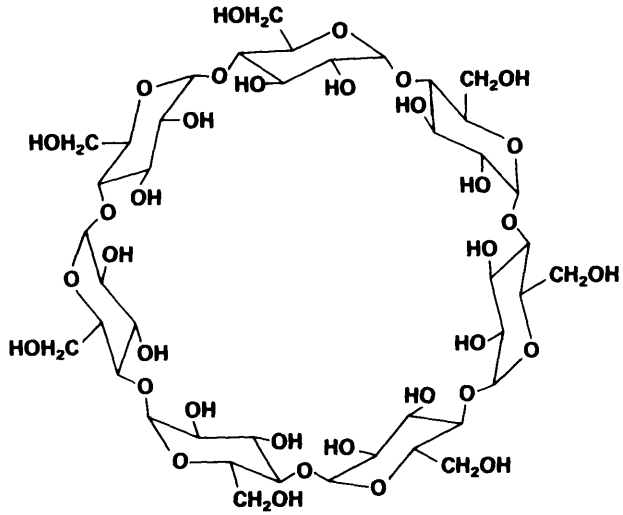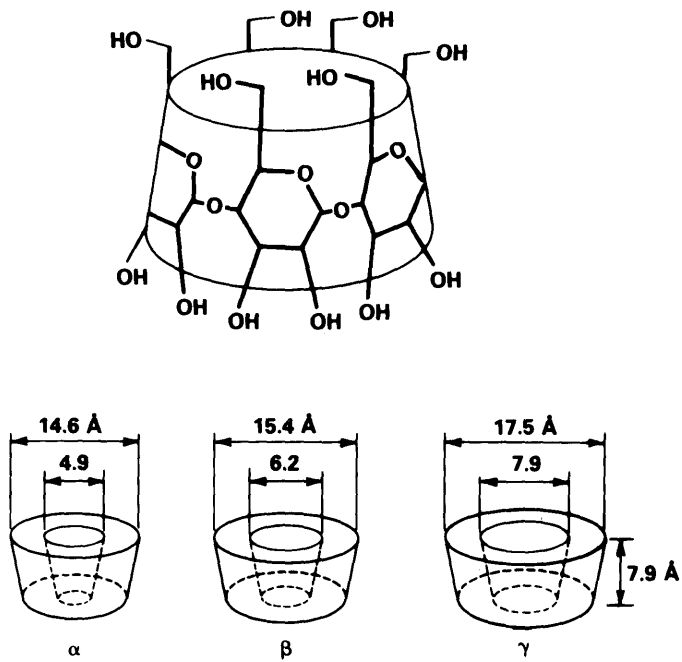
FIGURE 3.2 β-Cyclodextrin.

FIGURE 3.3 Shape and dimensions of the α-, β-, and γ-cyclodextrin molecules.[107]

[107]Szejtle, Ref. 109, p. 332; Nickon; Silversmith *The Name Game*; Pergamon: Elmsford, NY, p. 235.
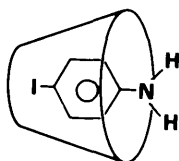
FIGURE 3.4 Schematic drawing of the complex of α-cyclodextrin and p-iodoaniline.[108]

side of the cones and secondary OH group from the wide side. As expected for carbohydrate molecules, all of them are soluble in water and the cavities normally fill with water molecules held in place by hydrogen bonds (6, 12, and 17 H_2O molecules for the α, β, and γ forms, respectively), but the insides of the cones are less polar than the outsides, so that nonpolar organic molecules readily displace the water. Thus the cyclodextrins form 1:1 cage complexes with many guests, ranging in size from the noble gases to large organic molecules. A guest molecule must not be too large or it will not fit, though many stable complexes are known in which one end of the guest molecule protrudes from the cavity (Figure 3.4). On the other hand, if the guest is too small, it may go through the bottom hole (though some small polar molecules such as methanol do form complexes in which the cavity also contains some water molecules). Since the cavities of the three cyclodextrins are of different sizes (Figure 3.3), a large variety of guests can be accommodated. Since cyclodextrins are nontoxic (they are actually small starch molecules), they are now used industrially to encapsulate foods and drugs.[109]

The cyclodextrins also form channel-type complexes, in which the host molecules are stacked on top of each other, like coins in a row.[110] For example, α-cyclodextrin (cyclohexaamylose) forms cage complexes with acetic, propionic, and butyric acids, but channel complexes with valeric and higher acids.

Catenanes and Rotaxanes[111]

These compounds contain two or more independent portions that are not bonded to each other by any valence forces but nevertheless must remain linked. *Catenanes* are made up of two or more rings held together as links in a chain, while in *rotaxanes* a linear portion

A [2]catenane   A [3]catenane   A rotaxane
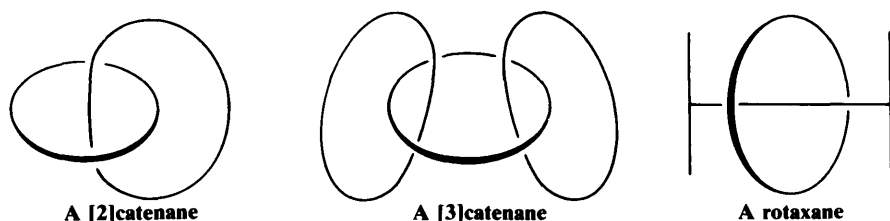
is threaded through a ring and cannot get away because of bulky end groups. Catenanes and rotaxanes can be prepared by statistical methods or directed syntheses.[112] An example of a statistical synthesis of a rotaxane is a reaction where a compound **A** is bonded at two

[108]Modified from Saenger; Beyer; Manor *Acta Crystallogr. Sect. B* **1976**, *32*, 120.

[109]For reviews, see Pagington *Chem. Br.* **1987**, *23*, 455-458; Szejtli, in Atwood; Davies; MacNicol, Ref. 60, vol. 3, 331-390.

[110]See Saenger, Ref. 106.

[111]For a monograph, see Schill *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971. For a review, see Schill, in Chiurdoglu *Conformational Analysis*; Academic Press: New York, 1971, pp. 229-239.

[112]For discussions, see Ref. 111; Walba *Tetrahedron* **1985**, *41*, 3161-3212.
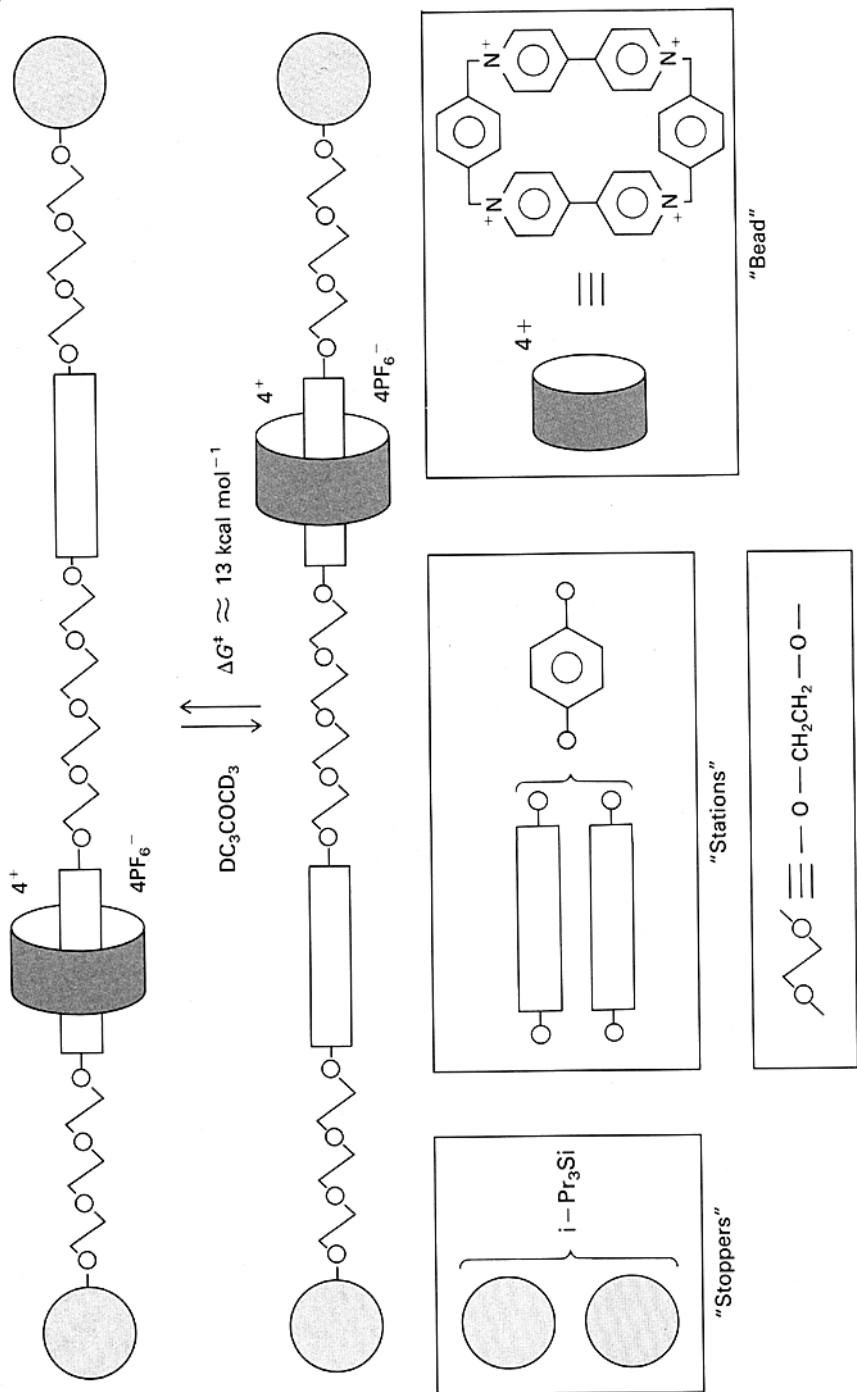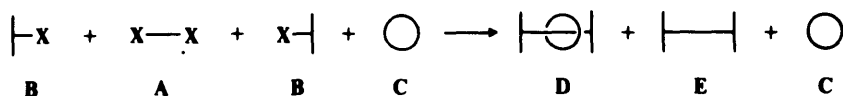
FIGURE 3.5 A molecular shuttle. The "bead", consisting of a macrocycle containing four pyridine rings and two benzene rings, moves back and forth between the two "stations", which are benzene rings. The "stoppers" prevent the bead from falling off the chain.[115]

positions to another compound **B** in the presence of a large ring **C**. It is hoped that some **A** molecules would by chance be threaded through **C** before combining with the two **B** molecules, so that some rotaxane (**D**) would be formed along with the normal product **E**.[113]

$$ \vdash\!\text{x} \quad + \quad \text{x}\!\!-\!\!\text{x} \quad + \quad \text{x}\!\dashv \quad + \quad \bigcirc \quad \longrightarrow \quad \vdash\!\ominus\!\dashv \quad + \quad \vdash\!\!-\!\!\dashv \quad + \quad \bigcirc $$

B   **A**   **B**   **C**   **D**   **E**   **C**

In a directed synthesis, the separate parts of the molecule are held together by other bonds that are later cleaved. See **9-65** for statistical and directed syntheses of catenanes.[114]

A rotaxane that is also an inclusion compound is shown schematically in Figure 3.5.[115] In this molecule the bulky end groups (or "stoppers") are triisopropylsilyl groups (i-Pr$_3$Si—) and the chain consists of a series of —O—CH$_2$CH$_2$—O— groups, but also contains two benzene rings. The ring (or "bead") around the chain is a macrocycle containing two benzene rings and four pyridine rings, and is preferentially attracted to one of the benzene rings in the chain. (The benzene moiety serves as a "station" for the "bead".) However, in this particular compound the symmetry of the chain makes the two "stations" equivalent, so that the "bead" is equally attracted to them, and the "bead" actually moves back and forth rapidly between the two "stations", as shown by the temperature dependence of the nmr spectrum.[116] This molecule has been called a *molecular shuttle*.

[113]Schemes of this type were carried out by Harrison and Harrison *J. Am. Chem. Soc.* **1967**, *89*, 5723; Ogino *J. Am. Chem. Soc.* **1981**, *103*, 1303. For a different kind of statistical syntheszis of a rotaxane, see Harrison *J. Chem. Soc., Chem. Commun.* **1972**, 231; *J. Chem. Soc., Perkin Trans. 1* **1974**, 301; Schill; Beckmann; Schweikert; Fritz *Chem. Ber.* **1986**, *119*, 2647. See also Agam; Graiver; Zilkha *J. Am. Chem. Soc.* **1976**, *98*, 5206.
[114]For a directed synthesis of a rotaxane, see Schill; Züllenkopf *Liebigs Ann. Chem.* **1969**, *721*, 53; Schill; Zürcher; Vetter *Chem. Ber.* **1973**, *106*, 228.
[115]Adapted from a diagram in Anelli; Spencer; Stoddart *J. Am. Chem. Soc.* **1991**, *113*, 5131.
[116]Ref. 115. For a review of the synthesis and properties of molecules of this type, see Philp; Stoddart *Synlett* **1991**, 445-458.