TATE AND LYLE LECTURE*

From Carbohydrates to Enzyme Analogues

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1 Why not?

One of the pleasures of belonging to our profession is that its membership provides us with a licence to dream. To my mind, dreaming is not only a professional privilege accorded to us all, it is an honourable duty to be performed by all of us objectively. Above all, it raises our expectations and encourages us to tackle problems which, one might say, are almost beyond our wildest dreams! Nobody has captured the spirit of dreaming more vividly or with as much feeling and hopefulness as did Robert Kennedy[1] in his much quoted lines:

> *Some men see things as they are and say, why.*
> *I dream things that never were and say, why not.*

In this context of 'why not', I have a dream, 'I have a dream that one day'[2] we shall be able to make molecules which will vie with Nature's receptor molecules in their ability to exhibit selective binding and to display recognition functions towards chosen target molecules. If, initially at least, I agree to moderate my vision of the man-made receptor molecules of the future, then the concept of enzyme modelling, for example, is not a new one, I grant, especially to those of us familiar with carbohydrates. Indeed, Nature has provided us with one of the most intensively investigated enzyme model systems to date in the shape of the cycloamyloses. This group of homologous oligosaccharides, which are comprised of α-1,4-linked D-glucopyranosyl residues in a cyclic constitution is elaborated by the action of *Bacillus macerans* amylase on starch.[3] The best known and studied representatives are those built up from six and seven glucose

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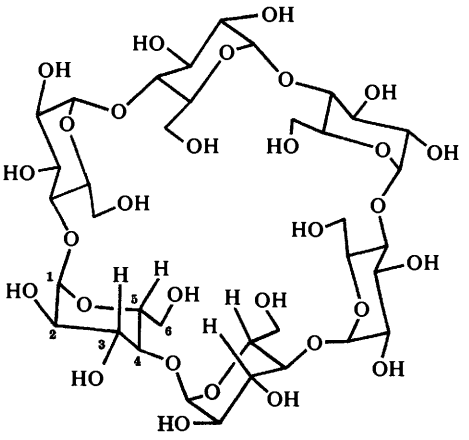
[1] Edward M. Kennedy's Eulogy at St Patrick's Cathedral, New York on 8th June 1968; see, for example, D. Ross, 'Robert F. Kennedy: Apostle of Change,' Pocket Books, New York, 1968.

[2] Plagiarised from the Address by Martin Luther King from the Washington Monument, August 1963; see, for example C. S. King, 'My Life with Martin Luther King Jr.,' Holt, Rinehart, and Winston, New York, 1969.

[3] D. French, *Adv. Carbohydrate Chem.*, 1957, **12**, 189.

units. The results of *X*-ray crystallographic studies[4] and an analysis of Corey-Pauling–Koltun (C.P.K.)-space-filling molecular models reveal that cyclohexa-amylose (1) is a doughnut-shaped molecule in which (i) the six D-glucopyranosyl residues are in the $^4C_1$ (D) chair conformation, (ii) the six glycosidic oxygens surrounded by four hydrogens (on C-3 and C-5 of neighbouring residues) are all pointing into the centre of the cavity, (iii) the hydroxymethyl groups on C-5 line one rim of the cavity, and (iv) the secondary hydroxy-groups (on C-2 and C-3) line the other rim. As a result of the work of Cramer in Germany, and Bender and Breslow in the United States, and others, it is now well established[5–7] that cyclohexa-amylose (1) serves as a *host* molecule



(1)

in aqueous solution for a whole range of organic *guest* molecules including aliphatic and aromatic hydrocarbons, alcohols, phenols, ethers, carboxylic acids, esters, amines, and so on. Since the cavity diameter of 4.5 Å in (1) is just sufficient to accommodate a benzene ring, these inclusion complexes, *e.g.* (2) and (3), can be viewed as owing their existence to a kind of hydrophobic bonding.[6,8] Association constants are moderately high (10^2—10^4 l mol^{-1}) and

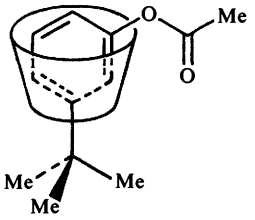
[4] A. Hybl, R. E. Rundle, and D. E. Williams, *J. Amer. Chem. Soc.*, 1965, **87**, 2779; B. Hingerty and W. Saenger, *J. Amer. Chem. Soc.*, 1975, **98**, 3357 and references therein; K. Harata, *Bull. Chem. Soc. Japan*, 1975, **48**, 2409; *ibid.*, 1976, **49**, 1493, 2006.

[5] R. Breslow, *Advances in Chemistry Series* 100, Bioinorganic Chemistry, American Chemical Society, Washington, 1971, p. 21; *Chem. Soc. Revs.*, 1972, **1**, 533; M. L. Bender and M Komiyama, 'Reactivity and Structure; Concepts in Organic Chemistry, Vol. 6: Cyclodextrin Chemistry,' Springer Verlag, Berlin, 1978.

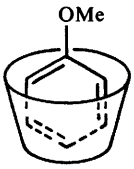
[6] D. W. Griffiths and M. L. Bender, *Adv. Catalysis*, 1973, **23**, 209.

[7] I. Tabushi, Y. Kiyosuke, T. Sugimoto, and K. Yamamura, *J. Amer. Chem. Soc.*, 1978, **100**, 916.

[8] W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw-Hill, New York, 1969, Ch. 8.



(2)



(3)

they have been shown, for example, to exhibit covalent catalysis with maximal rate enhancements of the order of several hundred times that of the uncatalysed reaction (*e.g.* the hydrolysis of *m*-t-butylphenylacetate can be accelerated[9] 260-fold) as well as non-covalent catalysis—the *p*-chlorination of anisole with hypochlorous acid proceeds 5.3 times faster with high regioselectivity (*para*: *ortho*, 96:4) when 72% of the anisole is bound[10] in (1). Enantiomeric differentiations have also been observed[11] during the catalytic hydrolysis of racemic esters by cyclohexa-amylose (1), which belongs to the rare chiral point group with C_6 symmetry.[12]

Whilst research aimed at uncovering the potential of the cycloamyloses as enzyme models will no doubt continue to thrive, it would appear that rapid progress in this area is going to be hampered by a number of factors, not least of them (i) the lack of sufficient structuring of the guests in their binding sites, (ii) the low degree of chirality inherent in their axial symmetry [despite the fact that (1) contains 30 chiral centres!], (iii) the constitutional difficulties associated with their chemical modification, and (iv) the constraints of always having to start with the same one or two basic building blocks. And so it seems obvious now that we must at least face up to the challenge of designing and synthesizing our own receptor molecules. For more than a century now, chemists have been elucidating the structures of natural products and unravelling the mechanisms of quite complex reactions. More often than not, synthetic objectives have emerged out of the harvested information from Nature's apparently boundless store. Occasionally, preparative goals have been pursued on molecules designed by the chemist's own imagination usually to test some structural or mechanistic hypothesis and sometimes just to indulge in an aesthetic vagary. It is only very recently that we have been able to contemplate the design and preparation of synthetic hosts to complex in a highly structured manner with both synthetic and naturally-occurring guests. As a result, I am willing to predict that synthetic chemistry is about to enter a new and exciting era and I want to try and explain

[9] R. L. Van Etten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *J. Amer. Chem. Soc.*, 1967, **89**, 3242.

[10] R. Breslow and P. Campbell, *J. Amer. Chem. Soc.*, 1969, **91**, 3085; *Bioorg. Chem.*, 1971, **1**, 140.

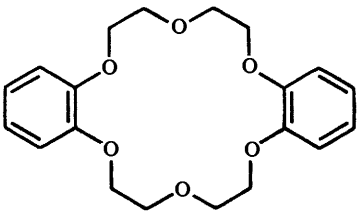
[11] F. Cramer and W. Dietsche, *Chem. Ber.*, 1959, **92**, 1739; K. Flohr, R. M. Paton, and E. T. Kaiser, *J. Amer. Chem. Soc.*, 1975, **97**, 1209.

[12] J. F. Stoddart, W. A. Szarek, and J. K. N. Jones, *Canad. J. Chem.*, 1969, **47**, 3213.

how and why I believe that carbohydrates are going to play an important role in this renaissance. First of all, however, we must digress to meet the new building blocks.

2 The Break and Some Facts

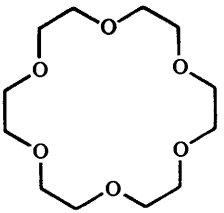
A great opportunity was afforded to us with the accidental synthesis by Pedersen[13] of dibenzo-18-crown-6 (4) and his reports[14] in 1967 that this compound forms



(4)

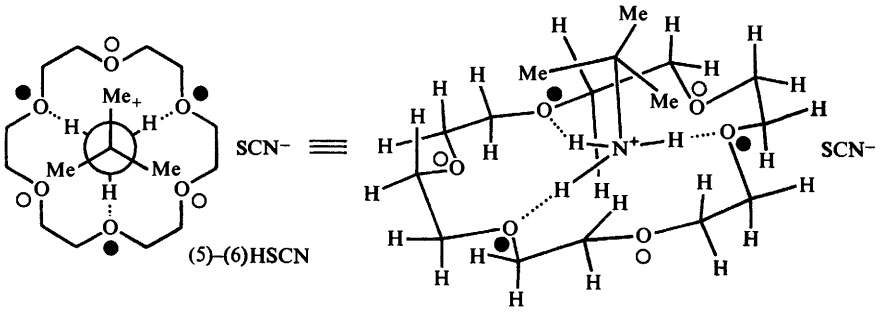
stable complexes, both in the crystalline state and in solution, with a whole range of metal (*e.g.* $Na^+NO_2^-$, K^+I^-, Rb^+SCN^-, Cs^+SCN^-, $Ca^{2+}Cl_2^-$, $Ba^{2+}(SCN)_2^-$, $Cd^{2+}Cl_2^-$, and $Hg^{2+}Cl_2^-$), ammonium, and substituted ammonium (*e.g.* $HONH_3^+Cl^-$, $H_2NNH_3^+Cl^-$, $Me_2CHCH_2NH_3^+Cl^-$, and $HO_2CCH_2NH_3^+Cl^-$) salts. In particular, the ability of the so-called crown ethers to complex with substituted ammonium cations forms a basis for building synthetic organic host molecules to bind organic cations in a highly structured manner. In ingenious fashion, Cram[15–21] suggested that binding in such complexes arises from hydrogen bonds involving the three hydrogens of the substituted ammonium cation with alternate oxygens on the 18-crown-6 constitution. The atomic dipoles associated with the lone pairs of electrons on the other three oxygens lend[21] some additional ion–dipole stabilization to the positively charged nitrogen of the cation. Inspection of framework molecular models of the complex (5)–(6) HSCN between 18-crown-6 (5) and $Me_3CNH_3^+SCN^-$ (6)HSCN, employing

[13] C. J. Pedersen, *Aldrichim. Acta*, 1971, **4**, 1.
[14] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 2495, 7017.
[15] E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 2691; E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *ibid.*, 1973, **95**, 2692.
[16] D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803.
[17] D. J. Cram, R. C. Helgeson, L. R. Sousa, J. M. Timko, M. Newcomb, P. Moreau, F. de Jong, G. W. Gokel, D. H. Hoffman, L. A. Domeier, S. C. Peacock, K. Madan, and L. Kaplan, *Pure Appl. Chem.*, 1975, **43**, 327.
[18] D. J. Cram, 'Synthetic Host-Guest Chemistry' in 'Applications of Biomedical Systems in Chemistry,' ed. J. B. Jones, C. J. Sih, and D. Perlman, Wiley-Interscience, 1976, Ch. V.
[19] D. J. Cram and J. M. Cram, *Accounts Chem. Res.*, 1978, **11**, 8.
[20] E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 2564.
[21] J. M. Timko, S. S. Moore, D. M. Walba, P. C. Hiberty, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 4207.



(3 000 000; −8.81)

(5)



(5)–(6)HSCN

an $\overset{+}{N}$—O distance of 2.88 Å for the three $\overset{+}{N}$—H . . . O hydrogen bonds,[22] indicates that the complex is of a face-to-face type.[23] The drawings in Figure 1, which are based[24] on photographs of C.P.K. space-filling molecular models of the cationic complex (5)–(7)H^+ formed between 18-crown-6 (5) and the $MeNH_3^+$ cation (7), H^+ reveal[20] a good 'fit' between the crown ether and the cation, with an obvious convergence of donor sites in (5) towards receptor sites in (7)H^+.

[22] C. G. Pimentel and A. L. McClellan, 'The Hydrogen Bond,' Reinhold, New York, 1960, p. 289.

[23] In the plane projection representation of the 'all-*gauche*-OCH_2CH_2O' conformation[19] of the 18-membered ring in the complex (5)–(6)HSCN, the 'up' oxygens are denoted by a dot and the 'down' oxygens by a circle. Although previously (W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S., Perkin I*, 1977, 1756) the hydrogen bonds have been associated formally with the 'down' oxygens in conformational representations, *X*-ray crystallographic evidence (D. J. Cram, personal communication, February 1978; I. Goldberg, *Acta Cryst.*, 1975, **B31**, 2592) on complexes of 18-crown-6 derivatives with $Me_3CNH_3^+SCN^-$ (6)HSCN indicates that 'up' oxygens are always involved in hydrogen bonding in the solid state. On this basis alone, a choice between the two stereochemically distinguishable three-point binding models has been made in (5)–(6)HSCN. See also, the crystal structure (O. Nagano, A. Kobayashi, and Y. Saski, *Bull. Chem. Soc. Japan*, 1978, **51**, 790) of the ammonium bromide dihydrate complex of 18-crown-6.

[24] This method has been employed previously[20] to represent an 'all-planar' conformation for the 18-membered ring in the cationic complex (5)–(7)H^+.

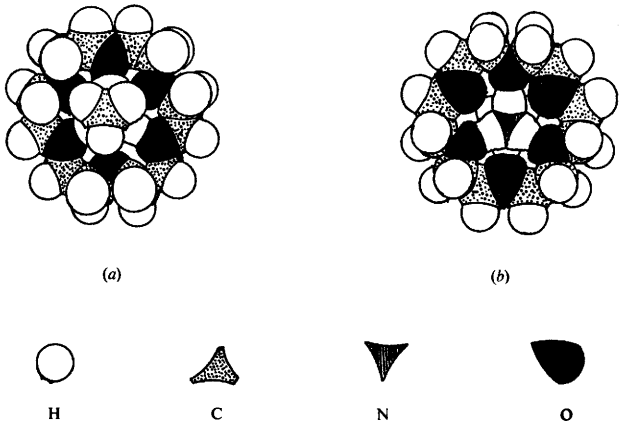


Figure 1 *View of the cationic complex* (5)—(7),H^+ *formed between* 18-*crown*-6 (5) *and the* $MeNH_3^+$ *cation* (7),H^+ *from the front* (a) *and from the back* (b)

In non-polar solvents, the anion will often form[18,25–28] a contact ion pair with the cationic complex if it can compete (*e.g.* Cl^-, $ArCO_2^-$, $CF_3CO_2^-$, and SCN^- ions) with the crown ether oxygens for hydrogen bonding with the cation. Nonetheless, Cram's three-point binding model provides a very useful working hypothesis for investigating the structures of these complexes and is supported by crystal structure data on complexes of 18-crown-6 derivatives.[19,23,29,30] It also allows us to interpret and predict the strengths of complexes formed in non-polar solvents. The stabilities of complexes in $CDCl_3$ can be measured spectroscopically by a procedure,[31] which involves partitioning of $Me_3CNH_3^+$ SCN^- (6)HSCN between D_2O and $CDCl_3$ in (i) the absence and (ii) the presence of the crown compound. From the ratio of $Me_3CNH_3^+SCN^-$ (6)HSCN to crown in the $CDCl_3$ layer, obtained conveniently from the ^1H n.m.r. spectrum of the $CDCl_3$ layer, the association constant (K_a/l mol^{-1}) for the equilibrium in equation (1) can be determined and the corresponding free energy of complexation can be calculated using equation (2). Where these thermodynamic para-

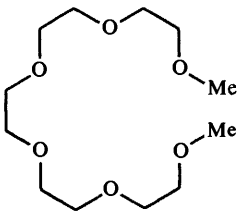
$$Me_3CNH_3^+SCN^- + Crown \underset{CDCl_3}{\overset{K_a}{\rightleftharpoons}} Me_3CNH_3Crown^+SCN^- \qquad (1)$$

[25] M. Newcomb, J. M. Timko, D. M. Walba, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 6392.
[26] S. S. Moore, T. L. Tarnowski, M. Newcomb, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 6398.
[27] J. C. Metcalfe, J. F. Stoddart, and G. Jones, *J. Amer. Chem. Soc.*, 1977, **99**, 8317.
[28] D. A. Laidler and J. F. Stoddart, *Tetrahedron Letters*, 1979, 453.
[29] I. Goldberg, *Acta Cryst.*, 1975, **B31**, 2592.
[30] M. Newcomb, S. S. Moore, and D. J. Cram, *J. Amer. Chem. Soc.*, 1977, **99**, 6405.
[31] J. M. Timko, R. C. Helgeson, M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1974, **96**, 7097.

$$\Delta G = -RT \ln K_a \qquad (2)$$

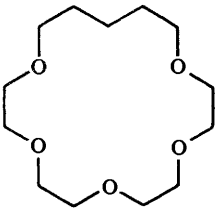
meters are known for complexes cited in this review, they will be quoted in parentheses (K_a; ΔG) underneath the formulae of the appropriate crown ethers.

First of all, let us consider the strengths of the complexes formed between ligands (8) to (*SS*)-(18) and $Me_3CNH_3^+SCN^-$ (6)HSCN in relation to the strong



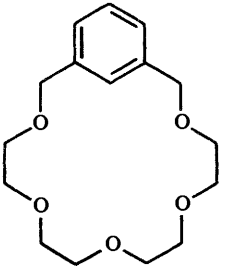
(130; −2.88)

(8)



(1650; −4.38)

(9)



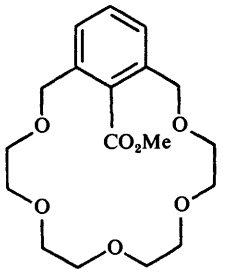
(3300; −4.78)

(10)

complex formed between 18-crown-6 (5) and $Me_3DNH_3^+SCN^-$ (6)HSCN in $CDCl_3$.[21,25,32] In the case of the open-chain analogue (8), the need to have the binding sites already organized to act co-operatively is demonstrated by the factor of $> 10^4$ in the K_a compared with that obtained for the cycle (5). The formal 'removal' of one of the oxygens in (5) by replacing a diethyleneglycol unit in (5) in turn by (i) a pentamethylene unit to give (9), (ii) a *m*-xylyl unit to give (10), and a 2-methoxycarbonyl-*m*-xylyl unit to give (11) also has a drastic effect upon complex strengths and brings about reductions in K_a of the order of $> 10^3$, 10^3, $< 10^2$, respectively. In fact, both the $CH_2 \ldots N^+$ and π-aryl $\ldots N^+$ interactions are believed[21] to be repulsive.[33] The CO_2Me group in (11) provides[30] an additional binding site to stabilize its complex relative to that of (10). The *o*-phenylyl unit in (12) reduces the basicity of the ligand as a result of the delocalization of the aryl oxygen lone pairs into the π-system of the aryl ring and is probably responsible for most of the reduction of *ca.* 5 in its K_a value relative to that for (5). A factor of > 10 in K_a is conceded when a furan-2,5-dimethylyl unit in (13) replaces a diethyleneglycol unit in (5). No doubt this reflects the fact that the furanyl oxygen lone pairs are delocalized into the furanyl ring. Not only is their effect removed when (13) is reduced to give the tetrahydrofuranyl derivative (14) but inspection of molecular models shows that the five-membered ring

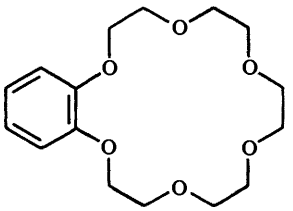
[32] The K_a values quoted[31] for (*S*)-(17) and (*SS*)-(18) have been corrected on the basis of a revised value[21] for the distribution constant for $Me_3CNH_3^+SCN^-$ (6)HSCN between $CDCl_3$ and D_2O. Since they were also measured on 'scale C' they have been 'corrected' (*cf.* ref. 21) by dividing the experimentally determined values by 2.

[33] There is evidence (H. F. Beckford, R. M. King, J. F. Stoddart, and R. F. Newton, *Tetrahedron Letters*, 1978, 171) for an attractive π-aryl $\ldots N^+$ interaction between primary alkylammonium cations and the phenylene ring of diazaparacyclophanes.



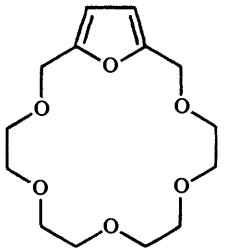
(55 000; −6.50)

(11)



(615 000; −7.88)

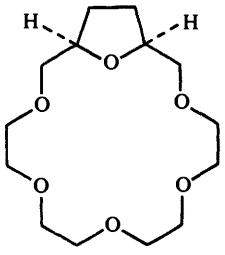
(12)



(209 000; −7.24)

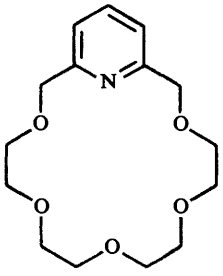
(13)

oxygen is turned in towards the cavity in such a way that the ion–dipole interaction with the positively charged nitrogen can be maximized. Thus, for this reason, at least in part, it is believed that (14) forms a slightly stronger complex than does (5). So does (15) which incorporates a 2,6-pyridinedimethylyl unit in place of a diethyleneglycol unit in (5). In this case, the reason for the slightly better complex probably resides in the ability of the pyridyl nitrogen to form a stronger hydrogen bond to the ammonium hydrogens than to an ether oxygen. In the *sym*-dipyridyl-18-crown-6 (16), only one pyridyl nitrogen can be involved



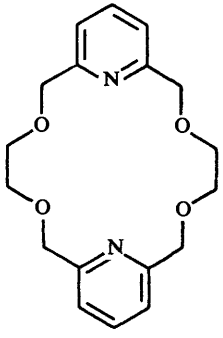
(4 180 000; −9.01)

(14)



(5 800 000; −9.20)

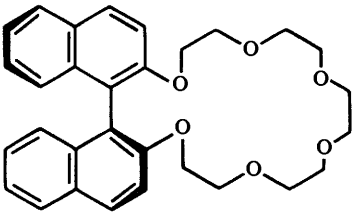
(15)



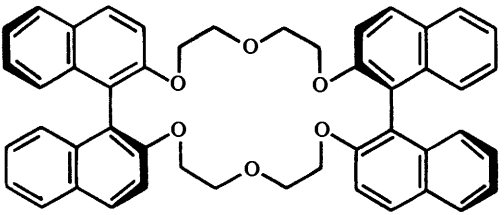
(1 830 000; −8.52)

(16)

in hydrogen bonding within a three-point binding model leaving the other pyridyl nitrogen to fulfil the function of stabilizing electrostatically the positive charge on nitrogen. Since nitrogen is less electronegative than oxygen it will be less efficient at this task and so (16) has a K_a value which is just less than that for (5) and *ca.* one-third smaller than that for (15). The (*S*)-2,2′-binaphthyl-20-crown-6 (*S*)-(17) and the (*SS*)-bisbinaphthyl-22-crown-6 (*SS*)-(18) both form very weak complexes on account of (i) steric interactions between the naph-



(< 1540; > −4.33)
(S)-(17)



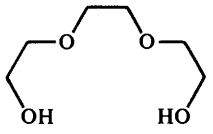
(< 150; > −2.96)
(SS)-(18)

thalene rings and the *t*-butyl group of the cation (6), H^+ and (ii) the reduced basicity of the aryl oxygens as a result of inductive effects and delocalization of their lone pairs into the naphthalene rings. Compounds (*S*)-(17) and (*SS*)-(18) illustrate the use[15–19,34] of the 1,1′-binaphthyl unit as a source of *axial* chirality in optically-active crown ethers.

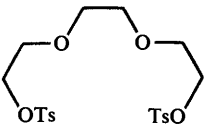
An added advantage of building synthetic receptor molecules around crown ethers is that relatively high yields can be obtained[13,14,20,35–42] in the synthesis of these compounds. Table 1 shows that 18-crown-6 (5) can be synthesized[37–39,41] in 33–93% yields from condensation of triethyleneglycol (19) with its bistosylate (20) in the presence of Me_3COK depending on the nature of the solvent. With less expensive reagents such as (i) triethyleneglycol (19), its dichloride (21), and KOH in aqueous tetrahydrofuran or (ii) tetraethyleneglycol (22) and di-

[34] E. P. Kyba, G. W. Gokel, F. de Jong, K. Koga, L. R. Sousa, M. G. Siegel, L. Kaplan, G. D. Y. Sogah, and D. J. Cram, *J. Org. Chem.*, 1977, **42**, 4173.
[35] C. J. Pedersen, *Org. Synth.*, 1972, **52**, 66.
[36] C. J. Pedersen and H. K. Frensdorff, *Angew. Chem. Internat. Edn.*, 1972, **11**, 16.
[37] J. Dale and P. O. Kristiansen, *J.C.S. Chem. Comm.*, 1971, 670; *Acta Chem. Scand.* 1972, **26**, 1471.
[38] R. N. Greene, *Tetrahedron Letters*, 1972, 1793.
[39] G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, 1974, **39**, 2445.
[40] K. Madan and D. J. Cram, *J.C.S. Chem. Comm.*, 1975, 427.
[41] G. Johns, C. J. Ransom, and C. B. Reese, *Synthesis*, 1976, 515.
[42] D. N. Reinhoudt, R. T. Gray, C. J. Smit, and I. Veenstra, *Tetrahedron*, 1976, **32**, 1161; *Rec. Trav. chim.* 1976, **95**, 258.

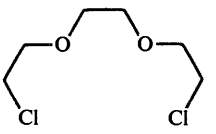
ethyleneglycol dichloride (23) and KOH in anhydrous tetrahydrofuran, yields of



(19)



(20)



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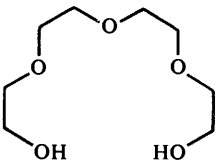
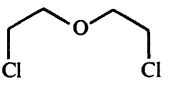


(22)



(23)

Table 1 *High yields in the synthesis of 18-crown-6* (5)

Diol	*Other reactant*	*Base*	*Solvent*	*Yield*/%	*Ref.*
(19)	(20)	Me_3COK	Me_3COH/Benzene	33[d]	37
		Me_3COK	THF[a]	30–60[e]	38
		Me_3COK	DMSO[b]	84[f]	38
		Me_3COK	DME[c]	93[f]	38
(19)	(21)	KOH	THF/H_2O	40–60[g]	39
(22)	(23)	KOH	THF	30[h]	41

[a]Tetrahydrofuran; [b]dimethyl sulphoxide; [c]dimethoxyethane; [d]obtained on heating for 5 hours; [e]reaction carried out at 35 °C; [f]reaction conditions not described; [g]obtained on refluxing and stirring for 18 hours; [h]obtained on refluxing for 18 hours.

30–60% can be achieved. These are remarkably high yields for the formation of an 18-membered ring. One asks, 'why?' The reasons are probably at least two-fold. First of all, there is the so-called *gauche* effect which characterizes the conformations of bismethylenedioxy units in so many different guises[43–52]

[43] C. B. Anderson, D. T. Sepp, M. P. Geiss, and A. A. Roberts, *Chem. and Ind.*, 1968, 1805.
[44] E. L. Eliel and M. K. Kaloustian, *Chem. Comm.*, 1970, 290.
[45] R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, *J. Amer. Chem. Soc.*, 1972, **94**, 1913.
[46] R. G. Snyder and G. Zerbi, *Spectrochim. Acta*, 1967, **23a**, 391.
[47] H. Tadokoro, Y. Chatani, T. Yoshihara, S. Tahara, and S. Murahashi, *Makromol, Chem.*, 1964, **73**, 109.
[48] J. E. Mark and P. J. Flory, *J. Amer. Chem. Soc.*, 1965, **87**, 1415; 1966, **88**, 3702; G. Fourche, *J. Chim. Phys.*, 1969, **66**, 320.
[49] E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1; *Pure Appl. Chem.*, 1971, **25**, 509.
[50] J. F. Stoddart, 'Stereochemistry of Carbohydrates', Wiley-Interscience, New York, 1971, pp. 64—66; N. S. Zefirou, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov, and S. Wolfe, *Tetrahedron*, 1978, **34**, 2953 and references cited therein.
[51] J. Dale, *Tetrahedron*, 1974, **30**, 1683.
[52] J. -P. Desvergne and H. Bouas-Laurent, *J.C.S. Chem. Comm.*, 1978, 403.

(see Figure 2). In systems close to 'home', the conformational free energy of the

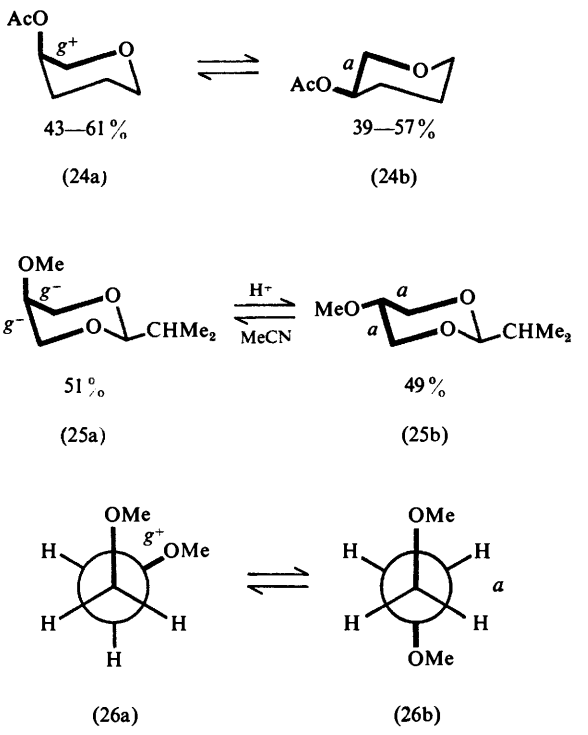
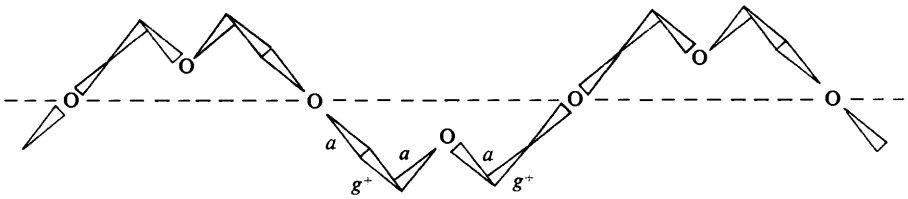


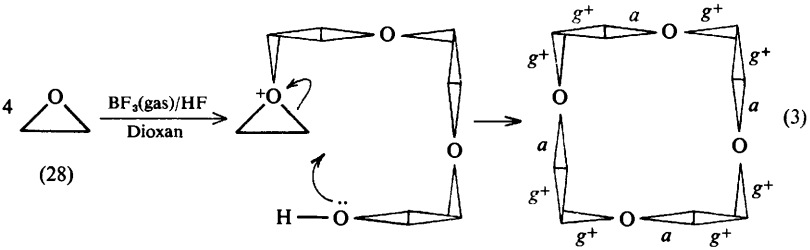
Figure 2 *Some examples of the* gauche *effect.* Gauche *and* anti *conformations about* C—C *bonds are indicated by* g *and* a, *respectively. The helicities of the* gauche *conformations are denoted by plus and minus signs (see later for a definition in absolute terms)*

acetoxy group in 3-acetoxytetrahydropyran (24) lies[43] in the range -0.27 to $+0.17$ kcal mol^{-1} depending on the nature of the solvent and is much smaller than the estimated value of $+0.5$ kcal mol^{-1} based on steric considerations alone. Clearly, an effect of an electronic nature is operating in favour of the axial conformation (24a). A similar kind of solvent dependence is observed[44,45] in the acid-catalysed equilibration of *cis* (25a) and *trans* (25b) 5-methoxy-2-isopropyl-1, 3-dioxans. Almost equal amounts of the two configurational isomers are present[45] in acetonitrile at 25 °C. Infrared spectroscopy indicates[46] that, although 1,2-dimethoxyethane (26) contains both *gauche* (26a) and *anti* (26b) conformations about the C—C bond in the liquid at 25 °C, it adopts only the *gauche* conformation (26a) about the C—C bond in the crystal at -195 °C. Polyoxyethylene (27) has a helical 'all-*gauche*' conformation about the C—C bonds in the crystal,[47] and comparisons between calculated and experimentally-determined physical properties indicate[48] that this is also the preferred conformation



(27)

in solution.[53] Moreover, the propensity during boron-trifluoride catalysed cyclo-oligomerizations of ethylene oxide (28) for macrocycle formation[51,54] to give 12-crown-4[55] in particular is compatible with a helical shape for the growing oligo-oxyethlene chain in (29), equation (3). In the synthetic approaches to 18-crown-6 (5) summarized in Table 1, a template effect[13,20,35–38,40,42,51,54,



(28) (29) (30) (3)

[56,57] involving the K^+ ion probably augments the helicity in the intermediates, *e.g.* (31), by entering into ion–dipole interactions with the oxygens and stabilizing

[53] To our knowledge a top view or bird's eye perspective drawing was used (J. F. Stoddart and W. A. Szarek, *Canad. J. Chem.*, 1968, **46**, 3061) for the first time in 1968 to represent the conformation of di-β-D-ribofuranose 1,5′:1′,5-dianhydride. Subsequently, this mode of representing the conformations of medium-sized and large-sized rings has been adopted (*Acta Chem. Scand.*, 1973, **27**, 1115) and popularized (*Topics Stereochem.*, 1976, 9, 199) by Dale.

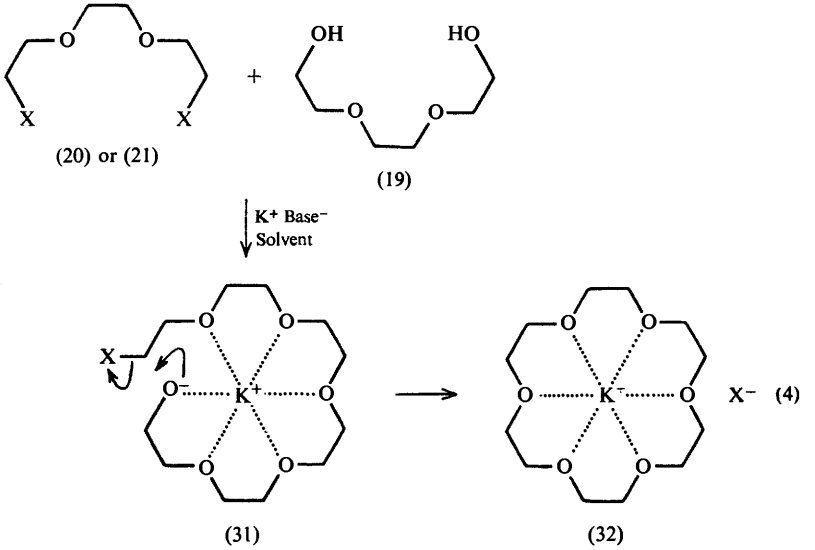
[54] J. Dale, G. Borgen, and K. Daasvatn, *Acta Chem. Scand.*, 1974, **28b**, 378; J. Dale and K. Daasvatn, *J.C.S. Chem. Comm.*, 1976, 295.

[55] Note that 12-crown-4 (30) has a 'square' conformation with all four oxygens directing their lone pairs on to one side of the ring (F.A.L. Anet, J. Krane, J. Dale, K. Daasvatn, and P. O. Kristiansen, *Acta Chem. Scand.*, 1973, **27**, 3395; F. P. van Remoortere and F. P. Boer, *Inorg. Chem.*, 1974, **13**, 2071; F. P. Boer, M. A. Neuman, F. P. van Remoortere, and E. C. Steiner, *ibid.*, p. 2826). Thus, it is hardly surprising that this crown ether complexes reasonably strongly (J. C. Metcalfe, J. F. Stoddart, and G. Jones, unpublished results) with secondary dialkylammonium cations as well as with primary alkylammonium cations (*cf.* ref. 27).

[56] F. L. Cook, T. C. Caruso, M. P. Byrne, C. W. Bower, D. H. Speck, and C. L. Liotta, *Tetrahedron Letters*, 1974, 4029.

[57] L. Mandolini and B. Masci, *J. Amer. Chem. Soc.*, 1977, **99**, 7709.

the 'all-*gauche* OCH_2CH_2O' conformation.[58] This can then be envisaged to undergo fast intramolecular reaction to give the cyclized product, *e.g.* (32) in



equation (4). Thus, the *gauche* effect and the template effect can be considered to operate in unison to enhance the entropy of activation and hence lower the free energy of activation for cyclization.[59] The existence of a template effect is also supported by additional thermodynamic and kinetic evidence insofar as (i) comparative yields[42] in competition experiments and (ii) rates of cyclizations[57] reflect a close correspondence between a catalytic effect and the relative complexing ability of crown ethers towards the cations used in their synthesis. We shall return to this point later. Now that we are armed with some facts, we are ready to pay a visit to dreamland!

3 A Visit to Dreamland

A few years ago, we decided[60] to meet the challenge of building synthetic receptor molecules around the crown ether constitution as the provider of the

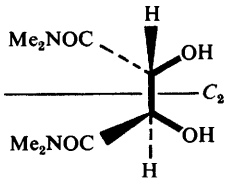
[58] There is evidence that complexes of 18-crown-6 (5) adopt the 'all-*gauche*-OCH_2CH_2O' conformation in solution (D. Live and S. I. Chan, *J. Amer. Chem. Soc.*, 1976, **98**, 3769) as well as in the crystalline state (J. D. Dunitz and P. Seiler, *Acta Cryst.*, 1973, **B29**, 589, J. D. Dunitz, M. Dobler, M. Seiler, and R. P. Phizackerly, *ibid.*, 1974, **B30**, 2733; H. B. Bürgi, J. D. Dunitz, and E. Schefter, *ibid.*, 1974, **B30**, 1517; I. Goldberg, *ibid.*, 1975, **B31**, 754.

[59] It has also been suggested[42] that a decrease in the enthalpy of activation for the reaction contributes to lowering the free energy of activation through ion-pair separation leading to an increase in the nucleophilicity of the alkoxide ion. However, it is difficult to reconcile this suggestion with the intermediate ion-pair (31) in equation 4.

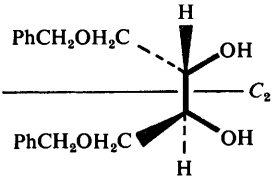
[60] W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Perkin I*, 1977, 1756.

primary binding site for complexation with substituted ammonium cations. However, we had to go out in search of two other basic requirements, namely chirality and functionality. Where better to go in this instance than to carbohydrates? Amongst their many attributes are the following seven: (i) They are rich in substituted bismethylenedioxy units for incorporation into the crown ether constitution. (ii) They are unusually well-endowed with functionality which can be used to build in secondary binding sites as well as catalytic sites. (iii) They are gifted with a high degree of chirality.[61] (iv) They are available in enantiomerically-pure form with known chiroptical properties.[62] (v) They are more often than not conformationally-biased (*i.e.* they are examples of anancomeric systems[63]), a feature which permits the design of both *convergent* and *divergent* side arms. (vi) They are blessed with good ^1H and ^{13}C n.m.r. probes. (vii) They are cheap! This is important.[62] More than any other attribute, it ensures a bright future for carbohydrates in this field of endeavour.

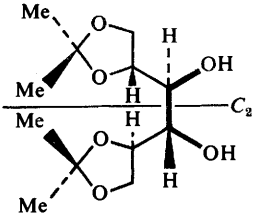
We are now in a position to give these attributes some real expression. Figures 3 and 4 list a number of suitably substituted carbohydrate derivatives which can



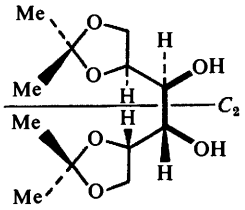
L-(33)



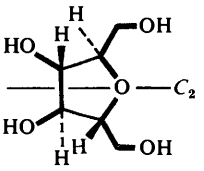
I-(34)



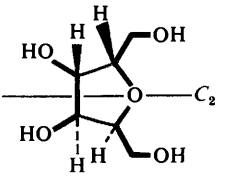
D-(35)



L-(36)



D-(37)



L-(38)

Figure 3 *Selected carbohydrate precursors with C_2 symmetry. 'Chiral ethyleneglycol' and chiral diethyleneglycol' units are represented by thickened bonds*

[61] It is intriguing to reflect on the fact that from a knowledge of *only* the molecular formula ($C_6H_{12}O_6$) of D-glucose, we could put an upper limit of six on the number of possible chiral centres. In fact, five of these are chiral centres in the cyclic forms (pyranose and furanose) of D-glucose! In general terms, the problem is to translate this numerical advantage of carbohydrates into steric and electronic expressions of chirality.

[62] Unfortunately, it must be conceded that more often than not only one enantiomer enjoys attribute (vii).

[63] M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. chim. Belges*, 1966, **75**, 396; M. Anteunis, in 'Conformational Analysis' ed. G. Chiurdoglu, Academic Press, New York, 1971, p. 32.

serve as precursors to chiral crown ethers. Some we have used, some we are using, and some we plan to use. We recognised at the outset that the attractions of selecting carbohydrates with C_2 symmetry are considerable because of the relative ease and efficiency this introduces into the synthesis of symmetrical crown ethers incorporating more than one sugar residue. For example, L-tartaric acid has been incorporated[64] into the 18-crown-6 constitution as its bis-(*NN*-dimethylamide) L-(33). While both tetritols and hexitols have the required constitutional symmetry, only threitol, mannitol, and iditol fulfil the C_2 symmetry requirement.[65] The 1,4-dibenzyl ether L-(34)[60] of L-threitol can be obtained[66] from L-tartaric acid and the 1,2:5,6-di-*O*-isopropylidene derivatives D-(35)[67] and L-(36)[68,69] of D-mannitol and L-iditol are available beginning with D-mannitol and L-sorbose,[70] respectively. Diols L-(34) to L-(36) are all examples of conformationally 'flexible' sources of 'chiral ethyleneglycol' units. D-Glucosamine and D-sorbital are inexpensive starting materials for the syntheses of the 2,5-anhydro derivatives D-(37)[71] and L-(38)[72] of D-mannitol and L-iditol, respectively. These derivatives have potential[73] as sources of 'chiral diethyleneglycol' units as well as 'chiral ethyleneglycol' units. The conformational freedom of both these units is somewhat impaired by their association with a five-membered ring.[74] The restrictions on finding suitable derivatives of asymmetric carbohydrates to employ in the preparation of asymmetric crown ethers is not nearly so great (see Figure 4). D-Mannitol is a potential source of 1-*O*-benzyl-D-glycerlol D-(39)[75–77] containing only one chiral centre and a conformationally 'flexible'

[64] J.-M. Girodeau, J.-M. Lehn, and J.-P. Sauvage, *Angew. Chem. Internat. Edn.*, 1975, **14**, 764; J.-P. Behr, J.-M. Lehn, and P. Vierling, *J.C.S. Chem. Comm.*, 1976, 621.

[65] J. F. Stoddart, in ref. 50, pp. 19–23.

[66] A route involving isopropylidene acetals (see M. Cormack and C. J. Kelley, *J. Org. Chem.*, 1968, **33**, 2171 and P. W. Feit, *J. Med. Chem.*, 1964, **7**, 14) is now preferred (*cf.* N. Ando, Y. Yamamoto, J. Oda, and Y. Inouye, *Synthesis*, 1978, 688) to one involving benzylidene acetals (see E. Ehrlenmeyer, *Biochem. Z.*, 1915, **68**, 351 and ref. 60).

[67] E. Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338; G. Kohan and G. Just, *Synthesis*, 1974, 192.

[68] W. D. Curtis, D. A. Laidler, J. F. Stoddart, J. B. Wolstenholme, and G. H. Jones, *Carbohydrate Res.*, 1977, **57**, C17.

[69] 1,2:5,6-Di-*O*-isopropylidene-D-iditol D-(36) can be prepared (M. A. Bukhari, A. B. Foster, and J. M. Weber, *J. Chem. Soc.*, 1964, 2514) from D-(35).

[70] W. G. M. Jones and L. F. Wiggins, *J. Chem. Soc.*, 1944, 363.

[71] B. C. Bera, A. B. Foster, and M. Stacey, *J. Chem. Soc.*, 1956, 4531.

[72] L. Vargha, *Chem. Ber.*, 1935, **68**, 1377; L. Vargha, T. Puskás, and E. Nagy, *J. Amer. Chem. Soc.*, 1948, **70**, 261; L. F. Wiggins, *Adv. Carbohydrate Chem.*, 1950, **5**, 191.

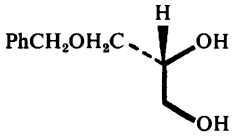
[73] I thank Dr R. A. Wall (University of Edinburgh) for drawing my attention to this fact in a personal communication, April, 1977.

[74] Another C_2 symmetrical diol which has appeal (J. C. Metcalfe and J. F. Stoddart, 1977, unpublished results; A. H. Haines, personal communication, April 1978) as a precursor to chiral crown ethers is 1,4:3,6-dianhydro-D-mannitol (R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 1948, 2204).

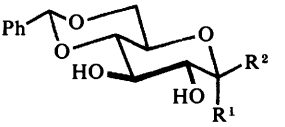
[75] J. C. Sowden and H. O. L. Fischer, *J. Amer. Chem. Soc.*, 1941, **63**, 3244.

[76] 1-*O*-Benzyl-L-glycerol L-(39) can also be obtained (J. Gigg and R. Gigg, *J. Chem. Soc.*, (*C*), 1967, 1865) from D-mannitol.

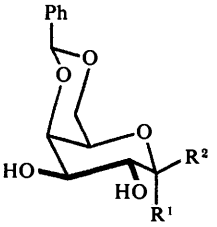
[77] 2,3-*O*-Isopropylidene-D-glycerol (E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, 1939, **128**, 463; E. Baer, 'Biochemical Preparations', ed. E. G. Ball, 1952, Vol. 2, John Wiley, New York, p. 31) has recently been employed in an elegant manner to prepare the 'in–out' isomers of two macrobicyclic polyethers (B. J. Gregory, A. H. Haines, and P. Karntiang, *J.C.S. Chem. Comm.*, 1977, 918).



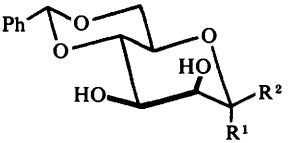
D-(39)



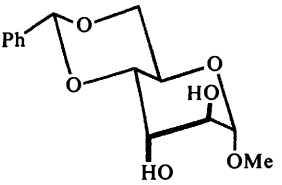
α-D-(40) R^1 = OMe; R^2 = H
β-D-(40) R^1 = H; R^2 = OMe



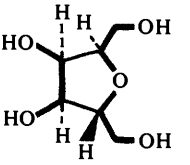
α-D-(41) R^1 = OMe; R^2 = H
β-D-(41) R^1 = H: R^2 = OMe



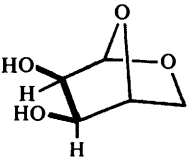
α-D-(42) R^1 = OMe; R^2 = H
β-D-(42) R^1 = H: R^2 = OMe



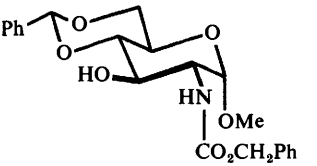
α-D-(43)



D-(44)



D-(45)



α-D-(46)

Figure 4 *Selected asymmetric carbohydrate precursors. 'Chiral ethyleneglycol' and 'chiral diethyleneglycol' units are represented by thickened bonds*

monosubstituted ethyleneglycol unit. Figure 4 also draws attention to the fact that the 4,6-*O*-benzylidene derivatives α-D-(40), β-D-(40), α-D-(41), β-D-(41), α-D-(42), and β-D-(42) of the methyl α- and β-glycosides of D-glucose, D-galac-

tose, and D-mannose are readily available.[78] These derivatives are all sources of conformationally 'rigid' *gauche* 'chiral ethyleneglycol units.' Methyl 4,6-*O*-benzylidene-α-D-altroside α-D-(43) can be obtained[79] from D-glucose and provides a ready source of conformationally 'rigid' *anti* 'chiral ethyleneglycol units.' D-Galactosamine is[80] a precursor of 2,5-anhydro-D-talitol D-(44) and 1,5-anhydro-D-ribose D-(45) can be synthesized[81] from D-ribose. These derivatives provide a ready chiral source of near to eclipsed and formally eclipsed C—O bonds for incorporation into chiral crown ethers. Finally, the benzyloxycarbonyl derivative α-D-(46) of methyl 4,6-*O*-benzylidene-α-D-glucosamine provides[82] a ready entry into chiral aza-crown ethers from D-glucosamine.

Now that the principle is established and the scene is set, let me add a comment on nomenclature. In looking for words to describe our chemistry I could not resist recalling Fischer's famous lock and key metaphor in which he likened an enzyme to a lock and its substrate (in the specific case under consideration, a 'glucoside') to a key. This analogy was drawn in 1894 by Fischer[83] in the statement:

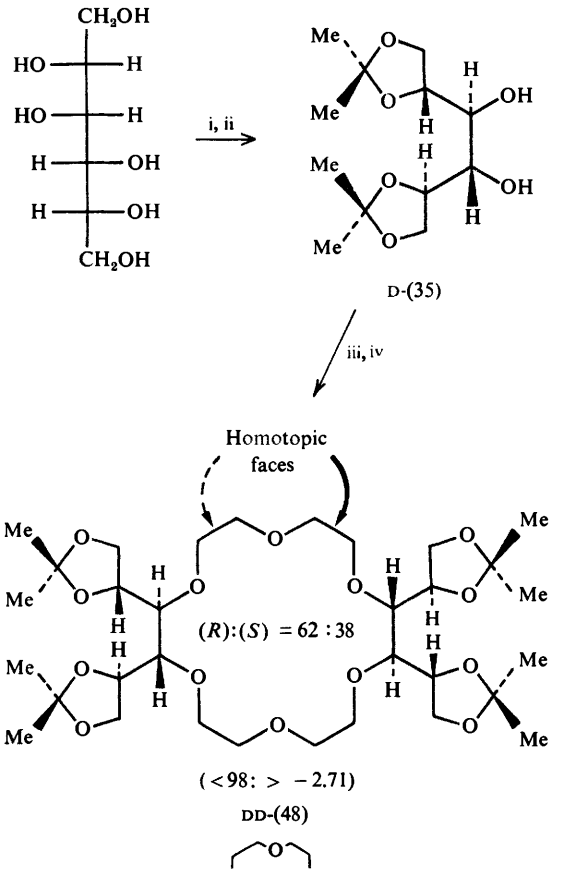
> *Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glucosid wie Schloss und Schlüssel zu einander passen müssen, um eine chemische Wirkung auf einander ausüben zu können.*

In the present context, the lock will refer to the crown ether and the key to the substituted ammonium ion. To my mind, it almost seems appropriate that a *synthetic* host molecule should be likened to an inanimate lock. Fischer must have had vision!

4 Reality

Our first practical ventures[60] were greeted with beginners' luck. The tetra-*O*-isopropylidenedi-D-mannitol 18-crown-6 derivative DD-(48) was obtained[60,84] from D-(35) and diethyleneglycol bistosylate (47) in 24% yield together with the 9-crown-3 and 27-crown-9 homologues by the route outlined in Scheme 1. It was isolated pure as an oil after chromatography on alumina. It solubilizes primary alkylammonium salts in CD_2Cl_2 and the formation of 1:1 complexes were indicated by significant changes in the ^1H n.m.r. spectrum of the lock as well as in the appearance of additional signals for the key. The lock has D_2 symmetry and hence its faces are homotopic. Thus, complexation of achiral or optically pure keys to either face affords identical complexes. On the other hand,

[78] A. N. deBelder, *Adv. Carbohydrate Chem.*, 1965, **20**, 219; *Adv. Carbohydrate Chem. Biochem.*, 1977, **34**, 179.
[79] N. K. Richtmeyer in Methods of Carbohydrate Chemistry, ed. R. L. Whistler and M. L. Wolfram, Vol. 1, Academic Press, New York, 1962, p. 107.
[80] J. Defaye, *Bull. Soc. chim. France*, 1964, 999.
[81] E. Vis and H. G. Fletcher jun., *J. Amer. Chem. Soc.*, 1957, **79**, 1182; T. B. Grindley and W. A. Szarek, *Carbohyd. Res.*, 1972, **25**, 187.
[82] A. B. Foster, M. Stacey, and S. V. Vardheim, *Acta Chem. Scand.*, 1959, **13**, 281.
[83] E. Fischer, *Ber.*, 1894, **27**, 2985.
[84] W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1975, **833**, 835.

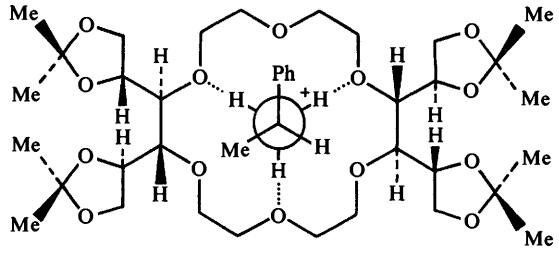


Reagents: i, MeCOMe; ii, $ZnCl_2$; iii, TsO OTs (47); iv, NaH, MeSOMe

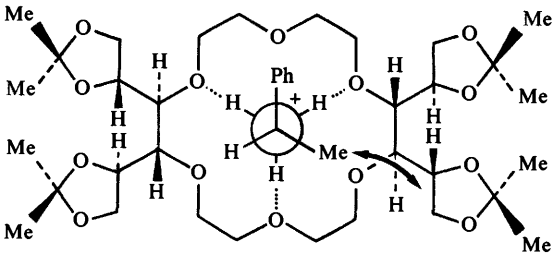
Scheme 1

complexation of enantiomeric keys to either face results in the formation of diastereoisomeric complexes. The big question was would our chiral lock exhibit differentiation under equilibrium conditions towards enantiomeric keys in a racemic salt? After partitioning (*RS*)-α-phenylethylammonium hexafluorophosphate (*RS*)-(49)HPF_6 between D_2O and $CDCl_3$ in the presence of DD-(48), the ^1H and ^{13}C n.m.r. spectra of the $CDCl_3$ layer were recorded. Although we only obtained rather modest chiral recognition lthe (*R*):(*S*) ratio[85] was 62:38] we were excited about the result because it meant our first chiral lock had 'worked'. The broad-band decoupled ^{13}C n.m.r. spectrum (see Figure 5) of the $CDCl_3$ layer provides the best visual representation of the enantiomeric differentiation. The spectrum displayed the expected eight resonances for the

[85] Where enantiomeric differentiations towards (*RS*)-(49)HPF_6 have been determined the (*R*) : (*S*) ratios are quoted inside the formulae of the chiral locks.



DD-(48)–(*R*)–(49)HPF_6



DD-(48)–(*S*)–(49)HPF_6

heterotopic carbons in the lock indicating fast exchange between the lock and the enantiomeric keys on the ^{13}C n.m.r. time scale. The methyl, methine, and quaternary aromatic carbons in the previously enantiomeric keys exhibit chemical shift non-equivalence. Assignments to diastereoisomeric complexes DD-(48)–(*R*)-(49)HPF_6 and DD-(48)–(*S*)-(49)HPF_6 were made on the basis of 'blank' experiments using the pure enantiomeric keys. Assuming three-point binding models for the diastereoisomeric complexes and selecting Newman projections which orient the phenyl groups over a region of the 18-crown-6 cycle free of substituent groups, the methyl group in the key is seen to interact more severely with a 2,2-dimethyl-1,3-dioxolanyl group in DD-(48)–(*S*)-(49)HPF_6 than in DD-(48)–(*R*)-(49)HPF_6. Since DD-(48) forms a very weak complex with $Me_3CNH_3^+SCN^-$(6)HSCN in $CDCl_3$, presumably mainly for steric reasons, we decided to investigate the effect upon chiral recognition of increasing the complexing ability by incorporating nitrogen atoms in the form of pyridyl residues[25,31] and tertiary amine functions[27,33,86] into the lock. In particular, the nitrogen atoms in the latter form stronger hydrogen bonds with $\overset{+}{N}$—H bonds than do oxygen atoms. Accordingly, we prepared[87] the *sym*-dipyridyl DD-(50) and *sym-NN*-dimethyldiaza DD-(51) derivatives of DD-(48) and found that they

[86] S. J. Leigh and I. O. Sutherland, *J.C.S. Chem. Comm.*, 1975, 414; L. C. Hodgkinson, S. J. Leigh, and I. O. Sutherland, *ibid.*, 1976, 639, and 640; M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J.C.S. Perkin I*, 1979, 357 and future parts in this series.

[87] D. A. Laidler and J. F. Stoddart, *J.C.S. Chem. Comm.*, 1976, 979.

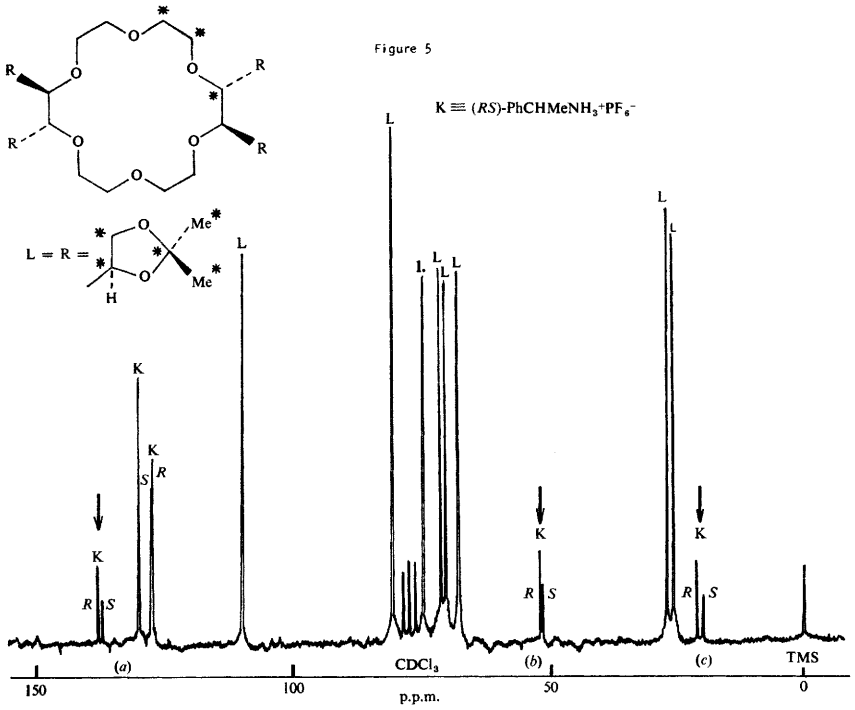
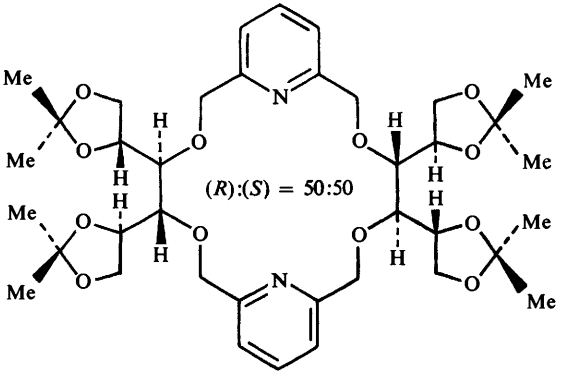


Figure 5 *The broad-band decoupled* ^{13}C *n.m.r. spectrum of the equilibrated complexes* DD-(48)–(*R*)–(49),HPF_6 *and* DD-(48)–(*S*),HPF_6 *in* $CDCl_3$; L *indicates lock and* K *indicates key signals. Key signals are assigned from low field to high as* (*a*) *substituted carbons in the* (*R*) *and* (*S*) *phenyl rings,* meta-*and* para-*carbons in the phenyl rings, and* ortho-*carbons in the* (*S*) *and* (*R*) *phenyl rings*; (*b*) (*R*) *and* (*S*) *methine carbons*; *and* (*c*) (*R*) *and* (*S*) *methyl carbons*

do indeed form appreciably stronger complexes with $Me_3CNH_3^+SCN^-$(6) HSCN in $CDCl_3$ than does DD-(48). However, neither lock showed any chiral recognition towards (*RS*)-$PhCHMeNH_3^+PF_6^-$ (*RS*)-(49)HPF_6 indicating that increasing binding strengths and chiral recognition do not necessarily go hand in hand.[88] This observation was also borne out by experiments on the tetra-*O*-isopropylidenedi-L-iditol-18-crown-6 derivative LL-(52) which is a factor of *ca.* 60 more efficient than DD-(48) at binding $Me_3CNH_3^+SCN^-$ (6)HSCN and does not show any chiral recognition towards (*RS*)-$PhCHMeNH_3^+PF_6^-$ (*RS*)-(49) HPF_6. However, LL-(52) does exhibit[89] enantiomeric differentiation to the extent of 60:40 for (*R*):(*S*) in equilibration experiments with (*RS*)-$PhCHCO_2MeNH_3^+$ ClO_4^-(*RS*)-(53), $HClO_4$. In the face of these apparent contradictions and only limited success on this front, we noted that, in relation to its chiral recognition properties, the lock DD-(48) is on a par with the (*SS*)-binaphthyl-22-crown-6

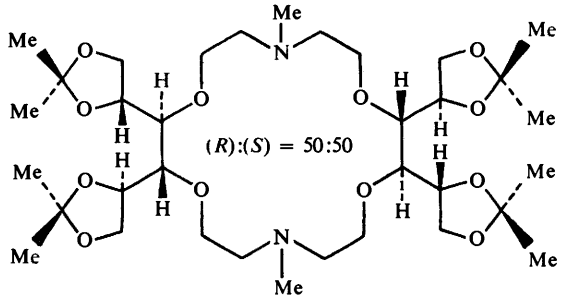
[88] Key-to-lock ratios in excess of 1.0, indicating some 2 : 1 complex formation, are probably partly responsible for this observation.

[89] In contrast, DD-(48) does not show chiral recognition towards (*RS*)-(53),$HClO_4$.



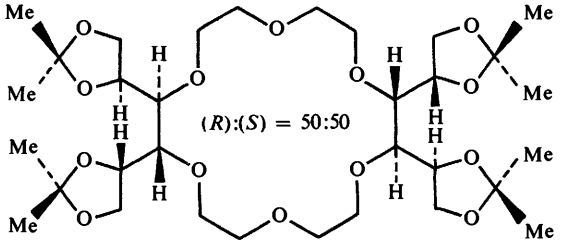
(1500; −4.32)

DD-(50)



(6500; −5.17)

DD-(51)



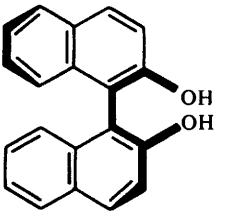
(5500; −5.08)

LL-(52)

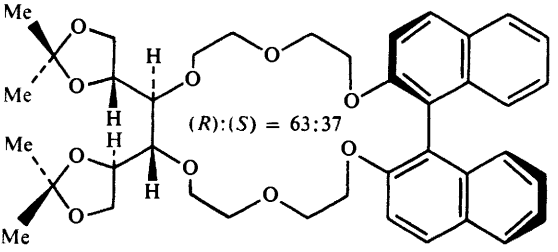
derivative (*SS*)-(18) popularized by Cram.[15–19,90] This led us to forge a link between the approaches developed independently at UCLA and Sheffield by

[90] E. P. Kyba, J. M. Timko, L. J. Kaplan, F. de Jong, G. W. Gokel, and D. J. Cram, *J. Amer. Chem. Soc.*, 1978, **100**, 4555.

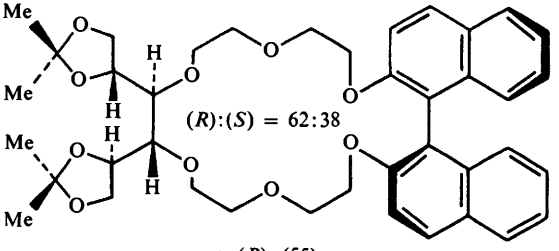
carrying out[91] a 'synthetic resolution' of the 1,1′-binaphthyl unit through incorporation of (*RS*)-2,2′-dihydroxy-1,1′-binaphthyl (*RS*)-(54) and di-*O*-isopropylidene-D-mannitol D-(35) into the synthesis of the diasteroisomeric locks D-(*R*)-(55) and D-(*S*)-(55). The assignments of the absolute configurations to



(*S*)-(54)



D-(*S*)-(55)



D-(*R*)-(55)

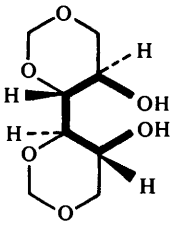
these locks were made on the basis of repeating the synthesis with (*S*)-2,2′-dihydroxy-1,1′-binaphthyl[92] (*S*)-(54) to afford only the D-(*S*)-(55) isomer. In view of the topological similarities between (*SS*)-(18), DD-(48), and D-(*S*)-(55), evident upon inspection of C.P.K. space-filling molecular models, we were not surprised to find the D-(*S*)-(55) isomer exhibited similar chiral recognition characteristics. What did surprise us was the competitive nature of the D-(*R*)-

[91] W. D. Curtis, R. M. King, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1976, 284.

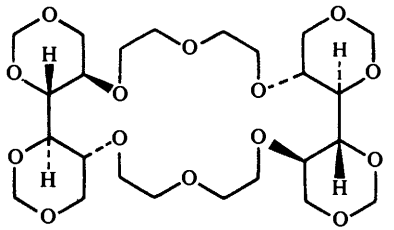
[92] J. Jaques and C. Fouquay, *Tetrahedron Letters*, 1971, 4617.

(55) isomer[93] as a chiral recognizer. But then, surprises abound in this field!

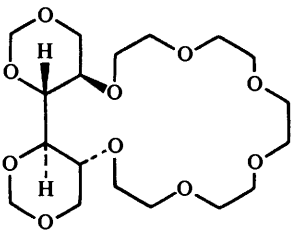
It was now clear to us that a much wider survey of carbohydrate derived locks was called for if we were to gain some real understanding in this area of lock and key chemistry. We decided at this stage to turn our attention to the incorporation[28] of 1,3:4,6-di-*O*-methylene-D-mannitol D-(56), which is readily accessible[94] from D-mannitol, into 22-crown-6 DD-(57) and 20-crown-6 D-(58)



D-(56)



DD-(57)



D-(58)

derivatives. Examination of C.P.K. space-filling molecular models indicates that they are not too different topologically from the corresponding (*RR*)-bisbinaphthyl-22-crown-6 (*RR*)-(18) and (*R*)-2,2′-binaphthyl-20-crown-6 (*R*)-(17) derivatives, respectively. Although the 22-crown-6 derivative DD-(57) forms exceedingly weak complexes with substituted ammonium salts in $CDCl_3$, the 20-crown-6 derivative D-(58) binds reasonably well with the thiocyanate and/or perchlorate salts derived from $MeNH_2$ (7), Me_2CHNH_2 (59), Me_3CNH_2 (6), $PhCH_2NH_2$ (60), (*R*)- and (*S*)-$PhCHMeNH_2$ (*R*)- and (*S*)-(49), (*S*)-$PhCHCO_2MeNH_2$ (*S*)-(53), and (*R*)- and (*S*)-$PhCH_2CHCO_2MeNH_2$ (*R*)- and (*S*)-(61). The association constant for 1:1 complex formation with $Me_3CNH_3^+SCN^-$ (6)HSCN in $CDCl_3$ is 520. By this time we had acquired at Sheffield a superconducting ^1H n.m.r. spectrometer operating at 220 MHz and so we were in a good position to study the kinetics of the complexation–decomplexation processes of locks with

[93] The D-(*R*)-(55) isomer could be considered to be topologically similar to the achiral (*RS*)-bisbinaphthyl-22-crown-6 (*RS*)-(18).

[94] W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 67; R. Allerton and H. G. Fletcher, jun., *ibid.*, 1954, **76**, 1957.

a range of keys by variable temperature ^1H n.m.r. spectroscopy.[95] The lock DD-(58) has C_2 symmetry and so the faces are homotopic. Figure 6 illustrates in

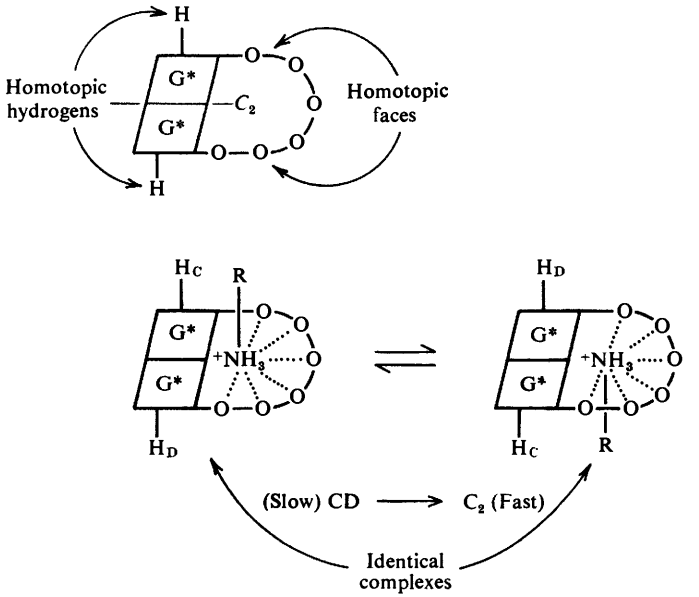


Figure 6 *The degenerate equilibration process of keys between the homotopic faces of C_2 symmetrical locks*

general terms the kind of degenerate equilibration process of keys between homotopic faces that can be studied by dynamic ^1H n.m.r. spectroscosy in locks with C_2 symmetry. Homotopic protons (H) in such locks become heterotopic (H_C and H_D) when 1:1 complexes with keys are formed. Furthermore, when dissociation of the key from the lock becomes slow on the ^1H n.m.r. time scale, anisochronous behaviour of the heterotopic protons can be observed on account of a site exchange process involving H_C and H_D. The ^1H n.m.r. spectra reproduced in Figure 7 demonstrate the power of this technique for investigating (i) the thermodynamics of complexation–decomplexation processes and (ii) the structures of complexes. Figure 7*a* shows the spectrum of the pure lock D-(58) in CD_2Cl_2 at +30 °C. The AB system can be assigned to the dioxymethylene protons, the A portion arising from the equatorial protons and the B portion from the axial protons.[96] The other assignments were made on the basis of homonuclear INDOR spectroscopy. Small chemical shift changes occur (see Figure 7*b*) in the signals for the lock when 1 molar equivalent of $PhCH_2NH_3^+$

[95] G. Binsch, *Topics Stereochem.*, 1968, **3**, 97: I. O. Sutherland, *Annual Reports NMR Spectroscopy*, 1971, **4**, 71; S. F. Lincoln, *Prog. Reaction Kinetics*, 1977 **9**, 1.

[96] R. U. Lemieux and J. Howard, *Canad. J. Chem.*, 1963, **41**, 393; T. B. Grindley, J. F. Stoddart, and W. A. Szarek, *J. Chem. Soc.*, (*B*), 1969, 172.

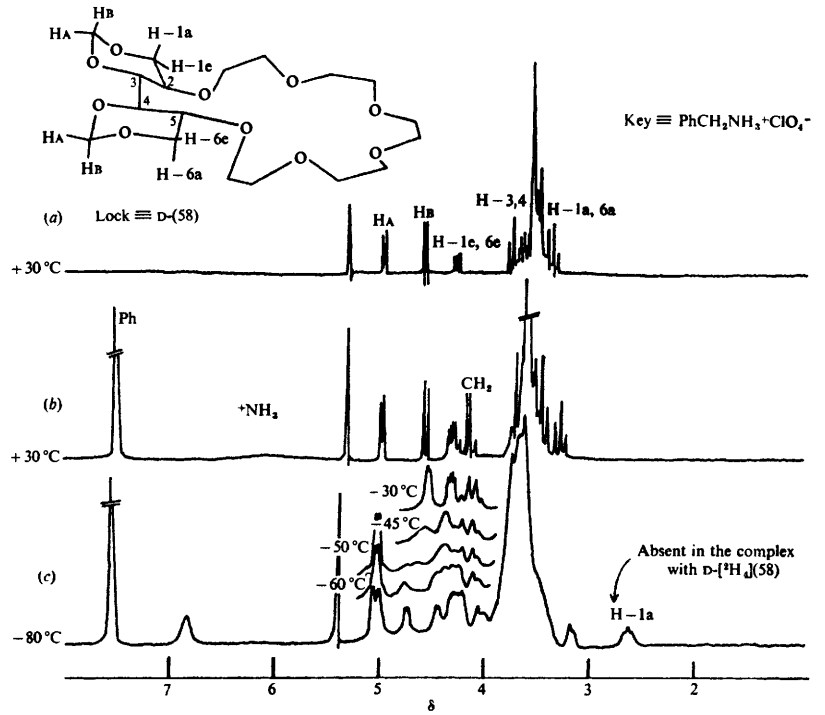


Figure 7 *The* ^{1}H *n.m.r. spectrum recorded at* 220 MHz *of lock* D-(58) *in* CD_2Cl_2. *The temperature dependent* ^{1}H *n.m.r. spectra—(b) and (c)—of the* 1:1 *complex formed with* (60)$HClO_4$

ClO_4^- (60)$HClO_4$ is added. Additional signals, of course, appear in the spectrum and they can be attributed to protons in the key. Most significant is the observation that the previously enantiotopic benzylic methylene protons in (60)$HClO_4$ become diastereotopic (in the chiral environment) as exhibited by their appearance as an AB system. This kind of observation gives one confidence that a molecular complex has been formed in solution. On lowering the temperature of the CD_2Cl_2 solution, line broadening occurs[97] in all regions of the spectrum, a phenomenon characteristic of the kind of equilibration and site exchange processes described in Figure 6. The line shape behaviour of the AB system for the dioxymethylene protons is most informative (see Figure 7*c*). The B part becomes very broad, goes through a coalescence temperature at $-55\,°C$, and eventually divides out into two signals of equal intensity separated by 64 Hz at $-80\,°C$. The A part behaves similarly with a lower coalescence temperature of $-65\,°C$ and a smaller chemical shift difference of 18 Hz at $-80\,°C$. Since the 20-membered ring in the lock D-(58) cannot ring-invert, the free energies

[97] A 'blank' experiment on D-(58) uncomplexed did not reveal any temperature dependence of the ^{1}H n.m.r. spectrum recorded in CD_2Cl_2.

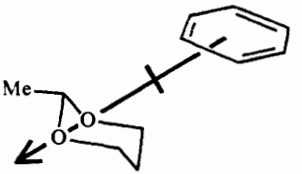
of activation (both 10.5 kcal mol^{-1}) calculated at the coalescence temperatures for both these spectral changes can be associated with the free energy of activation ($\Delta G^{\ddagger}_{d}$) for dissociation of the complex. The $\Delta G^{\ddagger}_{d}$ values for all the 1:1 complexes investigated are listed in Table 2. If we assume that the transition

Table 2 *The free energies of dissociation* ($\Delta G^{\ddagger}_{d}$ *for the* 1:1 *complexes formed between* RNH_3^+ *keys and the lock* D-(58)

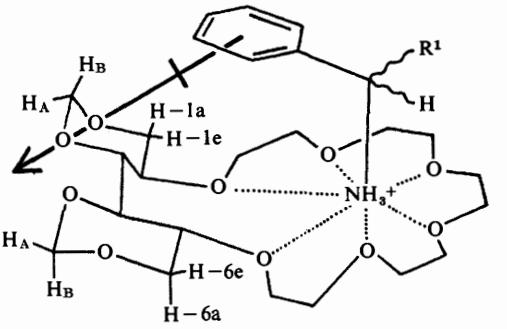
	$\Delta G^{\ddagger}_{d}$/kcal mol^{-1}	
Key	SCN^-	ClO_4^-
$MeNH_3^+$ (7)H^+	<8.2	<8.2
$Me_2CHNH_3^+$ (59)H^+	8.9	9.7
$Me_3CNH_3^+$ (6)H^+	<8.2	9.2
$PhCH_2NH_3^+$ (60)H^+	8.8	10.5
(*R*)-$PhCHMeNH_3^+$ (*R*)-(49)H^+	<9.3	—
(*S*)-$PhCHMeNH_3^+$ (*S*)-(49)H^+	<8.8	10.2
(*R*)-$PhCHCO_2MeNH_3^+$ (*R*)-(53)H^+	9.3	—
(*R*)-$PhCH_2CHCO_2MeNH_3^+$ (*R*)-(61)H^+	—	9.9
(*S*)-$PhCH_2CHCO_2MeNH_3^+$ (*S*)-(61)H^+	—	10.4

statefree energies in the complexation–decomplexation processes are characteristic of the locks more so than of the keys, then the values for $\Delta G^{\ddagger}_{d}$ will reflect the relative binding energies for different keys. On this basis, we may draw the following conclusions: (i) The $MeNH_3^+X^-$ (7)HX salts form the least stable complexes of all with D-(58), probably on account of the relative accessibility of their cation for ion pairing with the anion when the substituent on N^+ is small. (ii) Complexes involving the ClO_4^- ion are stronger than those involving the SCN^- ion. 'Destructuring' of complexes by the SCN^- ion through its ability to hydrogen bond with the cation is probably responsible (*cf.* refs. 27, 33, and 86) for this effect. (iii) The difference of 500 cal mol^{-1} in the $\Delta G^{\ddagger}_{d}$ values for the diastereoisomeric complexes D-(58)–(*R*)-(61)$HClO_4$ and D-(58)–(*S*)-(61)$HClO_4$ suggests that D-(58) is showing a small amount of chiral recognition towards (*RS*)-$PhCH_2CHCO_2MeNH_3^+ClO_4^-$ (*RS*)-(61)$HClO_4$ at low temperatures. (iv) Those complexes involving cations which contain phenyl groups are *ca.* 1 kcal mol^{-1} stronger than those without phenyl groups in the cations. This observation suggested to us that a secondary binding site is present within the complex. Recalling the weak 1:1 complexes (*e.g.* 62) formed[98] between benzene

[98] J. E. Anderson, *Tetrahedron Letters*, 1965, 4713; R. C. Cookson, T. A. Crabb, and S. Vary, *Tetrahedron*, 1968, **24**, 4559; K. D. Carlson, C. R. Smith, jun., and I. A. Wolff, *Carbohydrate Res.*, 1970, **13**, 403. It is interesting to note that comparison (R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kalonstian, *J. Amer. Chem. Soc.*, 1972, **93**, 1913) of calculated and experimental solvent effects in conformational equilibria of 5-heterosubstituted 1,3-dioxans indicates that benzene behaves as an "anomalous" solvent. I thank Professor Ernest L. Eliel for drawing my attention to this fact. The so-called "benzene effect" is now widely recognised (N. S. Zefirov, V. V. Samoshin, O. A. Subbotin, V. I. Baranenkov, and S. Wolfe, *Tetrahedron*, 1978, **34**, 2953).

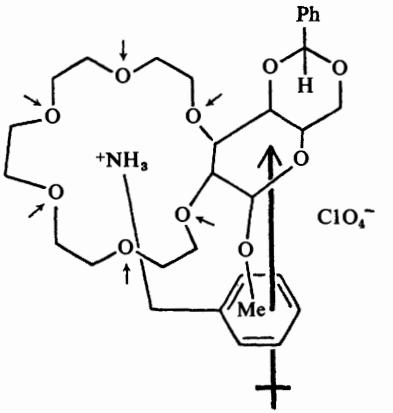


(62)

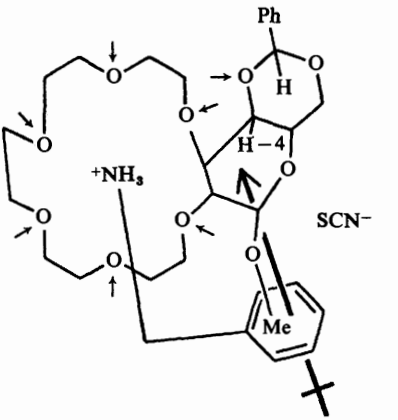


D-(58)–$PhCHR^1NH_3^+$

and variously substituted 1,3-dioxans in CCl_4, we examined C.P.K. space-filling molecular models of the complexes between D-(58) and a generalized substituted ammonium ion of the type $PhCHR^1NH_3^+$ (R^1 = H, Me, or Ph). Sure enough, it is possible for the phenyl group in such a cationic key, assuming a three-point binding model, to orient itself above one of the 1,3-dioxan rings in the lock so that it meets the directional requirements for a dipole-induced dipole interaction as shown in the complex D-(58)–$PhCHR^1NH_3^+$. Two observations in the low temperature ^1H n.m.r. spectra leave us feeling very confident about this structural proposal for the complex. First of all, the chemical shift differences for H_B are larger (44—64 Hz) for the complexes D-(58)–(*S*)-(49)$HClO_4$, D-(58)–(60) HSCN, and D-(58)–(60)$HClO_4$, which contain a phenyl group than they are (15—22 Hz) for the complexes D-(58)–(59)HSCN, D-(58)–(59)$HClO_4$, and D-(58)–(6)$HClO_4$, where the substituent groups on the ammonium cation are Me_2CH and Me_3C. It is clear from the low temperature spectra that the phenyl



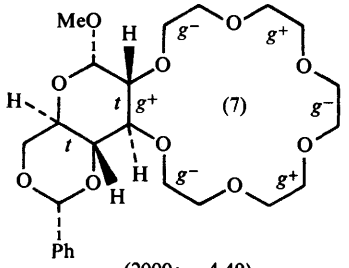
β-D-(63)–(60) $HClO_4$



β-D-(65)–α-(60) HSCN

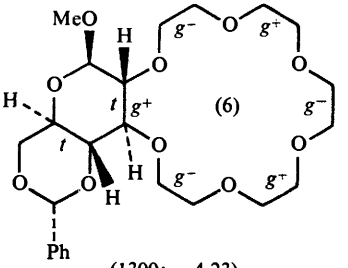
group is shielding preferentially one of the axial protons H_B in these complexes listed above. Even more intriguing is the emergence at high field (δ 2.50—3.00) of a signal which integrates for *one* proton in the low temperature spectra of the complexes D-(58)–(49)$HClO_4$, D-(58)–(*R*)-(53)$HClO_4$, and D-(58)–(60)$HClO_4$ but not in the corresponding thiocyanate complexes. Next we carried out a deuteriation study to clinch the argument. The tetradeuterio-20-crown-6 derivative D-[$^2H_4$](58) was prepared from D-[1,1,6,6-$^2H_4$]mannitol[99] and the low temperature spectrum of the complex D-[$^2H_4$](58)–(60)$HClO_4$ was recorded (see Figure 7*c*). The high field signal which integrated previously for *one* proton was absent. Thus, it can be assigned to H-1a which falls under the shielding influence of the phenyl group in the complex D-(58)–$PhCHR^1NH_3^+$. It is significant that the above chemical shift effects are absent in the less highly structured thiocyanate complexes and also in the $PhCH_2CHCO_2MeNH_3^+ClO_4^-$ complexes, D-(58)–(*R*)-(61)$HClO_4$ and D-(58)–(*S*)-(61)$HClO_4$, which contain an 'extra' methylene group.

The demonstration of the power of dynamic ^1H n.m.r. spectroscopy to probe the structures of complexes in solution, and to provide a rapid semi-quantitative assessment of the relative strengths of complexes in relation to particular locks leads logically into a discussion of our chiral asymmetric locks. To date, our



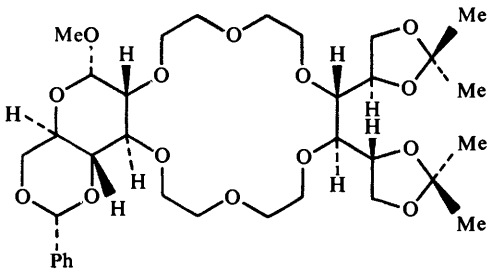
(2000; −4.49)

α-D-(63)



(1300; −4.23)

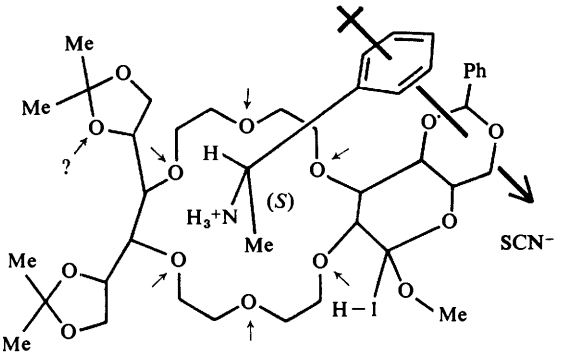
β-D-(63)



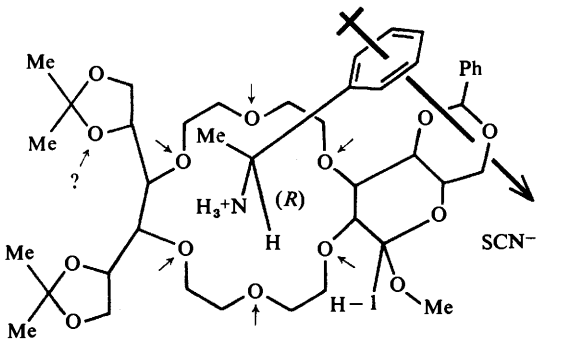
(640; −3.81)

α-DD-(64)

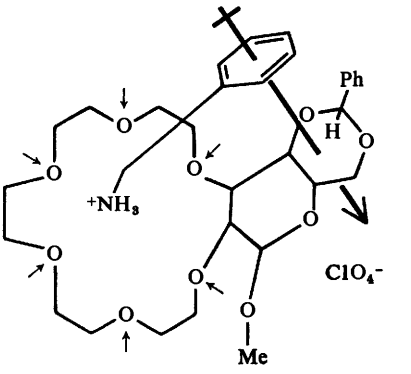
[99] J. F. Stoddart and W. A. Szarek, *J. Chem. Soc.*, (*B*), 1971, 437.



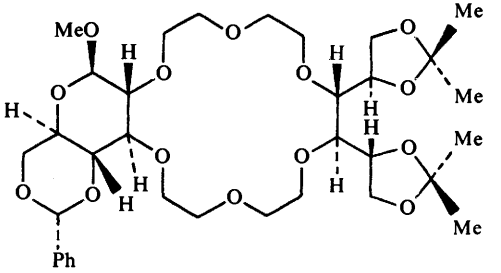
α-DD-(64)–β-(*S*)-(49)HSCN



α-DD-(64)–β-(*R*)-(49)HSCN

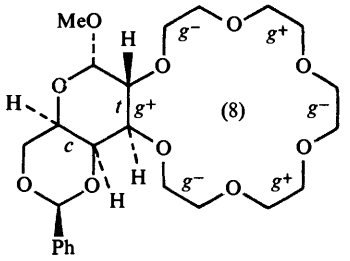


β-D-(63)–β-(60)$HClO_4$



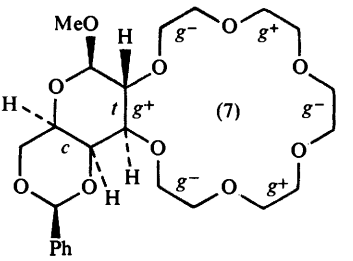
(1000; −4.08)

β-DD-(64)



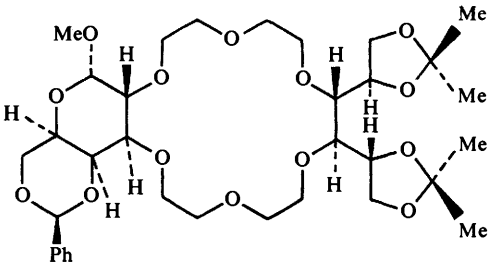
(201 000; −7.21)

α-D-(65)



(5800; −5.11)

β-D-(65)



(7800; −5.29)

α-DD-(66)

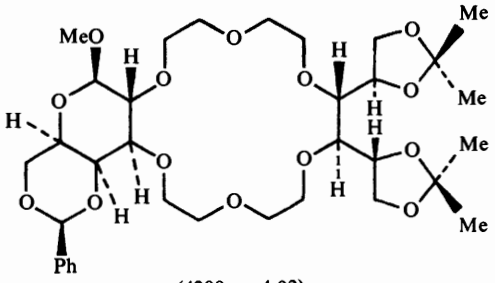
efforts[100–102] have been confined largely to a detailed investigation of the locks α-D-(63) to α-D-(69) incorporating the 4,6-*O*-benzylidene derivatives of methyl α- and β-D-glucosides, methyl α- and β-D-galactosides, methyl α-D-mannoside, and methyl α-D-altroside.[103] Before we examine the complexing ability of these two

[100] D. A. Laidler and J. F. Stoddart, *Carbohydrate Res.*, 1977, **55**, C1; *J.C.S. Chem. Comm.*, 1977, 481.

[101] R. B. Pettman and J. F. Stoddart, *Tetrahedron Letters*, 1979, 457.

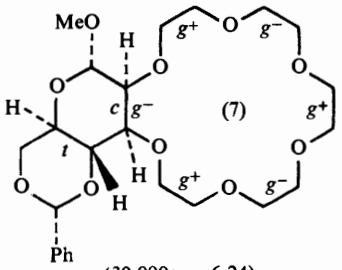
[102] R. B. Pettman and J. F. Stoddart, *Tetrahedron Letters*, 1979, 461.

[103] The locks α- and β-DD-(64), α- and β-DD-(66), and α-DD-(68) also comprise a 1,2:5,6-di-*O*-isopropylidene-D-mannitol D-(35) residue.



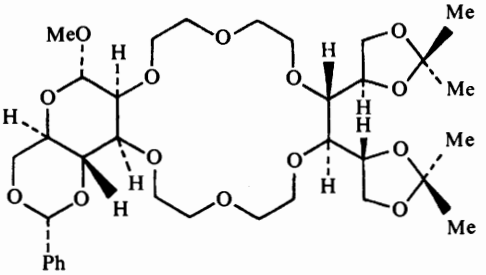
(4200; −4.92)

β-DD-(66)



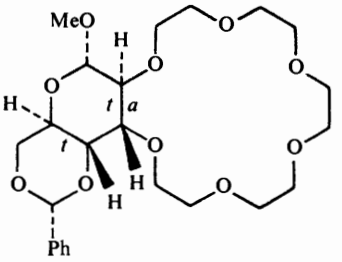
(39 000; − 6.24)

α-D-(67)



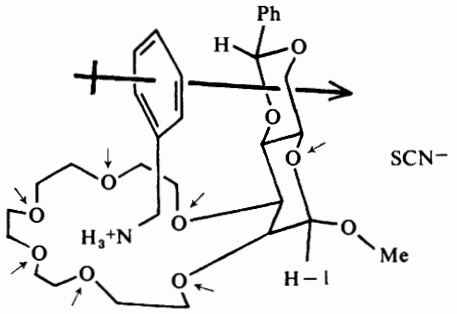
(1300; −4.23)

α-DD-(68)



(< 50; > −2.31)

α-D-(69)



α-D-(67)–β-(60) HSCN

classes (*i.e.* α and β) of diasteroisomerically related 18-crown-6 derivatives, let us consider how we prepared[104] them by reference to one example, that of the α-D-galactoside-D-mannitol-18-crown-6 α-DD-(66) shown in Scheme 2. Treatment of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside α-D-(41) with an excess of allyl bromide and potassium hydroxide in toluene gave the diallyl ether of α-D-(41) in good yield. Ozonolysis of the diallyl ether in methanol, followed by borohydride reduction afforded the 'half-crown' diol α-D-(70). 1,2:5,6-Di-*O*-isopropylidene-D-mannitol D-(35) was also converted into its diallyl ether, which was subjected to ozonolysis followed by reduction with borohydride to give the 'half-crown' diol of D-(35). Conversion of the 'half-crown' diol into the 'half-crown' ditosylate D-(71) was followed by condensation of equimolar proportions of α-D-(70) with D-(71) to afford the α-D-galactoside-D-mannitol-18-crown-6 derivative α-DD-(66) in 29% yield.[105] The compound is crystalline and optically active. Two points regarding the stereochemistry of this class of chiral asymmetric locks can be made by reference to α-DD-(66): (i) It has heterotopic faces. In keeping with established carbohydrate nomenclature, I shall refer to the 'bottom' face as being the α-face and the 'top' face as being the β-face. (ii) The 18-membered ring is 'rigid' as a result of its *trans* fusion to an anancomeric system. I shall adopt the 'dot and circle' notation introduced earlier to identify 'up' and 'down' oxygen atoms, respectively. In addition, the torsional angles associated with the carbon—carbon bonds will be denoted [see α- and β-D-(63), α- and β-D-(65), α-D-(67), and β-D-(69)] as *g* and *a* for *gauche* and *anti*, respectively. In accordance with the convention employed by Dale[51,106] the helicity of the *gauche* bonds will be described (see Figure 8) as g^+ if they are clockwise and g^- if they are anticlockwise.[107]

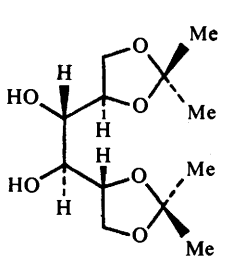
Let us now return to a comparison of the association constants for complex formation of α-D-(63) to α-D-(69) with $Me_3CNH_3^+SCN^-$ (6)HSCN in $CDCl_3$. Two features in relation to the K_a values did not surprise us. They are: (i) The decrease in the strengths of the complexes which arise from disubstitution of α-D-(63), β-D-(63), α-D-(65), β-D-(65), and β-D-(67) with bulky 2,2-dimethyl-1,3-dioxolanyl groups affording α-DD-(64), β-DD-(64), α-DD-(66), β-DD-(66), and α-DD-(68) in turn. This trend is to be expected on steric grounds. (ii) The very weak complexes formed by α-D-(69). This was also to be expected since introduction of one *anti* carbon—carbon bond into an 18-crown-6-derivative removes the opportunity for six oxygens to act co-operatively in binding substituted ammonium ions. However, another two features in relation to the K_a

[104] The asymmetric locks α-DD-(64) and α-DD-(68) were prepared in analogous fashion. The asymmetric locks α-D-(63), β-D-(63), α-D-(65), β-D-(65), α-D-(67), and α-D-(69) have been prepared by (i) condensing the methyl 4,6-*O*-benzylidene-D-glycosides with Ts $(OCH_2CH_2)_5OTs$ and (ii) condensing the derived 'half-crown' diols, *e.g.* D-(71). with Ts$(OCH_2CH_2)_3OTs$.

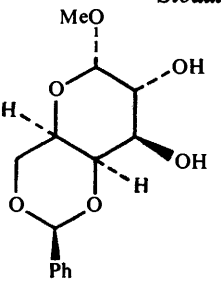
[105] The C_2 symmetry of the 'half-crown' ditosylate ensures that only *one* 18-crown-6 derivative. *i.e.* α-DD-(66), can be formed in this condensation.

[106] J. Dale, *Pure Appl. Chem.* 1971, **25**, 469; *Acta Chem. Scand.*, 1973, **27**, 1115; *Topics Stereochem.*, 1976, **9**, 199.

[107] IUPAC have recommended (*Pure Appl. Chem.*, 1976, **45**, 13) that g^+ be replaced by (*P*) (for plus) and g^- be replaced by (*M*) (for minus).



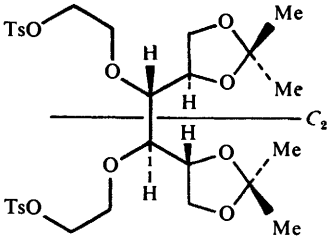
D-(35)



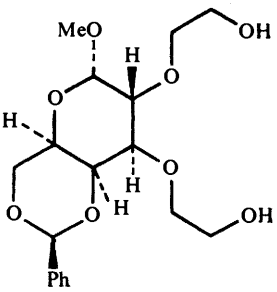
α-D-(41)

i, ii, iii, iv

i, ii, iii



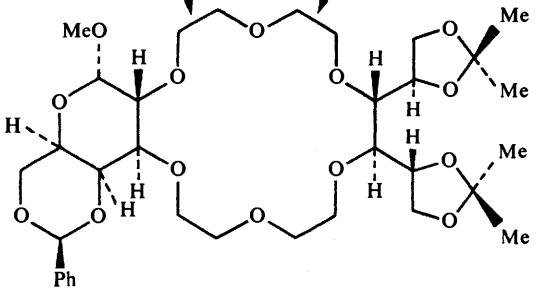
D-(71)



α-D-(70)

v

Heterotopic faces



m.p. 55—58°C
$[\alpha]_D$ + 90°($CHCl_3$)

α-DD-(66)

Reagents: i, $CH_2{=}CHCH_2Br$, KOH, toluene; ii. O_3, MeOH; iii, $NaBH_4$, MeOH; iv, TsCl, pyridine; v, NaH, MeSOMe

Scheme 2

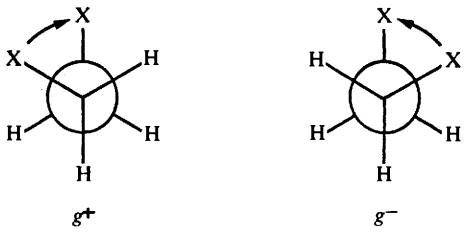


Figure 8 *The designation of absolute conformation in* gauche *1,2-disubstituted ethanes*

values were surprising. They were: (i) All the glucoside, galactoside, and mannoside crowns form much weaker complexes with $Me_3CNH_3^+SCN^-$ than does 18-crown-6 (5) (K_a, 3 000 000) itself. A discussion of this important and highly significant observation will be deferred until later. (ii) Despite the fact that in the galactoside and mannoside crowns one of the faces is more sterically hindered,—this is obvious on examination of CPK space-filling molecular models—they form much stronger complexes than the glucoside crowns. The clue to the reasons for these unexpected observations came from an investigation (see Figures 9 and 10) of the chemical shift dependences in the ^1H n.m.r. spectrum of H-1, H-4, and PhCH in the galactoside portion of α-D-(65) and H-1 and PhCH in the glucoside portion of α-DD-(64) on stepwise additions of $Me_3CNH_3^+SCN^-$ (6), HSCN. In all cases, the chemical shifts of these protons attain their limiting values at a 1:1 molar ratio of lock-to-key providing evidence for 1:1 complex formation. However, the relative magnitudes of the downfield shifts are also important. First of all, we notice in Figure 9 that H-1, H-4, and PhCH all experience substantial downfield shifts indicating that O-1 and O-4 are participating along with the crown ether oxygens in hydrogen bonding and/or ion–dipole electrostatic stabilization with the ammonium hydrogens of the $Me_3CNH_3^+$ (6), H^+ ions in two distorted face-to-face complexes. Indeed, inspection of CPK space-filling molecular models shows that the axial orientations of the carbon—oxygen bonds at C-1 and C-4 render both O-1 and O-4 available to participate in the weak non-covalent bonds to the cations in these complexes. Secondly, we notice (*cf.* Figures 9 and 10) that the downfield shifts for H-1 and PhCH are smaller for α-DD-(64) than for α-D-(65). This indicates that although O-1 is probably participating in complex stabilization in α-DD-(64), it is not doing so to the same extent as it does in α-D-(65). The influence on the chemical shift of the PhCH proton is, as expected, very slight since the equatorial orientation of the carbon—oxygen bond at C-4 in α-DD-(64) denies it the opportunity to co-operate with the crown ether oxygens in weak bonding to the cation. In a rather *qualitative* manner, the potential number of oxygens which are available as binding sites for the $Me_3CNH_3^+$ (6)H^+ ion can be correlated with the relative strengths of the complexes formed between the locks α-D-(63), β-D-(63), α-D-(65), β-D-(65), and α-D-(67) and the cationic key. We display in parentheses inside these locks the *potential* number of total binding sites that can be utilized in complex formation and we indicate by means

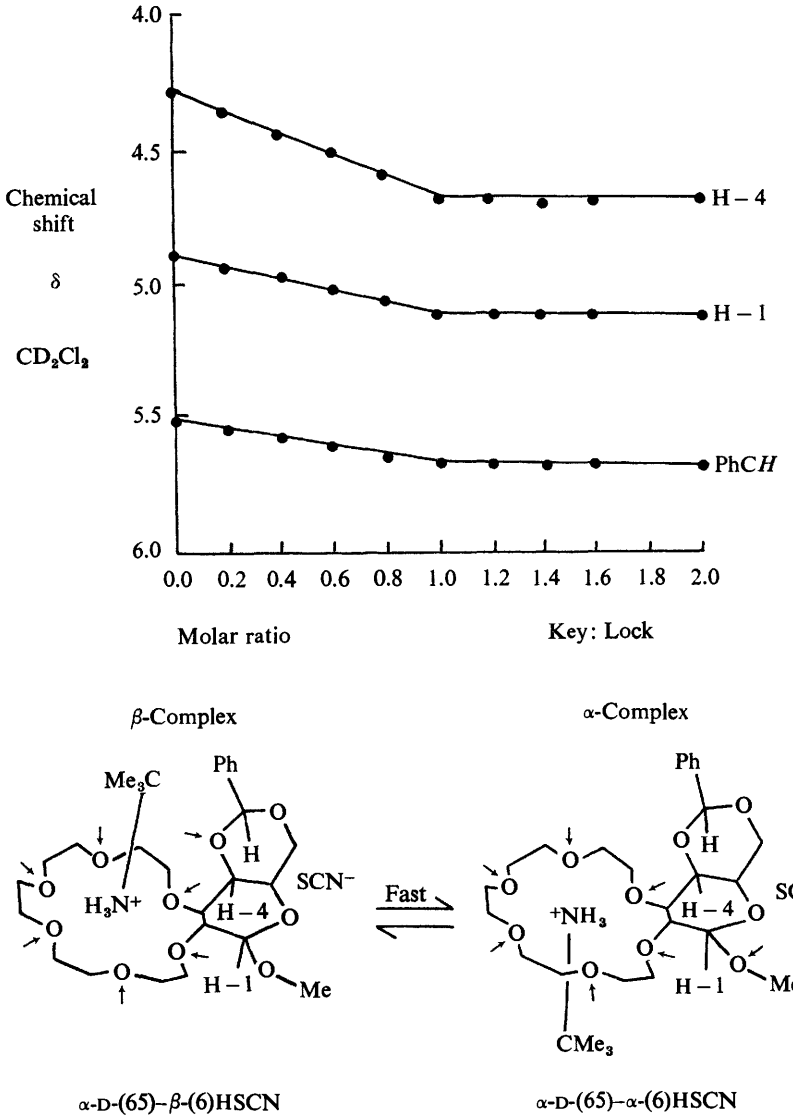


Figure 9 *Change in chemical shifts of the indicated protons with change in key:lock ratio. Oxygen atoms believed to be involved in hydrogen bonding and/or electrostatic stabilization with the ammonium hydrogens of the* $Me_3CNH_3^+$ *ions in the anisometric complexes* α-D-(65)–β-(6)HSCN *and* α-D-(65)–α-(6)HSCN *are indicated by means of arrows*(→)

of arrows (→) those oxygens which can serve as binding sites assuming that a minimum of two crown ether oxygens are always utilized in a three-point binding array. A problem in nomenclature now arises. Although the equilibra-

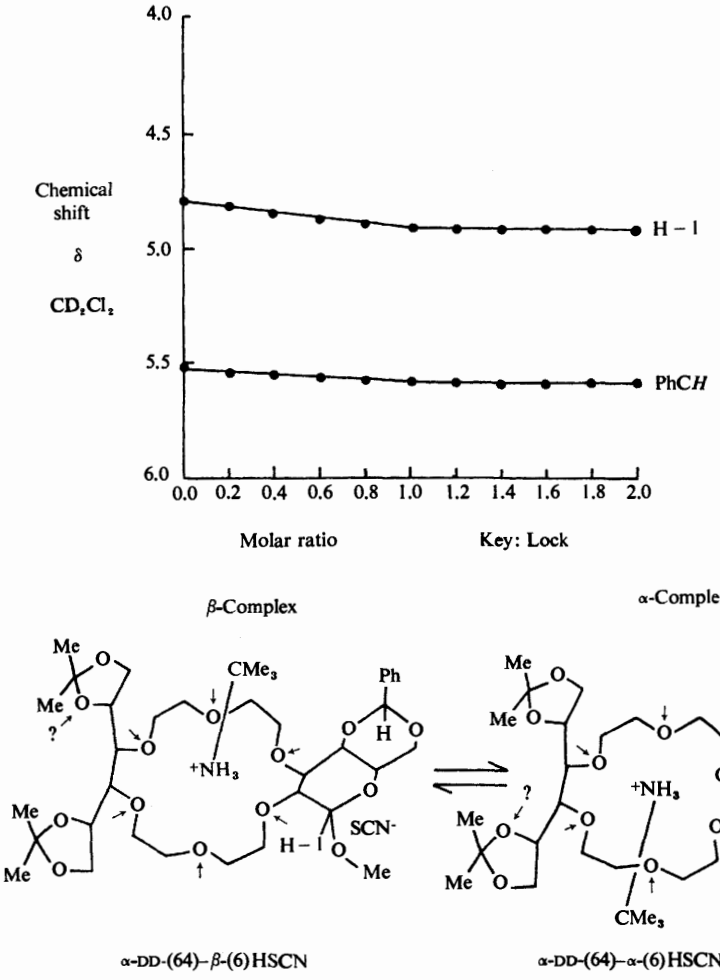


Figure 10 *Change in chemical shifts of the indicated protons with change in key:lock ratio. Oxygen atoms believed to be involved in hydrogen bonding and/or electrostatic stabilization with the ammonium hydrogens of the* $Me_3CNH_3^+$ *ions in the anisometric complexes* α-DD-(64)–β-(6)HSCN *and* α-DD-(64)–α-(6)HSCN *are indicated by means of arrows* (→)

tion between α- and β-complexes[108] on the ^1H n.m.r. time scale is fast (see Figures 9 and 10), they have now been identified (see above) as being 'different' in their weak non-covalent bond connectivity as well as in their stereochemistry. In anticipation of being able to identify α- and β-complexes in the low temperature ^1H n.m.r. spectra (see below) of 1 : 1 complexes in CD_2Cl_2, we have decided to adopt the classification of pairwise relations between isomeric structures

[108] In relation to these chiral asymmetric locks, we shall refer to complexes involving the α- and β-faces as α- and β-complexes, respectively.

proposed recently by Mislow.[109] Hence, we shall refer to a pair of α- and β-complexes as being *anisometric* in recognition of the fact that they may display the characteristics of *constitutional* isomerism as well as being distinguishable in a *stereochemical* sense. Thus, locks α-D-(63) to α-D-(69) all have heterotopic faces and can form anisometric α- and β-complexes [*cf.* α-D-(65)–α-(6)HSCN and α-D-(65)–β-(6)HSCN in Figure 9 and α-DD-(64)–α-(6)HSCN and α-DD-(64)–β-(6)HSCN in Figure 10] with both achiral and chiral keys.

Figure 11 illustrates in general terms the kind of equilibration process of keys

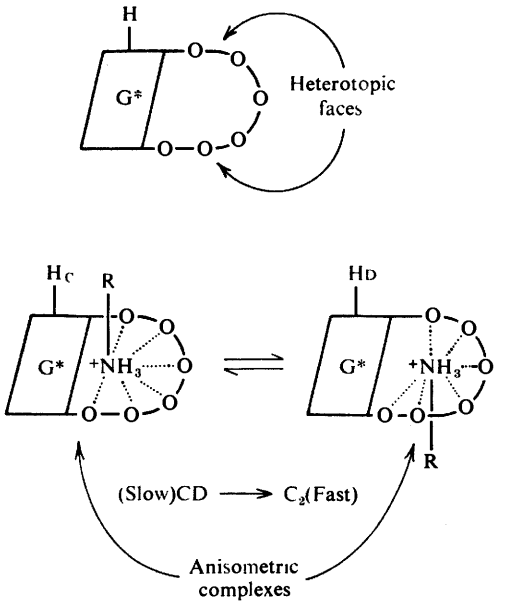


Figure 11 *The equilibration process of keys between the heterotopic faces of chiral asymmetric locks*

between heterotopic faces that can be studied by dynamic ^1H n.m.r. spectroscopy in chiral asymmetric locks. All protons in asymmetric locks are heterotopic. Hopefully, a suitable candidate (H), preferably one which resonates as a singlet and is chemically shifted from the others, emerges as a suitable ^1H n.m.r. probe for studying the equilibration between the α- and β-complexes by giving rise to anisochronous signals in the low temperature spectra attributable to say H_C and H_D in the anisometric complexes. Since the α- and β-complexes can have different free energies of complexation, the ratios of the signals at low temperature in the ^1H n.m.r. spectra will reflect the relative stabilities of the anisometric complexes. Moreover, the temperature dependent spectra resulting from the

[109] K. Mislow, *Bull. Soc. chim. Belges*, 1977, **86**, 595; J. Reisse, R. Ottinger, P. Bickart, and K. Mislow, *J. Amer. Chem. Soc.*, 1978, **100**, 911.

site exchange process involving H_C and H_D in equally or unequally populated sites can be subjected to line shape analysis[95] to give activation parameters for the equilibrium between the anisometric complexes. The spectra reproduced in Figures 12 and 14—17 serve to illustrate the mine of information that can be un-

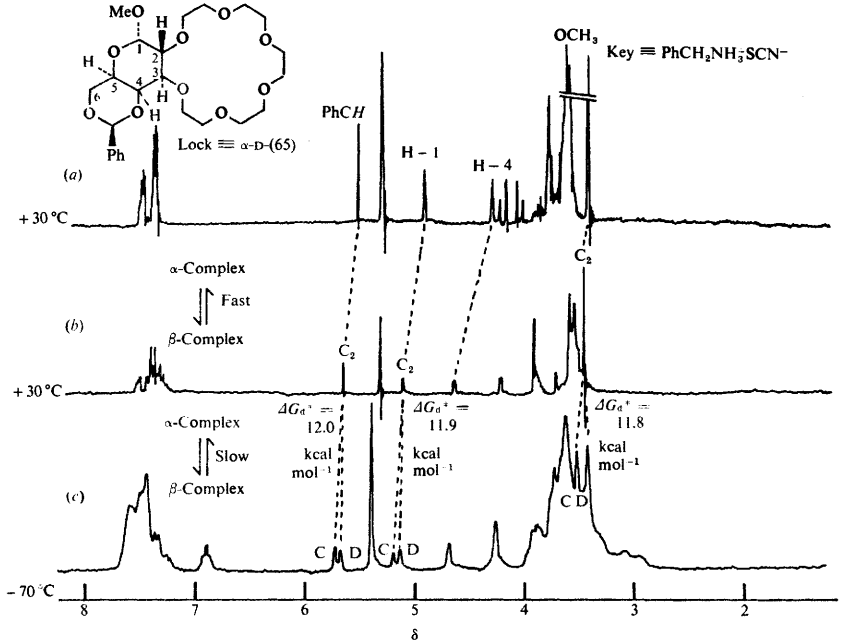


Figure 12 *The* ^{1}H *n.m.r. spectrum* (220 MHz) *of lock* α-D-(65) *in* CD_2Cl_2. *The temperature dependent* ^{1}H *n.m.r. spectra*—(b) *and* (*c*)—*of the* 1:1 *complex formed with* (60)HSCN

covered using this technique. Figure 12*a* shows the ^{1}H n.m.r. spectrum of the pure lock α-D-(65) in CD_2Cl_2 at +30 °C. The assignment of peaks to the PhC*H*, H-1, H-4, and OCH_3 protons can be made unambiguously and demonstrates the enormous potential of carbohydrate derivatives to provide good ^{1}H n.m.r. probes. In addition to the appearance of additional signals for the key, dramatic chemical shift changes occur (Figure 12*b*) in the resonances for the lock when 1 molar equivalent of $PhCH_2NH_3^+SCN^-$ (60)HSCN is added. As indicated previously (see Figure 9), the PhC*H*, H-1, and H-4 protons witness marked downfield shifts which signify the involvement of O-1 and O-4 in the weak non-covalent bonding pattern within the α- and β-complexes. On lowering the temperature of the CD_2Cl_2 solution, line broadening occurs in all regions of the spectrum and the behaviour of the signals for the PhC*H*, H-1, and OCH_3 protons is particularly interesting. In all cases the signals separate out into two signals at −70 °C in the ratio of 55:45 and the free energies of activation (12.0, 11.9, and 11.8 kcal mol^{-1}) calculated at the coalescence temperatures are in exellent agreement with each other (see Figure 12*c*). Let me now make some

general points by summarizing in Table 3 all the results we have obtained to date on our chiral asymmetric locks. Since the 18-membered ring in locks α-D-(63) to α-D-(69) cannot ring-invert, the free energies of activation, calculated

Table 3 *The complex ratios at low temperatures in* CD_2Cl_2 *and the free energies of dissociation* ($\Delta G^{\ddagger}_{d}$ *for the* 1 : 1 *complexes formed between* $RNH_3^+X^-$ *salts and the chiral asymmetric locks* α-D-(63) *to* α-D-(69)

Lock	$RNH_3^+X^-$	R	*Complex ratio*(T/°C)	$\Delta G^{\ddagger}_{d}$(kcal mol^{-1})
			Major : *Minor*	*Major*→*Minor*
α-D-(63)	(60)HSCN	CH_2Ph	67 : 33 (−70)	11.6
	(*S*)-(49)HSCN	CHMePh	72 : 28 (−75)	11.8
β-D-(63)	(60)HSCN	CH_2Ph	78 : 22 (−90)	10.2
	(60)$HClO_4$	CH_2Ph	68 : 32 (−90)	10.6
	(*R*)-(49)HSCN	CHMePh	76 : 24 (−100)	10.3
	(*S*)-(49)HSCN	CHMePh	68 : 32 (−80)	9.7
	(*S*)-(49)$HClO_4$	CHMePh	76 : 24 (−90)	10.2
α-DD-(64)	(60)HSCN	CH_2Ph	75 : 25 (−70)	12.2
	(*R*)-(49)HSCN	CHMePh	72 : 28 (−70)	11.6
	(*S*)-(49)HSCN	CHMePh	>97 : <3 (−60)	*ca.* 12.1
β-DD-(64)	(60)HSCN	CH_2Ph	86 : 14 (−90)	10.8
	(*S*)-(49)HSCN	CHMePh	72 : 28 (−90)	10.6
α-D-(65)	(6)HSCN	CMe_3	55 : 45 (−90)	10.2
	(60)HSCN	CH_2Ph	55 : 45 (−90)	11.9
	(*S*)-(49)HSCN	CHMePh	60 : 40 (−70)	11.9
β-D-(65)	(6)HSCN	CMe_3	76 : 24 (−100)	10.0
	(60)HSCN	CH_2Ph	78 : 22 (−90)	12.0
	(60)$HClO_4$	CH_2Ph	78 : 22 (−70)	10.8
	(*R*)-(49)HSCN	CHMePh	70 : 30 (−90)	10.5
	(*S*)-(49)HSCN	CHMePh	87 : 13 (−80)	11.7
	(*S*)-(49)$HClO_4$	CHMePh	73 : 27 (−90)	10.6
α-DD-(66)	(60)HSCN	CH_2Ph	50 : 50 (−90)	11.5
	(*S*)-(49)HSCN	CHMePh	50 : 50 (−90)	11.5
α-D-(67)	(60)HSCN	CH_2Ph	74 : 26 (−75)	11.1
	(60)$HClO_4$	CH_2Ph	74 : 26 (−60)	13.0
	(*R*)-(49)HSCN	CHMePh	82 : 18 (−80)	11.2
	(*S*)-(49)HSCN	CHMePh	82 : 18 (−90)	11.2
α-DD-(68)	(6)HSCN	CMe_3	88 : 12 (−95)	10.3
	(60)HSCN	CH_2Ph	93 : 7 (−55)	14.0
	(60)$HClO_4$	CH_2Ph	84 : 16 (−45)	14.0
	(*R*)-(49)HSCN	CHMePh	90 : 10 (−80)	11.5
	(*S*)-(49)HSCN	CHMePh	84 : 16 (−80)	12.2
α-D-(69)	(6)HSCN	CMe_3	50 : 50 (−108)	8.3

(i) at the coalescence temperatures in the case of α-D-(65), α-DD-(66), and α-D-(69) and (ii) by line shape analysis at selected temperatures in the case of all the other locks, can be equated with the free energies of activation ($\Delta G^{\ddagger}_{d}$) for dissociation of the anisometric complexes. Figure 13 portrays an energy profile

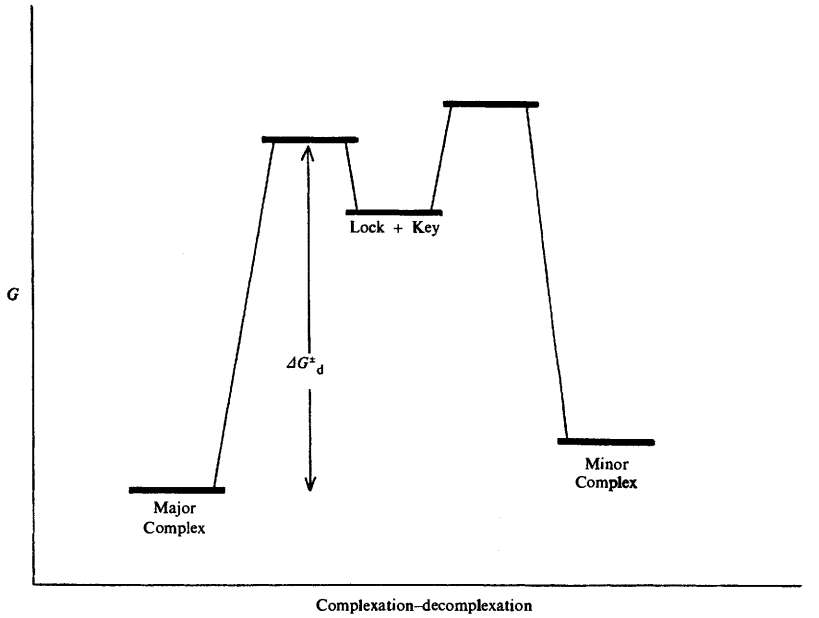


Figure 13 *The free energy profile diagram for equilibration of anisometric complexes*

diagram which illustrates the general situation. The $\Delta G^{\ddagger}_{d}$ values, which are listed in Table 3 are those relating to dissociation of the major anisometric complex where inequalities in complex populations are observed. The Table also records the ratios of the anisometric complexes formed at low temperatures in CD_2Cl_2. The following general observations can be made: (i) The temperature dependences of both the lock and key signals in the ^1H n.m.r. spectra are interpretable in terms of equilibrations between *two*, and *only* two, anisometric complexes. At this stage, the most reasonable explanation of our results is that these are the α- and β-complexes. This means that there is no evidence with this range of locks for other than rapid reorganisation of the non-covalent bonding pattern within each of the anisometric complexes on the ^1H n.m.r. time scale at temperatures down to −110 °C. This realisation prompts us to use the analogy that the key is spinning in the lock! (ii) As indicated in Figure 13, dissociation of the complexes is the slow rate determining step in the complexation–decomplexation process. In those cases—that is α-D-(65), β-D-(65), α-DD-(68), and α-D-(69)—where we have values for the free energies of complexation of $Me_3CNH_3^+SCN^-$

(6)HSCN in $CDCl_3$ comparisons with the $\Delta G^{\ddagger}_d$ values obtained in CD_2Cl_2 lead us to the conclusion that the free energies of activation ($\Delta G^{\ddagger}_a$) for association lie in the range of 3—6 kcal mol^{-1}. This implies that the rate of association, although fast is short of being a diffusion controlled process as observed[110] for 18-crown-6 (5) and $Me_3CNH_3^+SCN^-$ (6)HSCN. In the wake of these general observations we can return to the consideration of some more specific points. In contrast with the α-galactoside locks α-D-(65) and α-DD-(66), the α-glucoside locks α-D-(63) and α-DD-(64) bind all the keys examined stereoselectively (2:1, or better) to one of their heterotopic faces.

Figure 14 records the now familiar sequence of experiments—namely, the

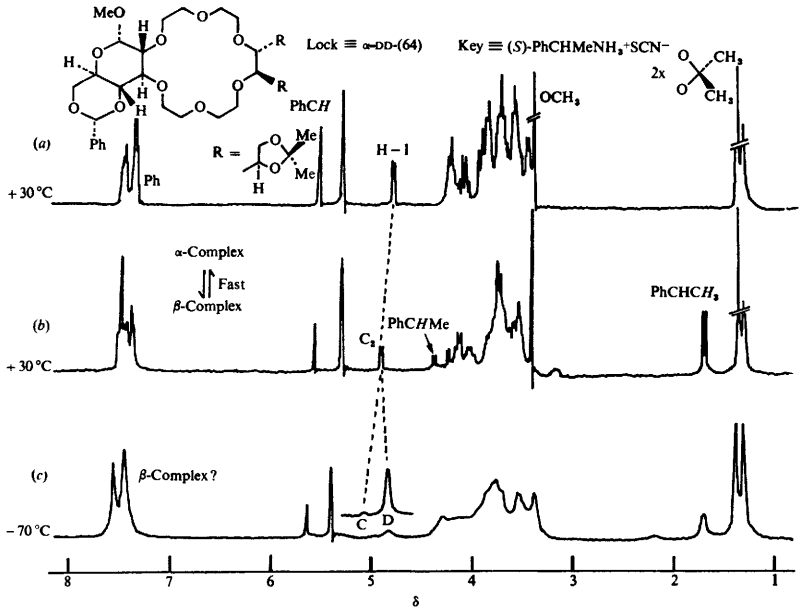


Figure 14 *The* ^{1}H *n.m.r. spectrum* (220 MHz) *of lock* α-DD-(64) *in* CD_2Cl_2. *The temperature dependent* ^{1}H *n.m.r. spectra—(b) and (c)—of the* 1:1 *complex formed with* (*S*)-(49)HSCN

^{1}H n.m.r. spectrum (Figure 14*a*) of the pure lock α-DD-(64) and the temperature dependent ^{1}H n.m.r. spectra (Figure 14*b* and *c*) of the 1:1 complex α-DD-(64)–(*S*)-(49)HSCN formed between α-DD-(64) and (*S*)-$PhCHMeNH_3^+SCN^-$ (*S*)-(49)HSCN in CD_2Cl_2 solution. However, on this occasion there is strong evidence that one of the anisometric complexes is being formed with high stereoselectivity (>97 : <3) at −70 °C. We believe that complexation occurs preferentially at the β-face because of the close similarities in the chemical shifts of the signals for H-1 in α-DD-(64) (δ 4.79) and for the major peak (δ 4.83) arising from H-1 in the complex at −70 °C. This observation suggests that O-1 is not involved in complexing in the major anisometric complex. However, the

[110] F. de Jong, D. N. Reinhoudt, and R. Huis, *Tetrahedron Letters*, 1977, 3987.

appearance of a minor peak (δ 5.08) at much lower field suggests that O-1 is involved in complexing in the minor anisometric complex. Inspection of CPK space-filling molecular models has led us to ascribe the high stereoselectivity of binding to the β-face to a dipole-induced dipole interaction[98] between the 2-phenyl-1,3-dioxan ring in α-DD-(64) and the phenyl group in (*S*)-PhCHMeNH$_3^+$ SCN$^-$ (*S*)-(49)HSCN. Support for this proposal comes from the observation that when we replace (*S*)-PhCHMeNH$_3^+$SCN$^-$ (*S*)-(49)HSCN in the α-DD-(64)–β-(*S*)-(49)HSCN, complex with (*R*)-PhCHMeNH$_3^+$SCN$^-$ (*R*)-(49)HSCN, the stereoselectivity of binding to the β-face is reduced to 72 : 28 in accordance with the steric interaction in the α-DD-(64)–β-(*R*)-(49),HSCN complex of the methyl group in the cationic key with the 2,2-dimethyldioxolanyl group in the lock.

We conclude that the major complex in all cases (see Table 3) involving the α-glucoside locks α-D-(63) and α-DD-(64) is the β-complex. For the most part,[111] the same conclusion has been reached on the basis of a similar argument for the α-mannoside locks α-D-(67) and α-DD-(68), which also form 1 : 1 complexes at +30 °C with selected SCN$^-$ and ClO_4^- salts derived from Me_3CNH_2 (6), $PhCH_2NH_2$ (60), and (*R*)- and (*S*)-PhCHMeNH$_2$ (*R*)- and (*S*)-(49), as indicated by the significant changes in the ^{1}H n.m.r. spectra of the locks. The signals for the H-1 protons are shifted downfield (0.23—0.28 p.p.m.) on 1 : 1 complex formation. Much smaller downfield shifts (0.03—0.07 p.p.m.) are observed for the OMe protons and significant upfield shifts (up to 0.11 p.p.m.) are experienced by the PhC*H* protons. These results indicate that the pyranosidic ring oxygens in α-D-(67) and α-DD-(68) participate along with the six crown oxygens in complex formation.

The ^{1}H n.m.r. spectrum (Figure 15*a*) of the pure lock α-D-(67) and the temperature dependent ^{1}H n.m.r. spectra (Figure 15*b* and *c*) of the 1 : 1 complex α-D-(67)–(60)HSCN serve to illustrate the more general case. At −75 °C the signals for the PhC*H* proton appear (Figure 15*c*) as a higher intensity singlet at high field and a lower intensity singlet at low field while the signal for the anomeric proton is seen to have separated into a higher intensity low field signal and a lower intensity high field signal. These observations suggest that the major complex is associated with the β-face of α-D-(67). Support for this hypothesis comes from inspection of CPK space-filling molecular models which reveal that the phenyl ring in the α-D-(67)–β-(60),HSCN complex can enter into a stabilizing dipole-induced dipole interaction[98] with the 4,6-*O*-benzylidene ring. This introduces the PhC*H* proton into the shielding zone of the phenyl ring. Thus, we can account for the *upfield* shift of this proton at +30 °C (see Figure 15*b*) as well as the emergence (see Figure 15*c*) at −75 °C of the higher intensity singlet for the major β-complex at δ 5.54.

So far in the α-series of locks we have considered the complexing ability of (i) anancomerically *trans*-fused 18-crown-6 locks in which the *gauche* crown oxygens at the ring junctions are diequatorial with respect to the pyranosidic

[111] Although, in the case of the α-DD-(68)–(6)HSCN complex, an unambiguous assignment of major and minor complexes to α- and β-complexes is not possible, we tend to favour associating the major complex with the α-face for steric reasons.

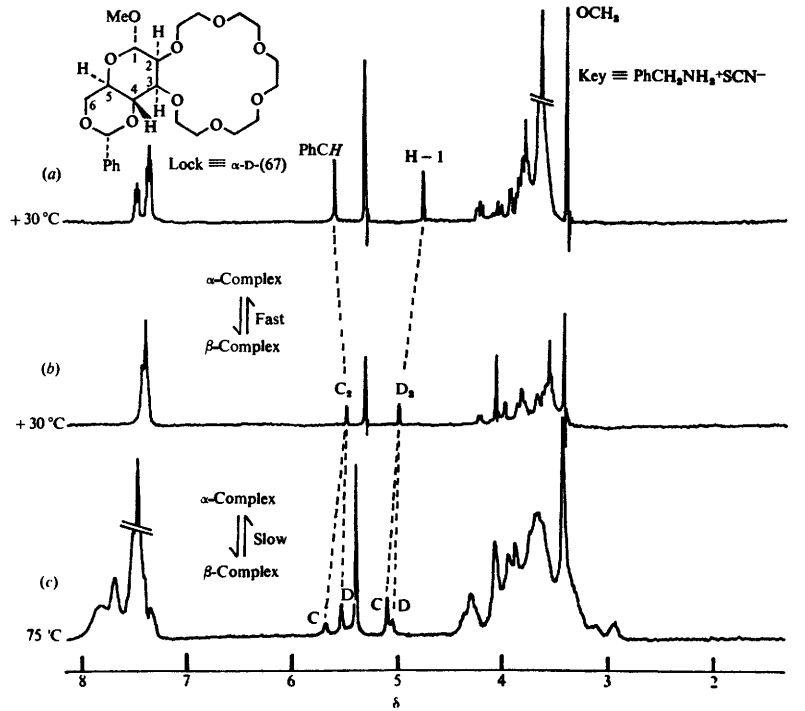


Figure 15 *The* ^{1}H *n.m.r. spectrum* (220 MHz) *of lock* α-D-(67) *in* CD_2Cl_2. *The temperature dependent* ^{1}H *n.m.r. spectra—*(*b*) *and* (*c*)*—of the* 1:1 *complex formed with* (60)HSCN

rings [*i.e.* α-D-(63), α-DD-(64), α-D-(65), and α-DD-(66)] and (ii) anancomerically *cis*-fused 18-crown-6 locks in which the *gauche* crown oxygens at the ring junctions are axial–equatorial with respect to the pyranosidic rings [*i.e.* α-D-(67) and α-DD-(68)]. In order to complete this stereochemical investigation it was necessary to study the complexing ability of the α-D-altroside lock α-D-(69). This anancomerically *trans*-fused 18-crown-6 derivative has *anti* crown oxygens with, of course, a diaxial arrangement at the pyranosidic ring junction. The $\Delta G^{\ddagger}_{d}$ value (8.3 kcal mol^{-1}) for the α-D-(69)–(6)HSCN complex in CD_2Cl_2 in conjunction with the low association constant for this complex in $CDCl_3$ indicate that stereochemical factors can play a crucial role in determining the thermodynamic and kinetic stabilities of organic cationic complexes of 18-crown-6 derivatives. In the α-series, the selectivity of binding to the heterotopic faces was found to be poor to non-existent for the α-galactoside and α-altroside locks and good to excellent for the α-glucoside and α-mannoside locks. Since the axial O-1 is involved in primary binding of the NH_3^+ ionic centre we reasoned that selectivity in favour of the β-face should be increased by inverting the configuration at C-1 and hence reducing the oxygens involved in the α-complexes to the six crown oxygens. Once again, there was a surprise waiting

for us when this speculation was put to the test. As observed previously in the α-series, β-D-(63), β-DD-(64), β-D-(65), and β-DD-(66) form 1 : 1 complexes with selected SCN^- and ClO_4^- salts derived from Me_3CNH_2 (6), $PhCH_2NH_2$ (60), and (*R*)- and (*S*)-$PhCHMeNH_2$ (*R*)- and (*S*)-(49) at +30 °C in CD_2Cl_2. The usual substantial changes in the ^1H n.m.r. spectra of these complexes relative to those of the pure locks was noted. The temperature dependent behaviour of the spectra of the β-D-(65)–(60)HSCN complex serves to illustrate (see Figure 16)

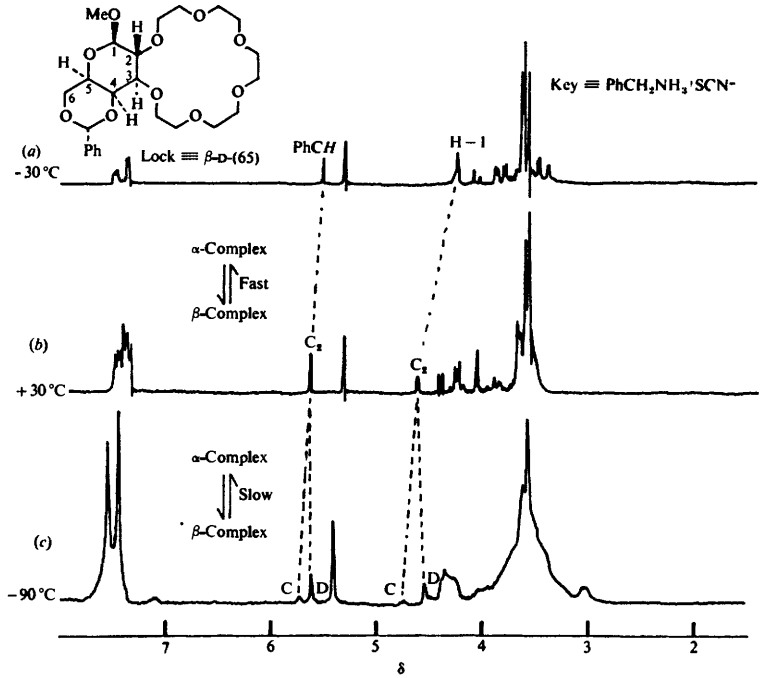


Figure 16 *The* ^1H *n.m.r. spectrum* (220 MHz) *of lock* β-D-(65) *in* CD_2Cl_2. *The temperature dependent* ^1H *n.m.r. spectra—*(*b*) *and* (*c*)*—of the* 1 : 1 *complex formed with* (60)HSCN

the general situation that exists for the β-galactoside locks. At +30 °C (Figure 16*b*), the signals for the PhC*H*, H-1, and H-4 protons are shifted considerably downfield in relation to their original chemical shifts in the spectrum (Figure 16*a*) of the pure lock. This observation indicates that O-4 participates along with the six crown oxygens in complex formation. On cooling the CD_2Cl_2 solution to −90 °C, the signals for the PhC*H* and H-4 protons both separate (Figure 16*c*) into high (δ 5.63 and 4.56, respectively) and low (δ 5.76 and 4.75, respectively) intensity signals. The fact that the lower field signals are the lower intensity signals in both cases suggests that the minor complex is associated with the β-face of β-D-(65). Hence, against all apparent reason, the major complex appears to involve binding to the α-face of β-D-(65). This finding is general for all the

1 : 1 complexes studied (see Table 3) involving phenyl-containing substituted ammonium keys.

As far as the β-D-glucoside locks are concerned, the ^{1}H n.m.r. spectral behaviour of the β-D-(63)–(60)$HClO_4$ complex with temperature serves to illustrate (see Figure 17) the general situation. Although the influence upon the chemi-

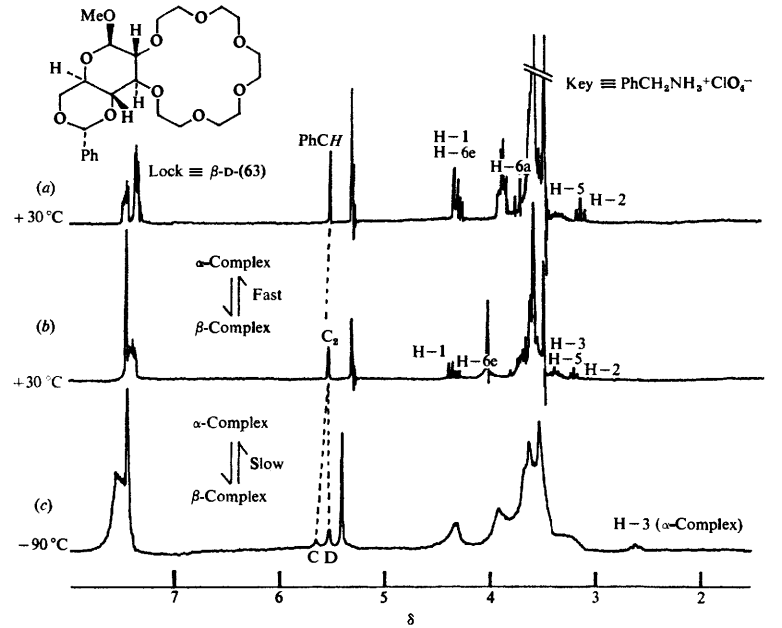


Figure 17 *The* ^{1}H *n.m.r. spectrum* (220 MHz) *of lock* β-D-(63) *in* CD_2Cl_2. *The temperature dependent* ^{1}H *n.m.r. spectra—*(*b*) *and* (*c*)*—of the* 1 : 1 *complex formed with* (60)$HClO_4$

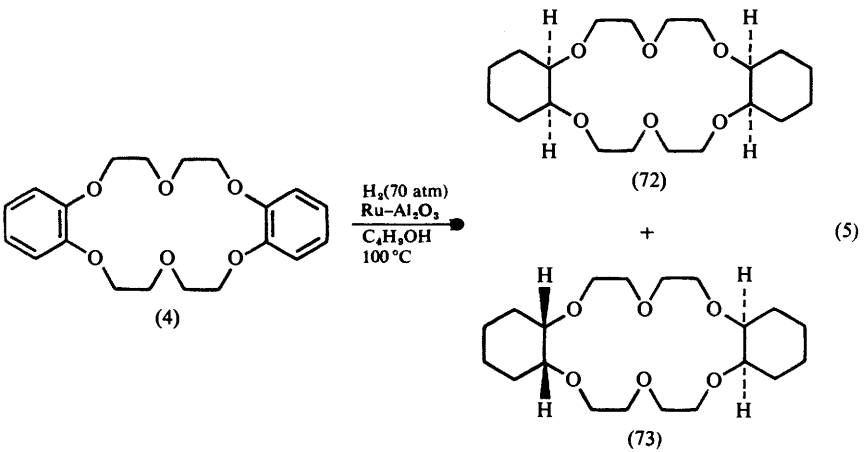
cal shift of the PhC*H* proton on complex formation is much less pronounced than in the β-galactoside locks, nonetheless this useful ^{1}H n.m.r. probe shows temperature dependence. This is presumably as a result of the dipole-induced dipole interaction[98] present in the β-D-(63)–β-(60)$HClO_4$ complex, which undoubtedly brings the PhC*H* proton under the influence of the diamagnetic ring current of the phenyl ring. At −90 °C, a triplet (J = 10 Hz) with a peak area corresponding to *ca.* 0.8 of a proton emerges (Figure (17*c*) at high field (δ2.62) and can be assigned to H-3 in the major α-complex on the basis of double irradiation studies. Since this upfield shift of H-3 is characteristic of nearly all the low temperature spectra of 1 : 1 complexes involving β-D-(63), β-DD-(64), β-D-(65), and β-DD-(66) and phenyl-containing substituted ammonium ions, we are led inexorably to propose the existence of a stabilizing *secondary anomeric effect* in α-complexes such as β-D-(63)–α-(60)$HClO_4$ and β-D-(65)–α-(60)HSCN, which involves the dipole[112] associated with the anomeric region of β-glycosides.

[112] J. F Stoddart, in ref. 50, p. 69.

Inspection of CPK space-filling molecular models shows that the acetal group associated with the anomeric centre in the β-D-(63)-α-(60)$HClO_4$ complex is more accessible sterically to the phenyl ring of the $PhCH_2NH_3^+$ ion than is the acetal group of the 1,3-dioxan ring in the β-D-(63)-β-(60)$HClO_4$ complex. Naturally, we find the possibility that the anomeric effect, which destabilizes β-glycosides intramolecularly may be a source of stability 'intermolecularly' within complexes of β-glycosides, an intriguing prospect. If this hypothesis is vindicated then serendipity will once again have played an important role in our science.

5 Why?

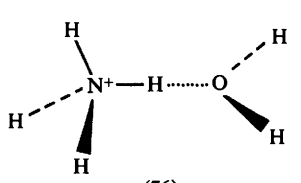
Previously, I have drawn attention to the fact that all the glucoside, galactoside, and mannoside locks form relatively weak complexes with $Me_3CNH_3^+SCN^-$ (6)HSCN in $CDCl_3$. The time has come to pose the question, 'why'? Before I do this, let me introduce some model compounds on to the scene. They are four of the five possible diastereoisomers of dicyclohexano-18-crown-6.[113,114] Catalytic hydrogenation[14,35,36] of dibenzo-18-crown-6 (4), followed by column chromatography of the product on alumina,[35] yields the *cis–cisoid–cis* (72) and *cis–transoid–cis* (73) isomers[115] as crystalline compounds, equation (5). The



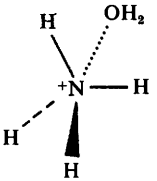
[113] I. J. Burden, A. C. Coxon, J. F. Stoddart, and C. M. Wheatley, *J.C.S. Perkin I*, 1977, 220.

[114] It has been suggested (P. A. S. Smith, *Aldrichim. Acta.*, 1977, **10**, 30) that this trivial nomenclature replace the older usage of dicyclohexyl-18-crown-6. In addition IUPAC have recommended (*Pure Appl. Chem.*, 1976, **45**, 13) that the relative configurational descriptors *cisoid* and *transoid* should be used rather than *syn* and *anti* respectively with tricyclic systems such as dicyclohexano-18-crown-6.

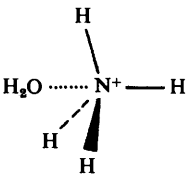
[115] M. Mercer and M. R. Truter, *J.C.S. Dalton*, 1973, 2215; N. K. Dalley, D. E. Smith, R M. Izatt, and J. J. Christensen, *J.C.S. Chem Comm.*, 1972, 90; N. K. Dalley, J. S. Smith, S. B. Larson, J. J. Christensen, and R. M. Izatt, *ibid.*, 1975, 43; N. K. Dalley, J. S. Smith, S. B. Larson, K. L. Matheson, J. J. Christensen, and R. M. Izatt, *ibid.*, p. 84.



(76)

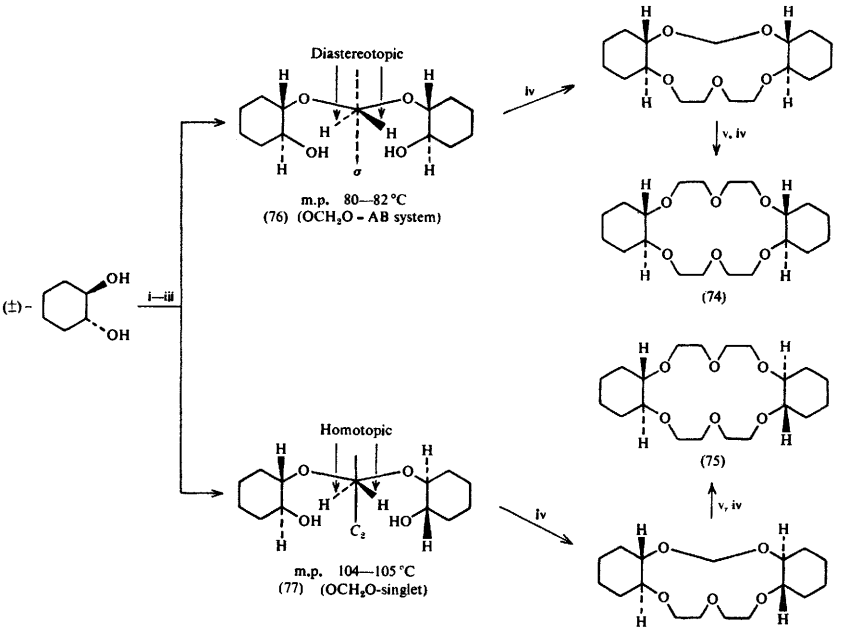


(77)



(78)

trans–cisoid–trans (74) and *trans–transoid–trans* (75) isomers have been synthesized (Scheme 3) stereospecifically[113,116] from (±)-cyclohexane-*trans*-1,2-diol.



Reagents: i, Ac_2O, pyridine; ii, MeSOMe, NBS; iii, NaOMe, MeOH; iv, $TsOCH_2CH_2OCH_2CH_2OTs$, NaH, MeSOMe, $MeOCH_2CH_2OMe$; v, H^+, H_2O

Scheme 3

[116] J. F. Stoddart and C. M. Wheatley, *J.C.S. Chem. Comm.*, 1974, 390.

This approach was made possible because of the following properties of the diastereoisomeric *meso*-(76) and (±)-(77) 2,2′-methylenedioxydicyclohexanols: (i) Their ready separation by fractional crystallization[117] and (ii) the symmetry properties of their dioxymethylene protons which are reflected[118] in their ^{1}H n.m.r. spectra.

The association constants and the corresponding free energies of complexation for the 1 : 1 complexes formed between $Me_3CNH_3^+SCN^-$ (6)HSCN in $CDCl_3$ and the isomers (72)—(74) of dicyclohexano-18-crown-6 and the chiral asymmetric locks α-D-(63), β-D-(63), α-D-(65), β-D-(65), and α-D-(67) are given in Table 4. They are seen to be considerably less than the corresponding K_a and ΔG values for 18-crown-6 (5) and $Me_3CNH_3^+SCN^-$ (6)HSCN in $CDCl_3$. A similar situation is found[113] to exist (Table 5) for the 1 : 1 complexes formed between Na^+, K^+, and Cs^+ chlorides in MeOH and the four isomers (71)—(75) of dicyclohexano-18-crown-6. In both tables, I have expressed the extent of the destabilization of the complexes relative to those formed by 18-crown-6 (5) in terms of $\Delta\Delta G$ values. The following observations[119] can be made: (i) Fusion to the 18-crown-6 constitution of either one, or two diametrically opposed six-membered rings leads to weaker complexes. (ii) When the ring junctions are *trans*-fused as in α-D-(63), β-D-(63), α-D-(65), β-D-(65), (74), and (75), or *cis*-fused as part of an anancomeric system as in α-D-(67), the strengths of complexes are generally speaking reduced to a much greater extent than they are when the ring junctions are *cis*-fused in conformationally 'flexible' systems such as (72) and (73). It is believed[120] that lower enthalpy changes rather than very large decreases in entropy on complexation of the cations by all of the locks discussed under (ii) are responsible for their lower free energies of complexation. The question then arises as to where these appreciable differences in enthalpy originate. We believe[121] they are stereochemical in origin.

[117] F. S. H. Head *J. Chem. Soc.*, 1960, 1778.

[118] T. B. Grindley, J. F. Stoddart, and W. A. Szarek, *J. Amer. Chem. Soc.*, 1969, **91**, 4722.

[119] A. C. Coxon, D. A. Laidler, R. B. Pettman, and J. F. Stoddart, *J. Amer. Chem. Soc.*, 1978, **100**, 8260.

[120] As a result of changes in ion-pairing phenomena and displacement of solvent molecules from cations and crown ethers, approximately uniform *increases* in translational and rotational entropy are anticipated to operate on formation of both organic and metal cationic complexes. However, the most important entropic contribution to complexation is probably the *decrease* in the rotational freedom component about bonds that accompany adoption of the 'all-*gauche*-OCH_2CH_2O' conformation in the complex. Indeed, significant *decreases* in entropy have been observed (R. M. Izatt, J. D. Lamb, G. E. Maas, R. E. Asay, J. S. Bradshaw, and J. J. Christensen, *J. Amer. Chem. Soc.*, 1977, **99**, 2365; R. M. Izatt, J. D. Lamb, R. E. Asay, G. E. Maas, J. S. Bradshaw, J. J. Christensen, and S. S. Moore, *ibid.*, p. 6134; R. M. Izatt, N. E. Izatt, B. E. Rossiter, J. J. Christensen, and B. L. Haymore, *Science*, 1978, **199**, 994) by calorimetry in MeOH at 25 °C on complexation by 18-crown-6 (5) of $Me_3CNH_3^+I^-$ (6)HI (log K_a = 2.90; ΔG = 4.00 kcal mol^{-1}; ΔH = −7.76 kcal mol^{-1}; $T\Delta S$ = −3.8 kcal mol^{-1}), of Na^+Cl^- (log K_a = 4.36; ΔG = −6.0 kcal mol^{-1}, ΔH = −8.4 kcal mol^{-1}; $T\Delta S$ = −2.4 kcal mol^{-1}), and of K^+Cl^- (log K_a = 6.05; ΔG = −8.2 kcal mol^{-1}, ΔH = −13.4 kcal mol^{-1}; $T\Delta S$ = −5.2 kcal mol^{-1}).

[121] J. F. Stoddart, 'Proceedings of the International Conference on Enzymic and Non-Enzymic Catalysis', London, April 1978, in the press.

Electrostatic interactions, including hydrogen bonds, are expected[122–125] to exhibit directional characteristics. Recent, *ab initio* molecular orbital calculations on model systems by Kollman[123] have shown that in attempting to discuss hydrogen bond directionality, the most important contribution appears to come from the electrostatic component. Moreover, in the case of the approach of a

Table 4 *The association constants* (K_a) *and free energies of complexation* (ΔG) *for the formation of* 1 : 1 *complexes between* $Me_3CNH_3^+SCN^-$ (6)HSCN *and* 18-crown-6 (5) *and the derivatives* (72)–(74) *and* α-D-(63), β-D-(63), α-D-(65), β-D-(65), *and* α-D-(67) *in* $CDCl_3$

Lock	K_a/l mol^{-1}	*log* K_a	ΔG^a/ kcal mol^{-1}	$\Delta\Delta G^a$/ kcal mol^{-1}
18-Crown-6 (5)	3 000 000[b]	6.48	−8.80	
cis–cisoid–cis-DCH-18-C-6 (72)	17 000[c,d]	4.23	−5.75	3.05
cis–transoid–cis-DCH-18-C-6 (73)	900 000[c,d]	5.95	−8.09	0.71
trans–cisoid–trans-DCH-18-C-6 (74)	7 100[c]	3.85	−5.23	3.57
α-D-Glu-18-C-6 α-D-(63)	2 000[c]	3.30	−4.49	4.31
β-D-Glu-18-C-6 β-D-(63)	1 300[c]	3.11	−4.23	4.57
α-D-Gal-18-C-6 α-D-(65)	210 000[c]	5.30	−7.21	1.59
β-D-Gal-18-C-6 β-D-(65)	5 800[c]	3.76	−5.11	3.69
α-D-Man-18-C-6 α-D-(67)	39 000[c]	4.59	−6.24	2.56

[a]The $\Delta\Delta G$ values correspond to the differences in the ΔG values between the particular lock and 18-crown-6 (5); [b]value from ref. 21; [c]values from ref. 118; [d]for a mixture of these isomers, K_a = 360 000 is reported (ref. 21).

water molecule to an ammonium ion, the interaction (76) in which the $\overset{+}{N}H_2 \ldots OH_2$ component has local C_{2v} symmetry is more stabilizing than any of the other approaches where the water molecule becomes tilted so that the $\overset{+}{N}H_2 \ldots OH_2$ component assumes C_s symmetry. The pole–dipole variety of electrostatic interactions met in the formal approach of a water molecule along the two-fold axis (77) and the three-fold axis (78) of an ammonium ion are much less stabilizing than the hydrogen bonding approach (76). The minimum energy geometries corresponding to (local) C_{2v} symmetry is also preferred in (i) the approach (79) of a lithium cation to a water molecule,[123] (ii) the hydrogen bonding approach (80) of a dimethyl ether molecule to an ammonium ion,[21] and (iii) the two-fold

[122] W. P. Jencks, 'Catalysis in Chemistry and Enzymology', McGraw-Hill, New York, 1969, Chapters 6 and 7.

[123] P. Kollman, *J. Amer. Chem. Soc.*, 1977, **99**, 4875; for an *ab initio* model study on cation binding to 12-crown-4 see A. Pulman, C. Giessner-Prettne, and Yu. v. Kruglyak, *Chem. Phys. Letters*, 1975, **35**, 156.

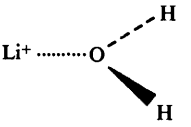
[124] P. Kollman, *Accounts Chem. Res.*, 1977, **10**, 365.

[125] G. A. Jeffrey and S. Takagi, *Accounts Chem. Res.*, 1978, **11**, 264; see also G. Klopman and P. Andreozzi, *Chem. Soc. Ann. Reports Prog. Chem.* 1977, **74**, 41.

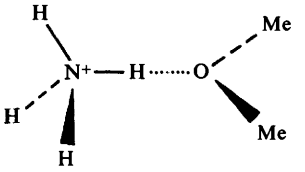
Table 5 *The log* K_a *(based on* K_a *in* 1 mol^{-1}*) and* ΔG *values for the formation of* 1 : 1 *complexes between* Na^+, K^+, *and* Cs^+ *chlorides in* MeOH

Lock	Na^+			K^+			Cs^+		
	log K_a[a]	ΔG[b]	$\Delta\Delta G$[b]	*log* K_a[a]	ΔG[b]	$\Delta\Delta G$[b]	*log* K_a[a]	ΔG[b]	$\Delta\Delta G$[b]
18-Crown-6 (5)	4.32[c]	−5.9	—	6.10[c]	−8.3	—	4.70	−6.3	—
cis–cisoid–cis-DCH-18-C-6 (72)	4.08[c]	−5.5	0.4	6.01[c]	−8.2	0.1	4.61[c]	−6.2	0.1
cis–transoid–cis-DCH-18-C-6 (73)	3.68[c]	−5.0	0.9	5.38[c]	−7.3	1.0	3.49[c]	−4.7	1.6
trans–cisoid–trans-DCH-18-C-6 (74)	2.99[d]	−4.0	1.9	4.14[d]	−5.6	2.7	3.00[d]	−4.0	2.3
trans–transoid–trans-DCH-18-C-6 (75)	2.52[d]	−3.4	2.5	3.26[d]	−4.3	4.0	2.27[d]	−3.0	3.3

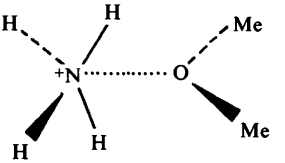
[a]Obtained for the equilibrium, M^+n-MeOH + Lock⇌M Lock$^+$ + n-MeOH, at 20—25 °C by potentiometry with ion selective electrodes; [b]in kcal $mol.^{-1}$ The $\Delta\Delta G$ values correspond to the differences in the ΔG values between the particular lock and 18-crown-6 (5); [c]values from H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600; [d]values from ref. 118.



(79)

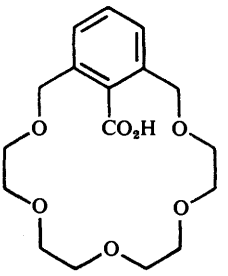


(80)



(81)

pole–dipole approach (81) of a dimethyl ether molecule to an ammonium ion. It is significant, however, that the interaction energy calculated for (81) is only about one-third that calculated for (80). This preference for the 'bisector' approach coupled with the additional strength of a hydrogen bond over a simple electrostatic bond is thought[121] to be responsible for the $Me_3CNH_3^+$ (6)H^+ ion choosing to hydrogen bond (*cf.* ref. 23) with 'up' oxygens rather than with 'down' oxygens in crown ethers, *e.g.* the crystal structure data[29] for the salt formed between the 2-carboxy-1,3-xylyl-18-crown-5 (82) and Me_3CNH_2 (6).[126,127]



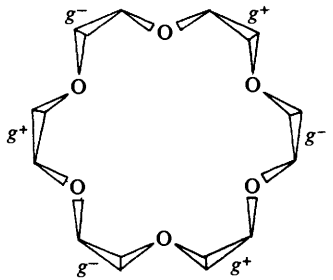
(82)

Let us address ourselves to the question 'why' again. In view of the directional characteristics of non-covalent bonds, and the dependence of conformation upon configuration, relatively small differences in the torsional angles associated

[126] Hydrogen bonding to 'up' oxygens is also characteristic of the crystal structures of the ammonium bromide dihydrate complex of 18-crown-6 (5) (O. Nagano, A. Kobayashi, and Y. Saski, *Bull. Chem. Soc. Japan*, 1978, **51**, 790) and the hydronium chloride complex of monoaza-18-crown-6 (G. W. Gokel and B. J. Garcia, *Tetrahedron Letters*, 1977, 317).

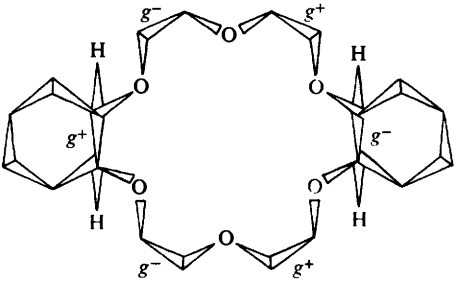
[127] Undoubtedly, the energy of complexation is maximized by the complex (i) seeking the best hydrogen bonding geometry at the expense of (ii) not being able to optimize its pole–dipole stabilization because of (iii) conformational constraints, mainly torsional, imposed by the 18-membered ring (*cf.* ref. 121).

with the bismethylenedioxy and substituted bismethylenedioxy units in the 18-membered rings might account for the observed changes (see Tables 4 and 5) in the $\Delta\Delta G$ values when six-membered ring systems are fused to the macro-ring



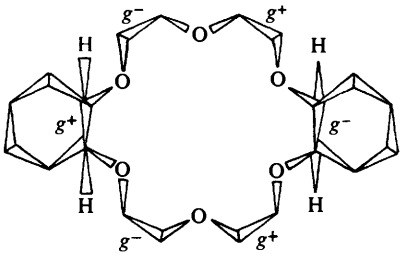
$g^{\pm}g^{\mp}g^{\pm}g^{\mp}g^{\pm}g^{\mp}$

(5)



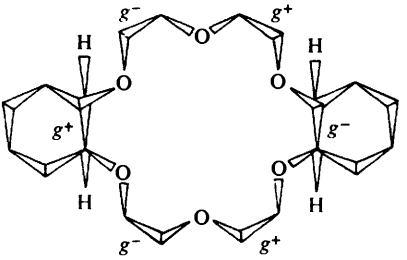
$g^{+}g^{-}g^{+}g^{-}g^{+}g^{-} \rightleftharpoons g^{-}g^{+}g^{-}g^{+}g^{-}g^{+}$

(72)



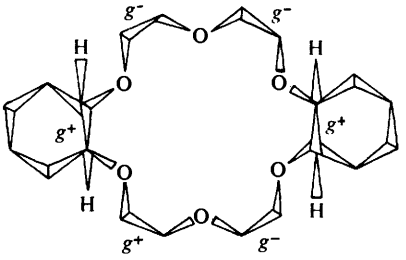
$g^{+}g^{-}g^{+}g^{-}g^{+}g^{-} \rightleftharpoons g^{-}g^{+}g^{-}g^{+}g^{-}g^{+}$

(73)



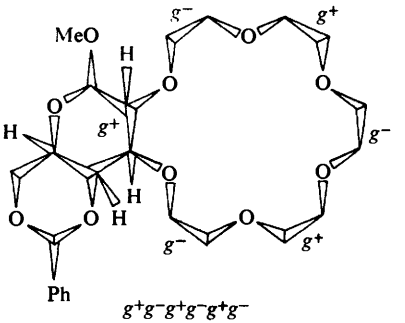
$g^{+}g^{-}g^{+}g^{-}g^{+}g^{-}$

(74)



$g^{+}g^{-}g^{-}g^{+}g^{-}g^{+}/g^{-}g^{+}g^{+}g^{-}g^{+}g^{-}$

(75)



$g^{+}g^{-}g^{+}g^{-}g^{+}g^{-}$

α-D-(63)

Figure 18 *The designation of conformational behaviour in complexes of* (5), (72)—(75), *and* α-D-(63)

as in (72)—(75) and in α-D-(63), β-D-(63), α-D-(65), β-D-(35), and α-D-(67). In Figure 18, the top view notation[53] has been employed to represent (72)—(75), α-D-(63), and 18-crown-6 (5). These representations serve to highlight the following important stereochemical differences: (i) When it is involved in complex formation, 18-crown-6 (5) adopts the diamond lattice 'all-*gauche*-OCH_2CH_2O' conformation with D_{3d} symmetry[53] and undergoes ring inversions[37] that are rapid relative to the rate of the decomplexation process.[128] We shall describe this lock as a $g^{\pm}g^{\mp}g^{\pm}g^{\mp}g^{\pm}g^{\mp}$ system. (ii) The di-*cis* isomers (72) and (73) of dicyclohexano-18-crown-6 can both attain 'ideal' complexing conformations for their 18-membered rings. However, they are 'flexible' systems in which the macro-rings are constrained[119] to invert at rates approximating to those of the decomplexation processes because of the need for both six-membered rings to invert as well. These locks will be described as $g^+g^-g^+g^-g^+g^- \rightleftharpoons g^-g^+g^-g^+g^-g^+$ systems. (iii) Although the 18-membered rings in the *trans–cisoid–trans* isomer (74) of dicyclohexano-18-crown-6, and in the carbohydrate derivatives α-D-(63), β-D-(63), α-D-(65), β-D-(65), and α-D-(67), can attain 'ideal' complexing conformations, they are 'rigid' systems and so cannot undergo macro-ring inversion. We shall describe these locks as $g^+g^-g^+g^-g^+g^-$ systems (iv). Not only can the 18-membered ring of the *trans–transoid–trans* isomer (75) of dicyclohexano-18-crown-6 not undergo inversion but it is also denied attaining the 'ideal' complexing conformation. Since this lock is a racemic modification we shall describe it as a $g^+g^-g^-g^+g^-g^+/g^-g^+g^+g^-g^+g^-$ system. It is clear that a rough qualitative correlation (see Figure 19) exists between the magnitude of the $\Delta\Delta G$ values in

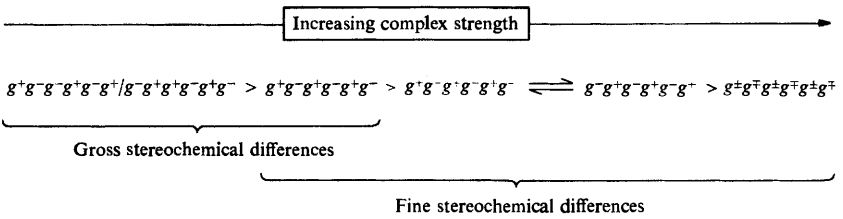
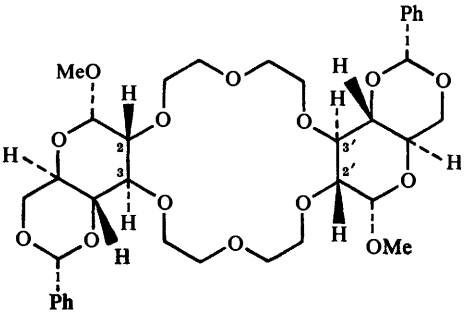


Figure 19 *The qualitative correlation between complex strength and stereochemistry*

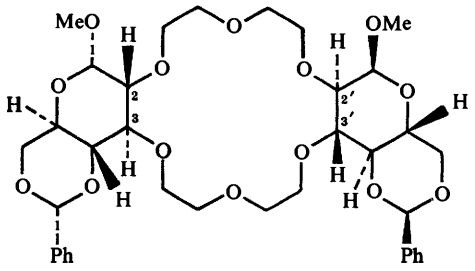
Tables 4 and 5 and the stereochemical classification developed above under (i) to (iv). The fact that the correlation exists for *both* metal and $Me_3CNH_3^+$ (6)H^+ cations suggests that it is the *highly directional nature of electrostatic interactions* which is the important feature in this stereochemical analysis. At this stage in our analysis, we can differentiate between (i) fine stereochemical differences involving conformational features only and (ii) gross stereochemical differences involving both configurational and conformational features. We propose that the fine stereochemical features emerge in the 'ideal' complexing conformations because of small and different conformational perturbations to

[128] F. de Jong, D. N. Reinhoudt, C. J. Smit, and R. Huis, *Tetrahedron Letters*, 1976, 4783.

the 18-membered rings caused by 1,2-*cis*- and 1,2-*trans*-fusion of six-membered rings. Although the torsional angles associated with bismethylenedioxy and substituted bismethylenedioxy units will vary[129] according to the relative configurations at the ring junctions, a more precise description of the influence of fine stereochemical features upon $\Delta\Delta G$ values is still not clear to us. By way of contrast, however, the influence of gross stereochemical features emerges very clearly. The denial to (75) of binding sites which act co-operatively[130] provides an obvious explanation as to why it forms weaker complexes with metal cations (see Table 5) than does (74). Although we did not study the relative binding capacity of (74) and (75) towards $Me_3NH_3^+$ (6)H^+ ions in our earlier work,[113,116] the availability[131] of bis-αα-glycoside-18-crown-6 derivatives[132] such as 2,3:2′,3′-

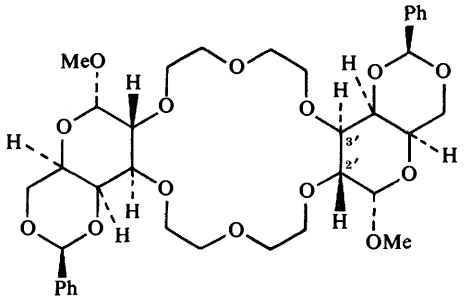


2,3:2′,3′-αα-DD-(83)

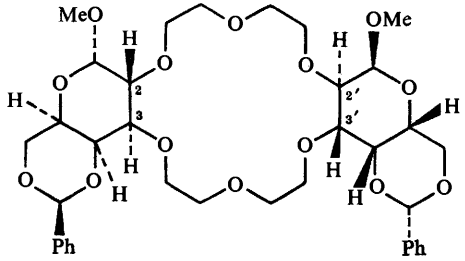


2,3:3′,2′-αα-DD-(84)

[129] C. Romers, C Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 1969, **4**, 39.
[130] Our earlier observation (A. C. Coxon and J. F Stoddart, *J.C.S. Perkin I*, 1977, 767) that 20-crown-6 derivatives and synthetically related macrobicyclic polyethers with bridgehead carbon atoms form extremely weak complexes with Na^+, K^+, Rb^+, and Cs^+ chlorides in MeOH can also be explained by lack of co-operativity of binding sites.
[131] W. Hain, R. Lehnert, H. Röttele, and G. Schröder, *Tetrahedron Letters*, 1978, 625.
[132] In giving these bis-αα-DD-glycoside-18-crown-6 derivatives formula descriptors, I have chosen to differentiate isomers as having 2,3:2′,3′ or 2,3:3′,2′ *constitutions* depending upon the nature of the two ring junctions with respect to the numbering of the pyranosidic rings proceeding in an anticlockwise fashion around the macro-ring.



2,3:2′, 3′-αα-DD-(85)



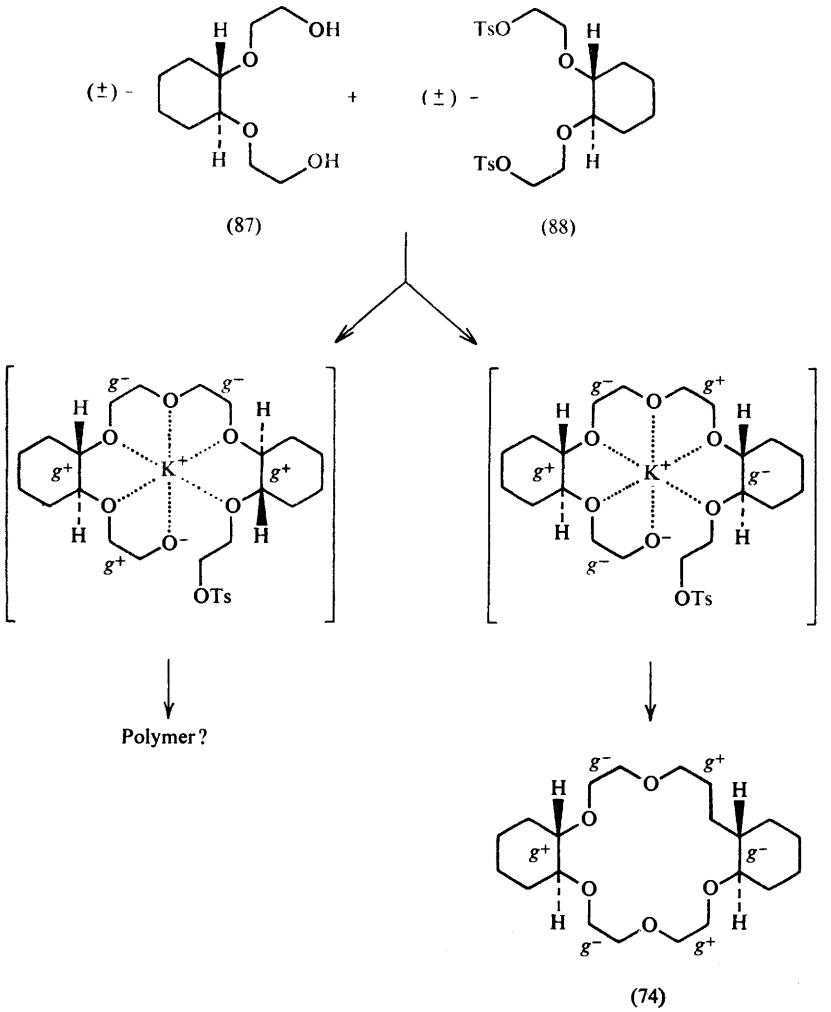
2,3:3′,2′-αα-DD-(86)

αα-DD-(83), 2,3:3′,2′-αα-DD-(84), 2,3:2′, 3′-αα-DD-(85), and 2,3:3′,2′-αα-DD-(86) with the *trans–transoid–trans* configuration provides[133] an ideal opportunity to investigate gross stereochemical features.

It will be recalled that in metal cation templated syntheses a catalytic effect has been observed[57] that relates rates of cyclization with the complexing ability of crown ethers towards the cations used in their synthesis. In this context it is significant that *only* the *trans–cisoid–trans* isomer (74) of dicyclohexano-18-crown-6 was isolated[134] after the attempted synthesis (see Scheme 4) of (74) and (75) by condensation of (±)-*trans*-2,2′-(1,2-cyclohexylidene)dioxyethanol (87) with its bistosylate (88) in benzene in the presence of $Me_3CO^-K^+$. The relative

[133] Since this lecture was delivered, we have completed a preliminary investigation (D. A. Laidler, J. F. Stoddart, and J. B. Wolstenholme, *Tetrahedron Letters*, 1979, 465) of these bis-αα-glycoside-18-crown-6 derivatives. The *constitutionally isomeric* glucosides 2,3:2′,3′-αα-DD-(83) and 2,3:3′,2′-αα-DD-(84) and galactosides 2,3:2′,3′-αα-DD-(85) and 2,3:3′,2′-αα-DD-(86) have all been prepared and their *constitutions* have been assigned on the basis of dynamic ^1H n.m.r. spectroscopy on suitable complexes. The K_a values for complexing of 2,3:2′,3′-αα-DD-(83), 2,3:3′,2′-αα-DD-(84), 2,3:2′,3′-αα-DD-(85), and 2,3:3′,2′-αα-DD-(86) by $Me_3CNH_3^+SCN^-$ (6)HSCN in $CDCl_3$ were estimated to be < 50, < 50, 4650, and 5750 l mol^{-1}, respectively. Comparison of these values with those of 2000 and 201 000 l mol^{-1} for complexing of α-D-(63) and α-D-(65), respectively with (6)HSCN in $CDCl_3$ illustrate the importance of gross stereochemical features in stabilizing complexes.

[134] R. C. Hayward, C. H. Overton, and G. H. Whitham, *J.C.S. Perkin I*, 1976, 2413.



Scheme 4

configurations of the products are established on formation of the first C—O bond in both of the intermediates in Scheme 4. The observed stereoselectivity is believed[119] to ensue from the greater stabilization through the templating action of the K^+ ions on the transition state leading to (74) than on the transition state leading to (75). In the latter case, intermolecular reaction to give polymer is probably competing successfully with intramolecular cyclization. If this explanation is correct, then the directional characteristics of non-covalent bonds can and will influence the diastereoisomeric ratios during cation-templated syntheses of crown ethers. Faster and more efficient cyclizations will result when

binding sites in the transition state act co-operatively in a stereochemical sense to lower the free energy of activation for the reaction. Thus, gross stereochemical features find kinetic as well as thermodynamic expression.

It is now evident that *small* conformational differences lead to *large* differences in (i) free energies of complexation by 18-crown-6 derivatives towards the same ion and (ii) free energies of activation for cyclization of open-chain precursors to 18-crown-6 derivatives templated by the same ion. Undoubtedly, the highly directional characteristics of non-covalent bonds is responsible for this particular phenomenon and we believe that a general principle is also established whereby it should be possible to build highly structured complexes by exercising appropriate constitutional and stereochemical control upon the lock in relation to the key.

During three decades now conformational analysis has been practised largely and traditionally at an intramolecular level. I predict that we are about to witness the development and growth of a relatively new and exciting area[135] in stereochemistry, that of *intermolecular conformational analysis* if you like!

6 Dreamland Revisited

Our journey from carbohydrates to enzyme analogues has only just begun. The lessons that we have learnt while taking our first steps include the following: (i) Constitution, configuration, and conformation define the structures of non-covalently bonded species in much the same way as they define the structures of covalently bonded species. Non-covalent bonds are highly directional! (ii) By utilizing secondary stabilizing interactions, keys can locate the heteroptopic faces of certain chiral asymmetric locks with high selectivity (> 1.4 kcal mol^{-1}).

[135] Examples which illustrate the importance of intermolecular conformational analysis within the static domain of stereochemistry abound in the field of natural polymers, *i.e.* nuclei acids, proteins, and polysaccharides, but are relatively few and far between in the realm of low molecular weight compounds (for some exceptions, however, see N. W. Alcock, *Adv. Inorg. Chem. and Radiochem.*, 1972, **15**, 1 and R. E. Rosenfield jun., R. Parthasarathy, and J. D. Dunitz, *J. Amer. Chem. Soc.*, 1977, **99**, 4860). In the dynamic domain of stereochemistry we recognise (*cf.* ref. 119) strong parallels between the highly directional characteristics of non-covalent bonds and the rather severe geometrical constraints governing the approaches of reactant centres in reactions, *e.g.* ligand exchange reactions (H. B. Bürgi, *Inorg. Chem.*, 1973, **12**, 2321), S_N2 displacements (L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta.*, 1970, **53**, 2059; H. B. Bürgi, *Angew. Chem. Internat. Edn.*, 1975, **14**, 460), carbonyl additions (H. B. Bürgi, J. D. Dunitz, and E. Shefter, *J. Amer. Chem. Soc.*, 1973, **95**, 5065; H. B. Bürgi, J. D. Dunitz, J.-M. Lehn, and G. Wipff, *Tetrahedron*, 1974, **30**, 1563; J. D. Dunitz, *Phil. Trans. Roy. Soc. London*, 1975, **B272**, 99; M. M. Kayser and P. Morand, *Tetrahedron Letters*, 1979, 695), and ring closures (J. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734, 738; J. Baldwin, J. Cutting W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *J.C.S. Chem. Comm.*, 1976, 736; J. Baldwin, 'Further Perspectives in Organic Chemistry', Ciba Foundation Symposium 43, Elsevier, Amsterdam, 1978; R. C. Cookson and S. A. Smith, *J.C.S. Chem. Comm.*, 1979, 145). The importance of relative orientation or 'orbital steering' of reactant molecules has been demonstrated (D. R. Storm and D. E. Koshland, jun., *J. Amer. Chem. Soc.*, 1972, **94**, 5805, 4815) in kinetic studies on the lactonization of hydroxyacids where rate acclerations can be associated with 'reactivity windows' in the hyperspace surrounding the reaction. The highly attractive hypothesis that this tight stereoselective control, which imposes a critical orientational requirement upon reactants, explains the high catalytic power and selectivity of enzymes has long been recognized (D. E. Koshland, jun., *J. Theor. Biol.*, 1962, **2**, 85; D. E. Koshland, jun.. and K. E. Neet, *Ann. Review Biochem.*. 1968. **37**, 359).

(iii) Reorganization of the non-covalent bonding pattern within complexes is generally fast. The key spins in the lock! (iv) Some chiral symmetrical locks show modest enantiomeric differentiation (0.3—0.5 kcal mol^{-1}) towards racemic keys. (v) Complexes seek all opportunities (the counterion or additional binding sites) to become destructured. (vi) Carbohydrates are a convenient source of chiral locks.

Our principal objectives at the moment are to (i) construct highly structured complexes in which the locks will show high chiral recognition towards racemic keys, and (ii) construct highly structured complexes in which the locks will catalyse reactions that show high regioselectivity and stereoselectivity towards heterotopic and enantiotopic ligands and faces in appropriate keys. In short, our task is to build enzyme analogues.[136,137] In principle, many chemical reactions are amenable to this kind of investigation—the challenges are both scientific and artistic insofar as our understanding of reaction mechanisms and stereochemistry is fast approaching the point where rapidly advancing synthetic skills can be put to the test in the design and preparation of man-made catalysts exhibiting the characteristics of enzymes. Some thoughts of Prelog's lend encouragement to those of us engaged in these challenges. He has said:[138]

Chemistry takes a unique position among the natural sciences for it deals not only with material from natural sources but creates the major part of its objects by synthesis. In this respect . . . the potential of its creativity is terrifying.

Armed with a challenge and the potential to meet it we are entitled to go on dreaming in this case that one day we shall indeed be able to go '*From Carbohydrates to Enzyme Analogues*'.

The account I have presented in this lecture was given life and substance through the supreme efforts of Howard F. Beckford, Geoffrey D. Beresford, Ian J. Burden, Andrew C. Coxon, W. David Curtis, Anthony J. Haslegrave, Dale A. Laidler, Janet C. Metcalfe, Roger B. Pettman, and John B. Wolstenholme. To them, I owe a lot including my thanks.

[136] The term enzyme analogue has connotations that the term enzyme model lacks (see ref. 121). Whereas an enzyme model seeks to mimic a known enzyme in its catalytic function, an enzyme analogue is merely a practical expression of the lessons learnt from Nature.

[137] For examples of enzyme analogues based on the crown ether constitution see Y. Chao and D. J. Cram, *J. Amer. Chem. Soc.*, 1976, 98, 1015; T. J. van Bergen and R. M. Kellog, *J.C.S. Chem. Comm.*, 1976, 964; T. J. van Bergen and R. M. Kellog, *J. Amer. Chem. Soc.*, 1977, 99, 3882; J.-P. Behr and J.-M. Lehn, *J.C.S. Chem. Comm.*, 1978, 143; T. Matsui and K. Koga, *Tetrahedron Letters*, 1978, 1115: J.-M. Lehn and C. Sirlin, *J.C.S. Chem. Comm.*, 1979, 949.

[138] V. Prelog, *Science*, 1976, 193, 17.