Complexation of Diquat by a Regiospecifically Synthesised Macrobicyclic Receptor Molecule

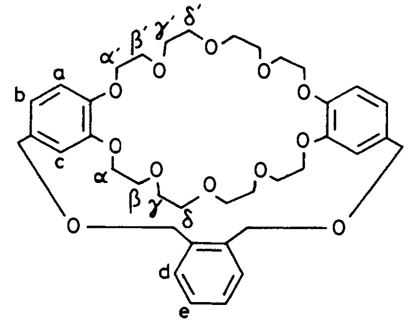
Billy L. Allwood,[a] **Franz H. Kohnke,**[b] **Alexandra M. Z. Slawin,**[a] **J. Fraser Stoddart,**[b] **and David J. Williams**[a]

[a] *Department of Chemistry, Imperial College, London SW7 2AY, U.K.*
[b] *Department of Chemistry, The University, Sheffield S3 7HF, U.K.*

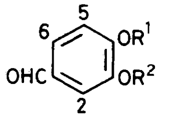
An *X*-ray structural investigation has shown that the macrobicyclic host (**1**), synthesised regiospecifically from 3,4-dihydroxybenzaldehyde (**2**) in eight steps, forms a deep red 1 : 1 crystalline complex with Diquat in which the guest dication is encapsulated by the host.

Designing receptor molecules that will encapsulate organic guest species has so far met with only limited success.[1] It has been suggested[2] that one way to overcome this problem is to design hosts in which polar binding subunits are connected by rigid apolar shaping components. Recently, it has been shown[3] that a chiral macrocycle containing two tartaric acid groups and two diphenylmethane fragments binds strongly with a range of cationic substrates including acetylcholine and methylviologen (Paraquat) in aqueous solution. Our observation[4] that dibenzo-3*n*-crown-*n* (DB3*n*C*n*) ethers (particularly *n* = 9—11) engulf the Diquat dication in organic solvents (*e.g.* MeCN and Me_2CO) relies upon a combination of (i) [C—H · · · O] hydrogen bonding and electrostatic interactions between the polyether chains and the $CHN^+CH_2CH_2N^+CH$ region of Diquat and (ii) charge transfer between the π-electron-rich catechol units and the π-electron-deficient bipyridinium ring system. However, the DB3*n*C*n* ethers are highly flexible hosts and clearly undergo[5] considerable conformational change during complexation of Diquat. We now report on (i) the regiospecific synthesis[†] of a more rigid and pre-organised macrobicyclic host (**1**) based on the optimum DB30C10 constitution and (ii) demonstrate by *X*-ray crystallography that it encapsulates Diquat in the solid state.[‡]

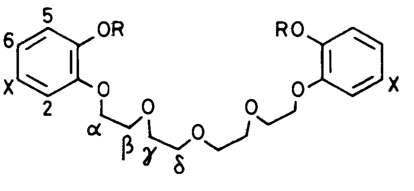
Reaction (80 °C; 24 h) of 3,4-dihydroxybenzaldehyde (**2**) with 0.9 mol. equiv. of $PhCH_2Cl$ in Me_2NCHO (DMF) in the presence of 1.0 mol. equiv. of K_2CO_3 afforded,[§] in order of their elution (EtOAc–light petroleum) from an SiO_2 column, (**5**), m.p. 87—89 °C, (**4**), m.p. 116 °C, and (**3**), m.p. 118 °C, in yields of 6, 9, and 50%, respectively. Treatment (NaOH, Bu^nOH, 85 °C, 30 h) of (**3**) with 0.6 mol. equiv. of $Ts[OCH_2CH_2]_4OTs$ (Ts = tosyl)[6] gave (*cf.* ref. 7) the acyclic polyether (**6**) as an oil (55%) after SiO_2 chromatography (EtOAc–light petroleum). Carefully controlled hydrogenolysis (10% Pd/C, CH_2Cl_2, 3.5 h) of the benzyl ether protecting groups in (**6**) proceeded selectively in preference to reduction of the CHO



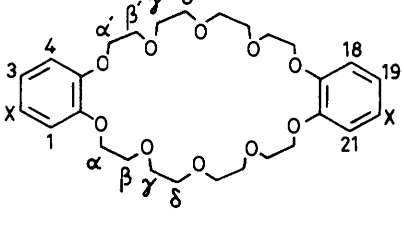
(**1**)



(**2**) $R^1 = R^2 = H$
(**3**) $R^1 = CH_2Ph$; $R^2 = H$
(**4**) $R^1 = H$; $R^2 = CH_2Ph$
(**5**) $R^1 = R^2 = CH_2Ph$



(**6**) $R = CH_2Ph$; $X = CHO$
(**7**) $R = H$; $X = CHO$
(**8**) $R = H$; $X =$



(**9**) X = CHO
(**10**) $X = CH_2OH$
(**11**) X = H

[†] All new compounds gave satisfactory analytical and ^1H n.m.r. spectroscopic data: (**6**) $\delta(CDCl_3$, 220 MHz) 3.59—3.79 (8H, AA′BB′ system, γ- and δ-OCH_2), 3.90 and 4.23 (2 × 4H, 2 × t, *J* 5 Hz, β- and α-OCH_2, respectively), 5.20 (4H, s, 2 × CH_2Ph), 7.00 (2H, d, *J* 8 Hz, H-5), 7.25—7.50 (14H, m, 2 × Ph, H-2 and H-6), and 9.78 (2H, s, 2 × CHO); (**7**) $\delta(CDCl_3$, 220 MHz) 3.71 (8H, br.s, γ- and δ-OCH_2), 3.87 and 4.23 (2 × 4H, 2 × t, *J* 5 Hz, β- and α-OCH_2, respectively), 7.00 (2H, d, *J* 8 Hz, H-5), 7.38—7.47 (4H, m, H-2 and H-6), 7.75 (2H, br.s, 2 × OH), and 9.77 (2H, s, 2 × CHO); (**8**) $\delta(CDCl_3$, 220 MHz) 3.56—4.20 (24H, m, 12 × OCH_2), 5.69 (2H, s, 2 × OCHO), 5.97 (2H, br.s, 2 × OH), and 6.85—7.01 (6H, m, 2 × H-2, 2 × H-5, and 2 × H-6); (**9**) $\delta(CDCl_3$, 220 MHz) 3.67—3.85, 3.93, and 4.23 (32H, m, 16 × OCH_2), 6.96 (2H, d, *J* 8 Hz, H-4 and H-18), 7.37—7.48 (4H, m, H-1, H-3, H-19, and H-21), and 9.80 (2H, s, 2 × CHO); (**10**) $\delta(CDCl_3$, 220MHz) 2.83 (2H, br.s, 2 × OH), 3.60—3.82, 3.87, and 4.12 (32H, m, 16 × OCH_2), 4.54 (4H, s, 2 × CH_2OH), and 6.78—6.92 (6H, m, ArH); (**1**) $\delta(CD_3COCD_3$, 400 MHz) 3.56—3.67 (6H, m, γ-, γ′-, δ-, and δ′-OCH_2), 3.80 and 3.84 (8H, 2 × t, *J* 5 Hz, β- and β′-OCH_2), 3.97 and 4.07 (8H, 2 × t, *J* 5 Hz, α- and α′-OCH_2), 4.39 (4H, s, 2 × $CH_2C_6H_3$), 4.50 (4H, s, $CH_2C_6H_4CH_2$), 6.71 (2H, d × d, *J* 2, 8 Hz, 2 × H-b), 6.79 (2H, d, *J* 8 Hz, 2 × H-a), 6.81 (2H, d, *J* = 2 Hz, 2 × H-c), and 7.29 and 7.43 (4H, AA′BB′ system with a small long range coupling of the AA′ portion to the singlet resonating at δ 4.50, 2 × H-e and 2 × H-d, respectively). The temperature dependence of this spectrum below 0 °C is discussed in the following communication.

[‡] Evidence is presented in the following communication which demonstrates that the gross supramolecular structure of the 1:1 complex in solution is similar to that observed in the solid state.

[§] Although it is claimed (*Fortschr. d. Teerfarbenfabr. P. Friedländer*, 1899, **4**, 1238; K. Krohn and J. Thiem, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1186) with good theoretical justification that benzylation of (**2**) gives either (**3**) or (**4**) predominantly depending on whether 1 or 2 mol. equiv. of alkali are employed in the reaction, we felt unable to assign constitutions with certainty to our two isomeric compounds on the basis of comparisons with either literature melting points ('Dictionary of Organic Compounds,' 4th edn., vol. 2, pp. 1053 and 1054, Eyre & Spottiswoode, London, 1965) or ^1H n.m.r. spectroscopic data. Crystallisation of the slowest moving component on SiO_2 chromatography from EtOAc–light petroleum gave single crystals suitable for *X*-ray analysis. This established that its constitution is indeed that of (**3**). *Crystal data:* for (**3**), $C_{14}H_{12}O_3$, $M = 228$, orthorhombic, space group $P2_12_12_1$, $a = 6.456(1)$, $b = 11.312(1)$, $c = 15.860(4)$ Å, $U = 1158$ Å^3, $Z = 4$, $D_c = 1.31$ g cm^{-3}. Data were obtained using Cu-K_α radiation (graphite monochromator) on a Nicolet R3m diffractometer. A total of 937 independent reflections were measured ($\theta \leqslant 58°$) using the ω-scan routine. Of these, 865 had $|F_o| > 3\sigma(|F_o|)$ and were classed as observed. The structure was solved by direct methods and refined anisotropically to $R = 0.036$. ^1H N.m.r. spectroscopic data: (**3**) $\delta(CDCl_3$, 220 MHz) 5.18 (2H, s, OCH_2), 5.90 (1H, br.s, OH), 7.02 (1H, d, *J* 8 Hz, H-5), 7.37—7.47 (7H, m, Ph, H-2, and H-6), and 9.77 (1H, s, CHO); (**4**) $\delta(CDCl_3$, 220 MHz), 5.16 (2H, s, OCH_2), 6.40 (1H, s, OH), 7.05 (1H, d, *J* 8 Hz, H-5), 7.32—7.55 (7H, m, Ph, H-2, and H-6), and 9.77 (1H, s, CHO).

groups, to yield (60%) the diphenol (**7**), m.p. 109 °C, after crystallisation of the product from EtOAc–light petroleum. All attempts using a range of bases (NaOH, NaH, Bu^{t}OK), solvents [Bu^{n}OH, DMF, tetrahydrofuran (THF)], and conditions to convert (**7**) and Ts[OCH_2CH_2]$_4$OTs directly into the bisformyl-DB30C10 derivative (**9**) have so far failed. However, protection ($HOCH_2CH_2OH$, TsOH, PhMe, reflux, 6 h) of the CHO groups in (**7**) to give the diacetal (**8**) in the form of an oil (77%) was followed successfully by (i) its base-promoted reaction (NaH, THF, reflux, 80 h) with Ts[OCH_2CH_2]$_4$OTs (1 mol. equiv.) and (ii) deprotection (MeOH, H_2O, HCl, reflux, 30 min) to afford (**9**), m.p. 123—124 °C, in 44% overall yield after SiO_2 chromatography ($CHCl_3$—MeOH). Reduction ($LiAlH_4$, THF, reflux, 16 h) of (**9**) gave (87%) the bishydroxymethyl-DB30C10 derivative (**10**), m.p. 91—94 °C. Reaction (NaH, THF, reflux, 36 h) of this diol with 1,2-bisbromomethylbenzene (1 mol. equiv.) afforded (**1**) as an oil (7%) after SiO_2 chromatography (PhMe-$CHCl_3$—MeOH). Addition of [Diquat][PF_6]$_2$[8] (1 mol. equiv.) to (**1**) dissolved in MeCN produced a dark orange solution, which, when crystallised by vapour diffusion[9] with Et_2O, afforded deep red crystals,¶ m.p. 170—173 °C (decomp.), suitable for *X*-ray structural investigation (Figures 1 and 2). The analysis reveals how this new bicyclic host (**1**) achieves again the classic mode of complexation of Diquat that we observed[4] with [Diquat·(**11**)]$^{2+}$. Here, the additional diether bridge confers both increased conformational stability and enhanced guest binding capability upon the host. The gross conformation of the DB30C10 portion of the host is, but for minor perturbations in the polyether chains, virtually unchanged from that observed[4] for one of the two independent complexes in [Diquat·(**11**)]$^{2+}$. In this instance, it should be noted that there is only one crystallographically independent complex in the asymmetric unit in the crystal. The only significant differences are a reversal of the sign of the torsion angle about C(5)–C(6) and changes in magnitude in those between C(8) and C(10). However, in this latter region, there is disorder both in [Diquat·(**11**)]$^{2+}$ and in [Diquat·(**1**)]$^{2+}$. Despite the opportunity for, and existence of, additional [C—H · · · O] interactions from the Diquat to the diether bridge, strikingly, the dication is drawn into the DB30C10 portion of the host to the same extent relative to the catechol units as in [Diquat·(**11**)]$^{2+}$. There is a characteristic[4] horizontal alignment of these aryl oxygen atoms with the nitrogen atoms of the Diquat consistent with electrostatic bonding between them. In addition to the previously described[4] binding interactions between the DB30C10 portion and the guest, the diether bridge is involved in a strong [C—H · · · O] interaction [between C(55) and O(40)] comparable to that between C(61) in the Diquat and O(4) in the polyether chain of the host.

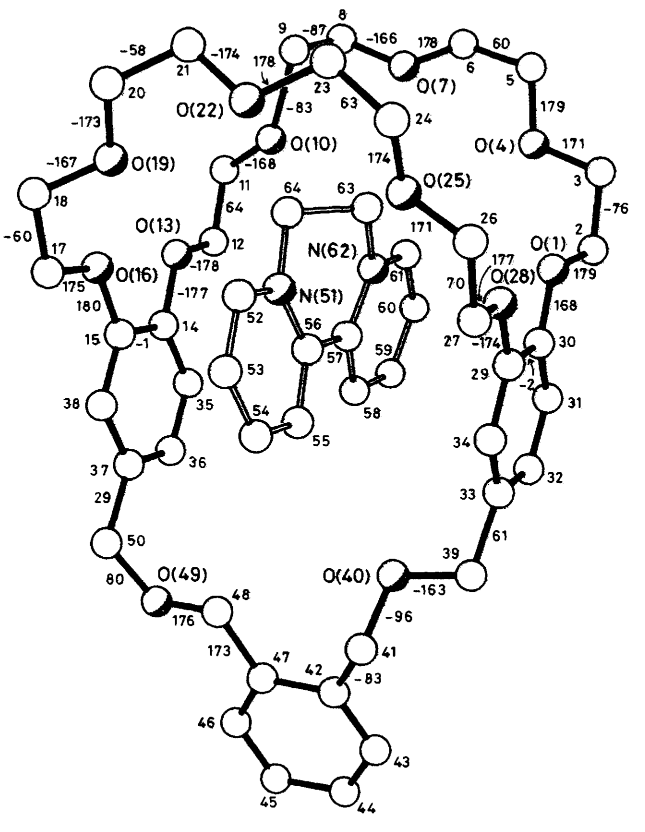


Figure 1. The solid-state structures of [Diquat·(**1**)]$^{2+}$. Torsional angles (°) (O–C–C–O and C–C–O–C) associated with the polyether chains and the diether bridge are shown beside the relevant C–C and C–O bonds. Torsional angles, taking into account the alternative position for C(9), are 154, −15, −136, and 177°, respectively, for the region O(7) to C(11). Selected hydrogen contact distances, *R*[C · · · O], *R*[H · · · O] (Å), angles (°) between COC planes and HO vectors, C–H · · · O angles (°) at H atoms assuming normal trigonal or tetrahedral geometry: [C(52) · · · O(19)] 3.11, [H(52) · · · O(19)] 2.44, 40, 127; [C(52) · · · O(22)] 3.31, [H(52) · · · O(22)] 2.46, 26, 147; [C(55) · · · O(40)] 3.17, [H(55) · · · O(40)] 2.31, 16, 149; [C(61) · · · O(4)] 3.12, [H(61) · · · O(4)] 2.36, 19, 136; [C(63) · · · O(28)] 3.32, [H(63) · · · O(28)] 2.48, 52, 146. Separation (Å) between pyridinium ring nitrogen atoms in the guest and phenolic oxygen atoms in the host: [N(51) · · · O(16)] 3.38; [N(52) · · · O(1)] 3.24. Twist angle between the pyridinium rings in the guest: 18°. Separation of the overlapping regions between the benzo rings in the host: 6.5 Å with a 9.8° departure from a parallel alignment of their mean planes.

Detailed structural information obtained previously[4] for [Diquat·(**11**)]$^{2+}$ led logically to the regiospecific synthesis of (**1**) incorporating design features necessary for encapsulation of Diquat both in the solid state and in solution.[10] The merits of designing and synthesising second-generation hosts such as (**1**), based upon the firmly established structural platform of the first generation hosts [*e.g.* (**11**)], have been vindicated for this particular guest.

¶ *Crystal data:* for [Diquat·(**1**)][PF_6]$_2$·1.5MeCN, $C_{12}H_{12}N_2$·$C_{38}H_{50}O_{12}P_2F_{12}$·$(C_2H_3N)_{1.5}$, M = 1234.51, triclinic, space group $P\bar{1}$, a = 11.471(1), b = 12.279(2), c = 23.062(4) Å, α = 76.71(1), β = 89.38(1), γ = 70.91(1)°, U = 2980 Å^3, Z = 2, D_c = 1.38 g cm^{-3}. Data were obtained using Cu-K_α radiation (graphite monochromator) on Nicolet R3m diffractometer. A total of 5859 independent reflections were measured ($\theta \leq 50°$) using the ω-scan measuring routine. Of these, 4708 had $|F_o| > 3\sigma(|F_o|)$ and were considered observed. The structure was solved by direct methods and refined anisotropically with the exception of the minor occupancy PF_6^- fluorine atoms, which were refined isotropically, to R = 0.106. Two discrete positions were observed for C(9) and each was refined with 50% occupancy. There are no close contacts between either acetonitrile molecule and the host (**1**). The atomic co-ordinates for [Diquat·(**1**)][PF_6]$_2$·1.5MeCN and (**3**) are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

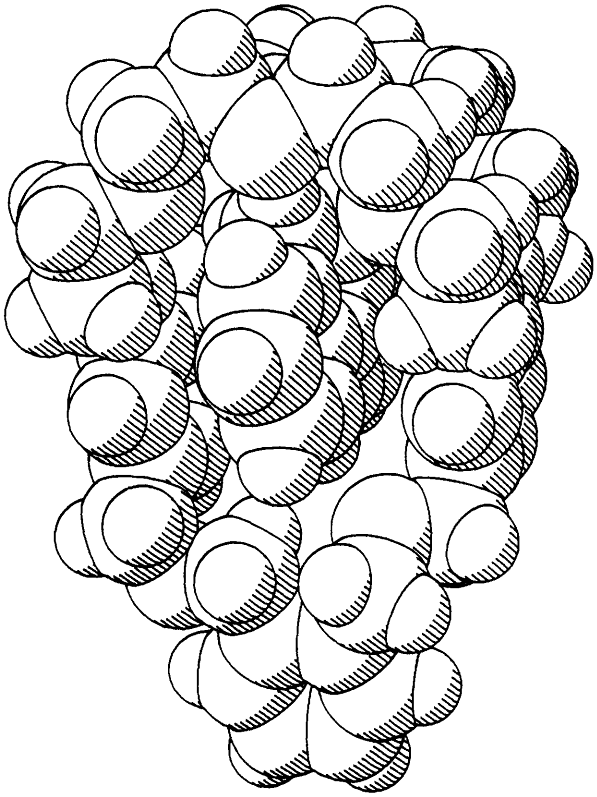


Figure 2. Space-filling representation of the structure of the 1:1 complex between (**1**) and the Diquat dication.

We thank the University of Messina in Italy, and the S.E.R.C. and A.F.R.C. in the U.K., for supporting this research.

Received, 10th November 1984; Com. 1640

References

1 For examples of some successful host designs, see K. Odashima, A. Itai, Y. Iitaka, and K. Koga, *J. Am. Chem. Soc.*, 1980, **102**, 2504; K. Odashima, A. Itai, Y. Iitaka, Y. Arata, and K. Koga, *Tetrahedron Lett.*, 1980, **21**, 4347, 4351; S. P. Adams and H. W. Whitlock, *J. Am. Chem. Soc.*, 1982, **104**, 1602; E. T. Jarvi and H. W. Whitlock, *ibid.*, 1982, **104**, 7196.

2 J.-M. Lehn, in 'Biomimetic Chemistry,' eds. Z. I. Yoshida and N. Ise, Kodansha, Tokyo, Elsevier, Amsterdam, 1983, p. 163, and references therein.

3 M. Dhaenens, L. Lacombe, J.-M. Lehn, and J.-P. Vigneron, *J. Chem. Soc., Chem. Commun.*, 1984, 1097.

4 H. M. Colquhoun, E. P. Goodings, J. M. Maud, J. F. Stoddart, D. J. Williams, and J. B. Wolstenholme, *J. Chem. Soc., Chem. Commun.*, 1983, 1140, *J. Chem. Soc., Perkin Trans. 2,* in the press.

5 See, for example, M. A. Bush and M. R. Truter, *J. Chem. Soc., Perkin Trans. 2,* 1972, 345.

6 J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, 1972, **26**, 1471.

7 B. L. Allwood, S. E. Fuller, P. C. Y. K. Ning, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1984, 1356; D. R. Alston, A. M. Z. Slawin, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 821.

8 C. M. Elliott and E. J. Hershenhart, *J. Am. Chem. Soc.*, 1982, **104**, 7519.

9 P. G. Jones, *Chem. Brit.*, 1981, **17**, 222.

10 F. H. Kohnke and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, following communication.