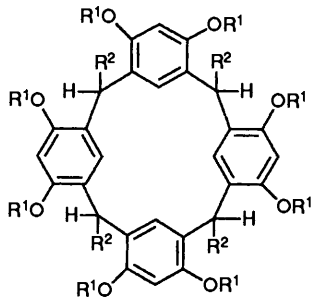
Nuclear Magnetic Resonance Elucidation of Ring-Inversion Processes in Macrocyclic Octaols[a]

Luigi Abis,* Enrico Dalcanale,*[b] Annick Du vosel, and Silvia Spera
Istituto G. Donegani, Via Fauser 4, I-28100 Novara, Italy

The conformational behaviour of the three macrocyclic octaols (**4**)–(**6**), obtained by acid-catalysed condensation of resorcinol with heptanal, is elucidated for the first time. Two of them, namely the diamond (**5a**) and the chair (**6a**) stereoisomers, undergo a ring-inversion conformational process in acetone to give the corresponding crown conformers (**5b**) and (**6b**). In DMSO or on addition of acetic acid to an acetone solution of diamond octaol (**5**), conformer (**5a**) is favoured. The presence of such equilibria and solvent effects are interpreted as an interplay between the tendency of the phenolic OH groups to form intramolecular hydrogen bonds and the alkyl chains to assume the *endo* position, avoiding steric repulsions and allowing self-aggregation.

The acid-catalysed condensation of resorcinol with aldehydes provides an easy, high-yield entry into macrocyclic octaols of general structure **A**. These cyclophanes, structurally related to the calix[4]arenes,[1] are particularly attractive since they have unusual, extremely interesting properties[2–5] correlated with their shape, solvation, and hydrogen-bonding distribution, which in turn are dictated by their conformation in solution. For this reason we became interested in their conformational behaviour in different solvents. In this paper we focus our attention on the products obtained by condensation of resorcinol with heptaldehyde. This reaction leads to a mixture of three stereoisomers of the four theoretically possible, assuming the existence of a ring-inversion conformational process. In a previous work[6] we were concerned with product distribution, stereochemistry, and conformational behaviour of acetylated octaols (**1**)–(**3**), obtained by acetylation of the above reaction mixture. For such derivatives, like on all other



A

1 R^1 = Ac, R^2 = C_6H_{13}; crown
2 R^1 = Ac, R^2 = C_6H_{13}; diamond
3 R^1 = Ac, R^2 = C_6H_{13}; chair
4 R^1 = H, R^2 = C_6H_{13}; crown
5 R^1 = H, R^2 = C_6H_{13}; diamond
6 R^1 = H, R^2 = C_6H_{13}; chair

octaol derivatives reported in the literature,[7,8] no macrocyclic ring inversion was observed, even at high temperature. Hydrolysis of acetates (**1**)–(**3**) yielded the free octaols (**4**)–(**6**), on which preliminary dynamic NMR analyses indicated the presence of a conformational equilibrium which could be rationalized by assuming the existence of a ring-inversion conformational process. The presence of such a process in macrocyclic octaols was proposed recently by Cram[9] on the basis of CPK model examinations. These facts prompted us to carry out a detailed analysis of the conformational equilibria of stereoisomeric octaols (**4**)–(**6**) in acetone and dimethyl sulphoxide (DMSO) solutions by means of dynamic NMR spectroscopy and a selective chemical probe.

Results

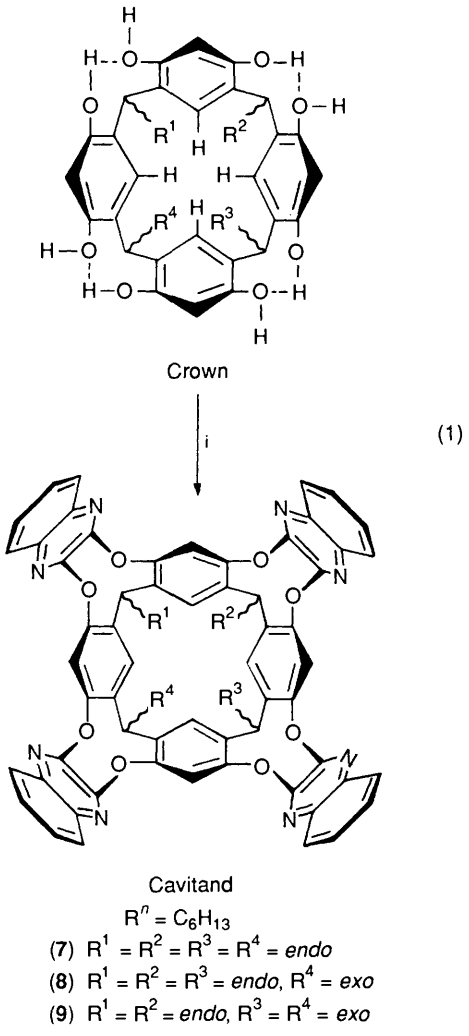
Synthesis.—Macrocyclic octaols (**4**)–(**6**) were obtained as a mixture by condensation of resorcinol with heptaldehyde. Since the isomeric mixture cannot be directly separated into their components, the acetylated derivatives (**1**)–(**3**) were prepared and purified as described in a previous paper.[6] Their conformations, as reported there, are crown for (**1**) (C_{4v}), diamond for (**2**) (C_s), and chair for (**3**) (C_{2h});† the corresponding relative configurations of the alkyl substituents are: all-*cis* (*ccc*), *cis-cis-trans* (*cct*), and *cis-trans-trans* (*ctt*).‡

The procedure then involves the hydrolysis of each of the isomeric acetates in ethanolic KOH, followed by column chromatographic purification, to give pure octaols (**4**)–(**6**). The hydrolysis does not change the relative configuration of the R groups with respect to the acetates (**1**)–(**3**).

In order to determine unambiguously the relative configuration of the R substituents in the crown conformers we devised a chemical probe. From the literature it is known that octaols in the crown conformation react with 2,3-dichloroquinoxaline to give compounds called cavitands.[10] This is due to the fact that only crown conformers have four pairs of adjacent phenolic OH groups, which can be bridged with four 2,3-disubstituted quinoxalines. Thus the position of the R groups in the resulting rigid bowl of the cavitand can be determined by NMR analysis and can then be related to that of the corresponding octaols (the relative configuration of the R groups is retained).

[a] Work presented in part at the XIV International Symposium on Macrocyclic Chemistry, Townsville, Queensland, Australia, 25th–28th June, 1989.
[b] *Present address:* Istituto di Chimica Organica, Università di Parma, Viale delle Scienze 1, I-43100 Parma, Italy.
† Calix[4]arenes show similar conformational behaviour. The corresponding designation for equivalent conformers is: crown = cone, diamond = 1,2-alternate, chair = flattened partial cone.[1]
‡ For the attribution rules see the IUPAC recommendations Section E, fundamental stereochemistry, *Pure Appl. Chem.*, 1976, **45**, rule E-2.3.3, p. 18.

The synthetic reaction is outlined in equation (1).



Equation (1). *Reagents and conditions:* i, Cs_2CO_3, 2,3-dichloroquinoxaline, acetone; stirred for 1 week at room temperature.

Table 1 reports the result of the reactions of octaols (**4**)–(**6**) with 2,3-dichloroquinoxaline (4 mol equiv.) at room temperature, in the presence of an excess of Cs_2CO_3, to give cavitands (**7**)–(**9**) with acetone as solvent. The **a,b** notation refers to the presence in solution of two different conformers of the same isomer, as discussed in the following sections.

NMR Analysis.— (i) *Octaol* (**4**). The ^1H NMR spectrum of octaol (**4**) was run in $[^2H_6]$acetone at different temperatures (Table 2) and in $(CD_3)_2SO$ (Table 3). In both solvents at all temperatures a single resonance for H^a, H^b, H^c, and OH protons was found. This spectral pattern is characteristic of a crown conformation (Figure 1) which, as previously reported for this

Table 1. Cavitands formed from octaols (**4**)–(**6**) in acetone.

Octaols in crown conformation	Positions of R substituents	Cavitand	Position of R substituents
(**4**)	4 R_{en}	(**7**)	4 R_{en}
(**5b**)	3 R_{en}, 1 R_{ex}	(**8**)	3 R_{en}, 1 R_{ex}
(**6b**)	2 R_{en}, 2 R_{ex}	(**9**)	2 R_{en}, 2 R_{ex}

en = *endo*; en = *exo*.

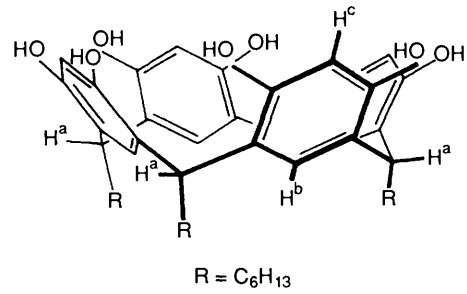


Figure 1. Crown conformation of octaol (**4**).

class of compounds,[6] is the average C_{4v} symmetry structure resulting from a fast equilibrium between two equivalent C_{2v} boat conformers.

In the case of compound (**1**) (acetylated homologue) a spectral pattern corresponding to a C_{2v} symmetry was observed at −60 °C in $[^2H_6]$acetone, indicating that the conformational mobility of the two boat conformers is frozen at this temperature, while for octaol (**4**) no changes in the spectrum were noticed under the same conditions (Table 2). This result suggests that the elimination of the acetyl moieties unlocks the conformational mobility of the macrocycle, decreasing considerably the interconversion energy between the conformers of the free phenolic compounds.

By reaction of octaol (**4**) with 2,3-dichloroquinoxaline (Table 1) only cavitand (**7**) (C_{4v}) was obtained, which, as found by X-ray crystal-structure determination,[10b] has all R substituents in the *endo* position.* Therefore the presence of a ring-inversion conformational process in the above solvents for octaol (**4**) is highly improbable: no cavitand derived from a crown conformer with all-*exo* substituents was detected within the limits of our measurements.

(ii) *Octaol* (**5**). Variable-temperature ^1H NMR spectra of compound (**5**) in $(CD_3)_2SO$ (26–120 °C) showed features, *i.e.* number of peaks for each H^a, H^b, H^c proton and chemical-shift distribution, similar to those of the corresponding acetylated material[6] (Table 3). We can therefore deduce that the conformation of octaol (**5**) in $(CD_3)_2SO$ is still a diamond (C_s) with all-*endo* substituents. In contrast, in $[^2H_6]$acetone a broad spectrum was observed at room temperature, which narrowed at high temperature (+55 °C) and which split into several peaks at low temperature (−50 °C; Figure 2). In the low-temperature spectrum in $[^2H_6]$acetone, the eight peaks between δ 8.20–9.50 are assigned to the OH groups since upon addition of $[^2H_4]$acetic acid their intensities decreased. The seven peaks between δ 6.00–8.00 remain unchanged and therefore they belong to aromatic protons. The relative intensities of the aromatic and H^a peaks do not correspond to a single structure; they can be rationalized by assuming the presence in solution of two different conformations, (**5a**) and (**5b**), in a slow, temperature-dependent, equilibrium.

The assignment of the aromatic signals for each conformer to the respective H^b and H^c protons is based on the assumption that the relaxation time T_1 is longer for H^c than for H^b (Table 4), as found for the corresponding acetylated compounds.† The relative areas of H^b protons provided data for the calculation of the conformer molar ratio K_c = [(**5a**)]/[(**5b**)], the natural logarithm of which is plotted against (1/*T*) in Figure 3.

* The axial–equatorial designation used in references 6–9 is equivalent to the *endo–exo* one applied to the related calixarene macrocycles. We switched to the *endo–exo* designation for clarity reasons.

† The above reported relaxation times for the H^c protons are considerably shorter than those for the equivalent protons in the corresponding acetylated isomer (**2**)[6] because of the presence of free OH groups which contribute to their dipolar relaxations.

Table 2. ^{1}H NMR chemical shifts (δ) of the octaols at different temperatures in [$^2H_6$]acetone.

Compd.	T/°C	H^{b1}	H^{b2}	H^{c1} [a]	H^{c2} [a]	$H^{a2,3,4}$	H^{a1}
(4)	room temp.	7.55		6.23		4.29	
	−60	7.64		6.19		4.20	
(5)	+55	7.45	7.19	6.32	6.24	4.39	4.03
	room temp.	7.46	n.d.	6.29	6.23	4.33	4.02
(5a)	−50	7.34	6.22	6.46	6.29	4.50	3.99
(5b)	−50	7.58		6.22	6.16	4.18	3.99
(6)	room temp.	6.82	6.54		6.33	4.37	
	−60	6.87	6.44	6.36	6.34	4.45	

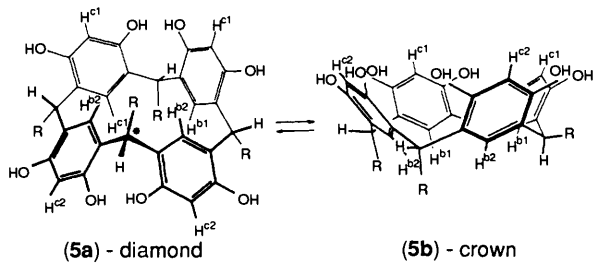
[a] H^{c1} and H^{c2} can be interchanged.

Table 3. ^{1}H NMR chemical shifts (δ) of the octaols at different temperatures in $(CD_3)_2SO$.

Compd.	T/°C	H^{b1}	H^{b2}	H^{c1}	H^{c2}	H^{a3}	$H^{a2,4}$	H^{a1}
(4)	room temp.	7.20		6.20			4.27	
(5a)	room temp.	7.30	6.24	6.32		4.66	4.32	4.18
	+120	7.32	6.41	6.33	6.25	4.62	4.42	4.15
(6a)	room temp.	6.75	6.20	6.32	6.26		4.33	
	+120	6.81	6.45	6.35	6.32		4.34	

Table 4. T_1 Proton relaxation times (s) of compound (5) at −60 °C in [$^2H_6$] acetone.

Compd.	OH	H^{b1}	H^{b2}	H^{c1}	H^{c2}
(5a)	1.44, 1.37, 1.31, 1.31	0.42	0.44	1.63	1.85
(5b)	1.20, 1.23, 1.32, 1.30	0.47	0.47	1.64	1.88



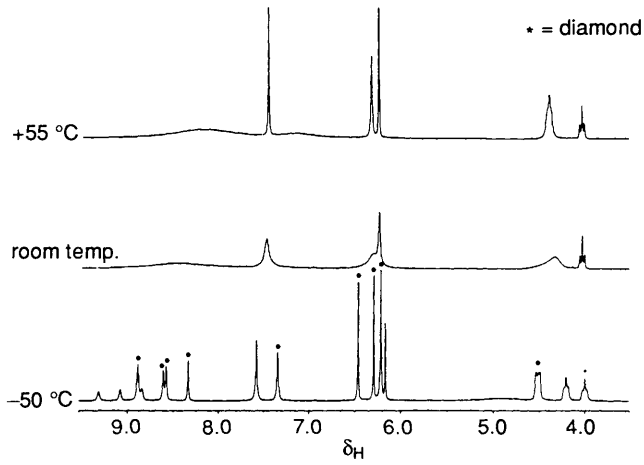


Figure 2. NMR spectrum of octaol (5) (diamond isomer) in [$^2H_6$]acetone at +55 °C, at 25 °C, and at −50 °C.

Since octaol (5) derives from the acetylated diamond (2) (C_s) the above two structures (5a) and (5b) maintain the *cct* relative configuration. Conformer (5a) showed spectral features which

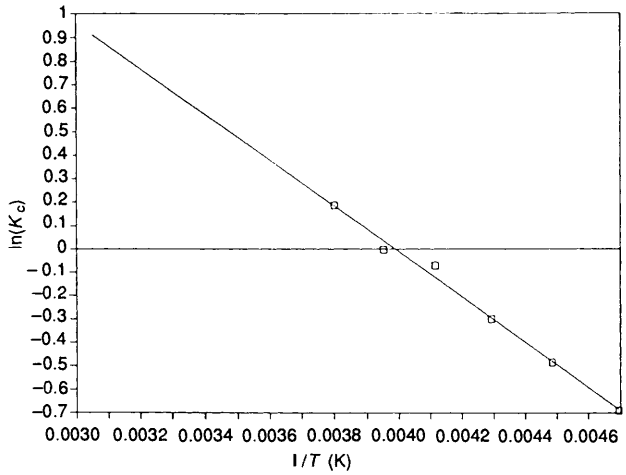


Figure 3. Plot of ln K_c *versus* $1/T$ (K^{-1}) for the interconversion diamond–crown in compound (5); K_c is calculated as [crown]/[diamond] from the ^{1}H NMR spectrum.

clearly belong to a diamond conformation with all-*endo* substituents (C_s). Conformer (5b), showing one single peak for H^b protons, two peaks for H^c and four for OH (Table 3), possesses one plane of symmetry (C_s). The only conformation which complies with these findings is a crown with three *endo* substituents and one *exo* or *vice versa*. This requires a ring inversion of the diamond conformer.

To verify the above hypothesis we treated octaol (5) with 2,3-dichloroquinoxaline, which gave cavitand (8) (Table 1). The product showed, in the H^a region, three triplets at δ 5.62, 5.57, and 3.94, with relative intensity 2:1:1 (Table 5; Figure 4). Comparing this spectrum to that of cavitand (7) (C_{4v}) we can assign the first two signals to protons in the *endo* position. The third one, whose chemical shift is very different from the others, must occupy an *exo* position. Thus cavitand (8) (C_s) clearly derives from crown octaol (5b) in which one substituent is *exo* and the other three are *endo*, in agreement with the above ring-inversion hypothesis.

In the high-temperature spectrum in [$^2H_6$]acetone at 55 °C the equilibrium between conformers (5a) and (5b) became fast on the NMR time-scale; the result is a spectrum correspond-

Table 5. ^{1}H NMR chemical shifts (δ) of cavitands (**7**)–(**9**) at room temperature in $CDCl_3$.

Compd.	H^c	H^b	H^a	R position
(**7**)	8.13**	7.20**	5.52**	4 R_{en}
(**8**)	8.21,* 8.17*	7.20,* 7.16*	5.62,* 5.57, 3.94	3 R_{en}, 1 R_{ex}
(**9**)	8.22,* 8.20, 8.18	7.18, 7.12, 7.12*	5.60,* 3.89*	2 R_{en}, 2 R_{ex}

* Signal intensity which corresponds to two protons.
** Signal intensity which corresponds to four protons.

Table 6. Calculated and experimental ^{1}H NMR chemical shifts of compound (**5**) in [$^2H_6$]acetone at 55 °C.

	H^{b1}	H^{b2}	H^{c2}	H^{c1}	$H^{a2,3,4}$
Diamond at −10 °C	7.36	6.23	6.29	6.46	4.53
Crown at −10 °C	7.54	7.54	6.19	6.23	4.24
Average structure at +55 °C	7.45	7.19	6.24	6.32	4.39
	(7.45)[a]	(7.16)	(6.22)	(6.30)	(4.32)

[a] The numbers in parenthesis are calculated as the average of the two chemical shifts at −10 °C, weighted on the basis of the conformer concentration ratio K_c extrapolated at +55 °C.

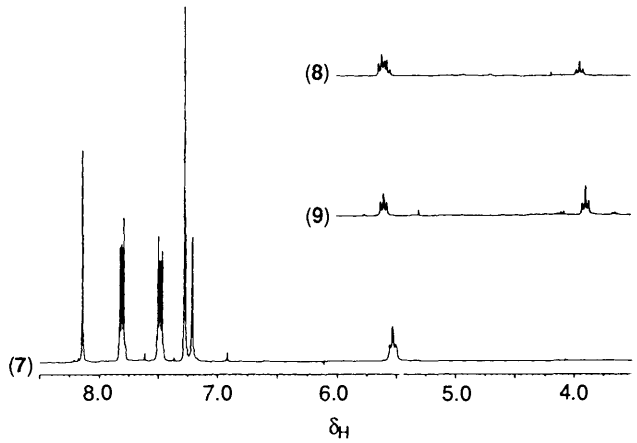


Figure 4. ^{1}H NMR spectra of cavitands in $CDCl_3$ at 25 °C; (**7**) – derived from a *ccc*-crown; (**8**)–derived from a *cct*-crown; (**9**) – derived from a *ctt*-crown.

ing to a single average structure. Therefore the chemical shifts found at 55 °C are the weighted average of the resonances of the same protons belonging respectively to the frozen conformations (**5a**) and (**5b**). From Figure 3 the molar ratio K_c is extrapolated at 55 °C and the average spectrum is calculated starting from the chemical shifts taken at −10 °C (Table 6). The agreement with the experimental values is perfect, thus confirming the resonance assignment.

Variable-temperature spectra allow the calculation of $\Delta G^{\ddagger}$ activation energies for ring inversion at the coalescence temperatures T_c of H^{b1} and $H^{a2,3,4}$ resonances on the basis of tabulated values[11] and the experimental parameters, as reported in Table 7.

To understand why only the diamond conformer (**5a**) is found in $(CD_3)_2SO$, the following experiment was devised: an acetone solution containing conformer (**5a**) and (**5b**) in equilibrium was evaporated, and the residue was dissolved in $(CD_3)_2SO$; only the diamond conformer (**5a**) was found by ^{1}H NMR spectroscopy. Furthermore, by addition of [$^2H_4$]acetic acid to the [$^2H_6$]acetone solution, we observed that the relative amount of conformer (**5b**) decreased with respect to (**5a**). These two results suggested that hydrogen bond-accepting and

Table 7. Activation energy $\Delta G^{\ddagger}$ for ring-inversion of conformers (**5a**) ⇌ (**5b**).

	H^{b1}	$H^{a2,3,4}$
T_c (K)	328	303
Δp[a]	0.41	0.31
Δν (Hz)[b]	408	96
K^c (s^{-1})	588	148
$\Delta G^{\ddagger}$ (kJ mol^{-1})	80.5 ± 1	74.5 ± 1

[a] Taken at T_c from K_c plot (Figure 4). [b] Taken at −50 °C from Table 2. [c] Calculated from tabulated values.

-donating solvents shift the equilibrium toward the diamond form, since intermolecular hydrogen bonds with solvent substitute for mainly intramolecular hydrogen bonds in conformer (**5b**).

(iii) *Octaol* (**6**). The ^{1}H NMR spectrum of octaol (**6**) in $(CD_3)_2SO$ showed very sharp signals (Table 3), close to those of the corresponding acetylated derivative (**3**)[6] (C_{2h}). In [$^2H_6$]acetone the spectrum is broad, due to the presence of fluxionality (Table 2; Figure 5). By analogy with the behaviour of octaol (**5**), the presence of a slow conformational equilibrium in acetone between the chair-(**6a**) (C_{2h}) and the crown-(**6b**) (C_s) is supposed. To support the equilibrium hypothesis we treated octaol (**6**) in acetone solution with 2,3-dichloroquinoxaline to give cavitand (**9**). The ^{1}H NMR spectrum of cavitand provided the following features (Table 5; Figure 4): two H^a triplets at 5.60 and 3.89 of relative intensity 2:2, the first assigned to the two *endo* H^a protons and the second to the two *exo* ones; two equivalent H^c protons at δ 8.22 and two non-equivalent ones at δ 8.20 and 8.18; the same situation is observed for H^b protons as well. This non-equivalence implies that cavitand (**9**) (C_s) has two adjacent *exo* R substituents, in agreement with the proposed equilibrium. Further support for this interpretation came from a careful inspection of the spectra of octaol (**6**) in [$^2H_6$]acetone at various temperatures: the existence of conformer (**6b**) was confirmed by the presence of small peaks which were broad at room temperature (see peaks marked with an asterisk in Figure 5).

Conclusions.—The presence of ring-inversion processes in macrocyclic octaols of general structure **A** is unambiguously demonstrated for the first time: dynamic ^{1}H NMR analysis and

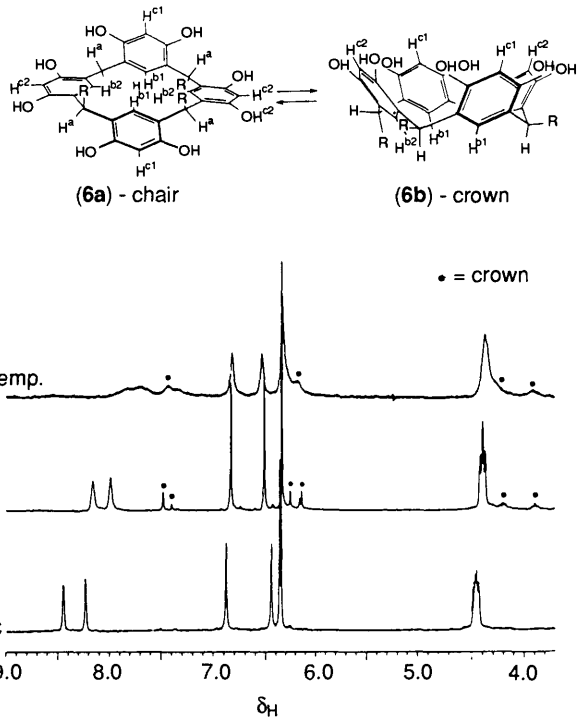


Figure 5. ^{1}H NMR spectrum of octaol (**6**) in [$^2H_6$]acetone from −60 °C to 25 °C. * Marks the resonances of crown conformer (**6b**).

selective chemical derivatization indicated the existence of a conformational equilibrium between octaols (**5a**) and (**6a**) and the corresponding crown conformers (**5b**) and (**6b**) in acetone solution.

The inversion of the macrocyclic ring requires the exchange of the R positions from *endo* to *exo* and *vice versa*. Cavitand (**7**) (C_{4v}) has all the R substituents *endo*, as shown by X-ray crystal structure.[10b] This implies the absence of any ring-inversion process for octaol (**4**). Cavitand (**8**) (C_s) instead presents one *exo* substituent; this is consistent with the ring inversion of the two metaphenylene rings connected to the methine labelled with an asterisk in compound (**5a**) (Figure 2). Cavitand (**9**) (C_s) has two adjacent *exo* substituents; therefore, it exclusively derives from octaol (**6a**) by ring inversion of one of the two metacyclophane rings perpendicular to the macrocyclic plane.

We interpret the ring-inversion process as an interplay among the intramolecular hydrogen bonds of the phenolic OH groups, the tendency of the R groups to assume the *endo* position, and the intermolecular hydrogen bondings with solvent.

By CPK model examination all crown isomers (*ccc*, *cct*, *ctt*) readily form four O • • • H intramolecular hydrogen bonds (confirmed by X-ray crystal structure analysis on a similar *ccc* crown octaol[9]), while only two are present in the corresponding *cct*-diamond and *ctt*-chair isomers.

The tendency of the R groups to occupy the less hindered *endo* position has been generally observed in this class of compounds.[6] The *exo* substitution is unfavourable because of the steric repulsion between the R and the OH groups[4] and because the *endo* alkyl chains 'solvate' one another better than does a polar solvent.[9]

In the case of the *ccc*-isomer (**4**) these two effects contribute to stabilize the all-*endo* crown conformation: in fact no trace of all-*exo* crown conformation was detected either by ^{1}H NMR spectroscopy or by chemical derivatization. In the other equilibria we observed that the crown conformer was progressively destabilized on an increase in the number of equatorial substituents [50% of (**5b**), 10% of (**6b**)],* by addition of acetic acid (hydrogen-bond donator) or by dissolution in $(CD_3)_2SO$ (hydrogen-bond acceptor). In these compounds all three effects compete with each other for dominance: in octaols (**5b**) and (**6b**), in which the intramolecular O • • • H hydrogen bonds are dominant, some substituents are *exo*, while in octaols (**5a**) and in (**6a**) where the R groups are all *endo*, intramolecular O • • • H interactions are less dominant.

We suggest that intramolecular O • • • H interactions compensate for the loss of stability introduced by the *exo* substituents, thus stabilizing the crown conformers, while the addition of proton-donor or -acceptor solvents breaks the hydrogen bonds and shifts the equilibrium toward the more stable conformers, *i.e.* the all-*endo* ones.

It is now possible, by means of the solvent, to control the three effects governing the relative stability of the octaol conformers, *i.e.* the intramolecular hydrogen bonding, intermolecular hydrogen bonding, and *endo versus exo* positioning of the R substituents.

Experimental

General.—ACS-grade reagents were used without further purification. Column chromatography was performed on silica gel 60 (Merck, 230–400 mesh ASTM). Analytical TLC was conducted on precoated Merck silica gel 60 plates. NMR spectra were recorded on a Bruker AM-300 spectrometer equipped with a variable-temperature device. Solutions were prepared by dissolution of compounds (~5 mg) in deuteriated solvent (0.5 ml) and removal of oxygen by blowing gaseous nitrogen into the NMR tube for a few minutes. Chemical shifts use, as internal reference, the solvent peak referred to $SiMe_4$ (δ 2.04 for acetone, 2.56 for DMSO, 7.25 for $CDCl_3$). Relaxation times were obtained by using the inversion-recovery technique and elaboration of the spectral data with a Bruker library program.

Mass spectra were recorded on a Finnigan MAT 8400 spectrometer, using the DCI technique (current gradient 40 mA s^{-1}, isobutane as carrier gas). Elemental analyses were performed by the microanalytical laboratory of the Donegani Institute. M.p.s were measured on a Kofler apparatus and are uncorrected. All products were identified through their elemental analysis, NMR, and DCI-MS spectra.

Standard Procedure for Hydrolysis.—The pure phenolic derivatives (**4**), (**5**), and (**6**) were obtained by hydrolysis of the respective octa-acetates (**1**)–(**3**) in ethanolic KOH. A mixture of an octa-acetate (1.16 g, mmol) and KOH (1.20 g) in ethanol (30 cm^3) was refluxed for 30 min. Then acetic acid (1.2 g) was added. The solvent was distilled off under reduced pressure, and the crude product was treated with water (20 cm^3) and kept at 0 °C overnight. After filtration, the pure product (0.66 g, 80%) was obtained by chromatography on silica gel [(30:1) diethyl ether–methanol] (analytical samples dried 8 h at 10^{-3} Torr†).

r-2,c-8,c-14,c-20-*Tetrahexylpentacyclo*-[19.3.1.1^{3,7}.1^{9,13}.-1^{15,19}]-*octacosa*-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-*dodecaene*-4,6,10,12,16,18,22,24-*octaol* (**4**). R_f 0.58 [(30:1) Et_2O–MeOH], m.p. > 315 °C (decomp.) (Found: C, 75.55; H, 9.0. $C_{52}H_{72}O_8$ requires C, 75.60; H, 8.79%); δ_H[$(CD_3)_2SO$] 0.90 (12 H, t, *J* 6.7 Hz, Me), 1.28 (32 H, br m, $[CH_2]_4$), 2.06 (8 H, m, CH_2^{α}), 4.27 (4 H, t, *J* 7.5 Hz, H^a), 6.20 (4 H, s, H^c), 7.20 (4 H, s, H^b), and 8.92 (8 H, s, OH); *m/z* 825 (MH^+, 100%).

* Values obtained by comparison of the relative intensities of the peaks of each couple of conformers ([$^2H_6$]acetone spectra).
† 1 Torr = 133.322 Pa.

r-2,c-8,c-14,t-20-*Tetrahexylpentacyclo*-[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]*octacosa*-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-*dodecaene*-4,6,10,12,16,18,22,24-*octaol* (**5**). R_f 0.53 [(30:1) Et_2O–MeOH], m.p. 130–132 °C (Found: C, 72.4; H, 8.6. $C_{52}H_{72}O_8 \cdot 2H_2O$ requires C, 72.52; H, 8.85%); δ_H[$(CD_3)_2SO$] 0.88 (12 H, m, Me), 1.05 (8 H, br m, CH_2), 1.27 (24 H, br m, $[CH_2]_3$), 1.66 (2 H, m, CH_2^{α}), 1.84–1.93 (6 H, m, CH_2^{α}), 4.18 (1 H, t, *J* 7.2 Hz, H^{a3}), 4.32 (2 H, dd, *J* 11.2 and 3.6 Hz, H^{a2}), 4.66 (1 H, t, *J* 7.7 Hz, H^{a1}), 6.24 (2 H, s, H^{b2}), 6.32 (4 H, s, H^{c}), 7.30 (2 H, s, H^{b1}), 8.61 (2 H, s, OH), 8.67 (2 H, s, OH), 8.84 (2 H, s, OH), and 8.88 (2 H, s, OH); *m/z* 825 (MH^+, 25%).

r-2,c-8,t-14,t-20-*Tetrahexylpentacyclo*-[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]*octacosa*-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-*dodecaene*-4,6,10,12,16,18,22,24-*octaol* (**6**). R_f 0.68 [(30:1) Et_2O–MeOH], m.p. 245–246 °C (Found: C, 72.5; H, 8.7. $C_{52}H_{72}O_8 \cdot 2H_2O$ requires C, 72.52; H, 8.85%); δ_H[$(CD_3)_2SO$] 0.88 (12 H, t, *J* 6.7 Hz, Me), 1.25 (32 H, br m, $[CH_2]_4$), 1.52 (4 H, m, CH_2^{α}), 1.67 (4 H, m, CH_2^{α}), 4.33 (4 H,dd, *J* 10.0 and 4.7 Hz, H^{a}), 6.20 (2 H, s, H^{b2}), 6.26 (2 H, s, H^{c2}), 6.32 (2 H, s, H^{c1}), 6.75 (2 H, s, H^{b1}), 8.47 (4 H, s, OH), and 8.70 (4 H, s, OH); *m/z* 825 (MH^+, 10%).

General Procedures for Cavitand Formation.—To a stirred solution of an octaol (**4**), (**5**), or (**6**) (0.300 g, 0.364 mmol) in dry acetone (30 cm^3) were added 2,3-dichloroquinoxaline (0.290 g, 1.46 mmol) and Cs_2CO_3 (0.540 g, 1.66 mmol). The resulting suspension was stirred for 1 week at 25 °C under argon, then treated with water and the precipitate formed was filtered off and washed to neutrality. The crude product was chromatographed on silica gel [(75:25) cyclohexane–ethyl acetate] to give (analytical samples dried 8 h at 10^{-3} Torr; 300 °C):

from octaol (**4**): cavitand (**7**) (0.120 g, 25%)
from octaol (**5**): cavitand (**8**) (0.024 g, 5%)
from octaol (**6**): cavitand (**9**) (0.024 g, 5%)

r-9,c-11,c-13,c-15-*Tetrahexyl*-7,17:8,16-*dimetheno*-9H,11H,13H,15H-*quinoxalino*[2‴,3‴:2‴,3‴][1,4]*benzodioxonino*-[10‴,9‴:5,6]*quinoxalino*[2′,3′:2′,3′]*quinoxalino*[2″,3″:2″,3″]-[1,4]*dioxonino*[6″,5″:9′,10′][1,4]*benzodioxonino*[6′,5′:9,10]-[1,4]*benzodioxonino*[2,3-b]*quinoxaline*, *Stereoisomer* (**7**). R_f 0.50 [(75:25) cyclohexane–ethyl acetate], m.p. >315 °C (Found: C, 75.8; H, 6.1; N, 8.4. $C_{84}H_{80}N_8O_8$ requires C, 75.88; H, 6.06; N, 8.43%); δ_H($CDCl_3$) 0.92 (12 H, t, *J* 6.7 Hz, Me), 1.23–1.47 (32 H, m, $[CH_2]_4$), 2.26 (8 H, m, CH_2^{α}), 5.52 (4 H, t, *J* 7.9 Hz, H^{a}), 7.20 (4 H, s, H^{b}), 7.45–7.50 (8 H, m, AA′ part of an AA′BB′ system), 7.77–7.82 (8 H, m, BB′ part of an AA′BB′ system), and 8.13 (4 H, s, H^{c}); *m/z* 1 328 (M^-, 100%).

r-9,c-11,c-13,t-15-*Tetrahexyl*-7,17:8,16-*dimetheno*-9H,11H,13H,15H-*quinoxalino*[2‴,3‴:2‴,3‴][1,4]*benzodioxonino*-[10‴,9‴:5,6]*quinoxalino*[2′,3′:2′,3′]*quinoxalino*[2″,3″:2″,3″]-[1,4]*dioxonino*[6″5″:9′,10′][1,4]*benzodioxonino*[6′,5′:9,10]-[1,4]*benzodioxonino*[2,3-b]*quinoxaline*, *Stereoisomer* (**8**). R_f 0.53 [(75:25) cyclohexane–ethyl acetate], m.p. >315 °C (Found: C, 75.50; H, 6.0; N, 8.4%); δ_H($CDCl_3$) 0.83–0.95 (12 H, m, Me), 1.22–1.46 (32 H, m, $[CH_2]_4$), 2.19–2.41 (6 H, m, CH_2^{α}), 2.89 (2 H, m, CH_2^{α}), 3.94 (1 H, t, *J* 8.2 Hz, H^{a}), 5.57 (1 H, t, *J* 7.9 Hz, H^{a}), 5.61 (2 H, t, *J* 7.3 Hz, H^{a}), 7.16 (2 H, s, H^{b}), 7.20 (2 H, s, H^{b}), 7.44–7.48 (8 H, m, AA′ part of an AA′BB′ system), 7.77–7.82 (8 H, m, BB′ part of an AA′BB′ system), 8.17 (2 H, s, H^{c}), and 8.21 (2 H, s, H^{c}); *m/z* 1 328 (M^-, 100%).

r-9,c-11,t-13,t-15-*Tetrahexyl*-7,17:8,16-*dimetheno*-9H,11H,13H,15H-*quinoxalino*[2‴,3‴:2‴,3‴][1,4]*benzodioxonino*-[10‴,9‴:5,6]*quinoxalino*[2′,3′:2′,3′]*quinoxalino*[2″,3″:2″3″]-[1,4]*dioxonino*[6″,5″:9′,10′][1,4]*benzodioxonino*[6′,5′:9,10]-[1,4]*benzodioxonino*[2,3-b]*quinoxaline*, *Stereoisomer* (**9**). R_f 0.50 [(75:25) cyclohexane–ethyl acetate], m.p. >315 °C (Found: C, 75.75; H, 6.1; N, 8.3%); δ_H($CDCl_3$) 0.86–0.95 (12 H, m, Me), 1.22–1.44 (32 H, m, $[CH_2]_4$), 2.30 (4 H, m, CH_2^{α}), 2.90 (4 H, m, CH_2^{α}), 3.89 (2 H, t, *J* 8.22 Hz, H^{a}), 5.60 (2 H, t, *J* 7.33 Hz, H^{a}), 7.12 (3 H, s, H^{b}), 7.18 (1 H, s, H^{b}), 7.44–7.49 (8 H, m, AA′ part of an AA′BB′ system), 7.77–7.82 (8 H, m, BB′ part of an AA′BB′ system), 8.18 (1 H, s, H^{c}), 8.20 (1 H, s, H^{c}), and 8.22 (2 H, s, H^{c}); *m/z* 1 328 (M^-, 100%).*

* *Supplementary material:* ^{1}H NMR spectra of compound (**4**) in [$^2H_6$]acetone at −60 °C and at room temperature, and of compounds (**5a**) and (**6a**) in $(CD_3)_2SO$ at room temperature are available as Supplementary Publication no. SUP 56791 (4pp.). See section 4.4 of 'Instructions for Authors (1990)' in the January issue.

Acknowledgements

We thank Professor D. J. Cram (UCLA) for helpful suggestions.

References

1 For a general discussion see: C. D. Gutsche, 'Calixarenes,' ed. J. F. Stoddart, Royal Society of Chemistry, Cambridge, 1989.
2 Y. Aoyama, Y. Tanaka, H. Toi, and H. Ogoshi, *J. Am. Chem. Soc.*, 1988, **110**, 634.
3 Y. Aoyama, Y. Tanaka, and S. Sugahara, *J. Am. Chem. Soc.*, 1989, **111**, 5397.
4 H.-J. Schneider, D. Güttes, and U. Schneider, *J. Am. Chem. Soc.*, 1988, **110**, 6449.
5 H.-J. Schneider, D. Güttes, and U. Schneider, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 647.
6 L. Abis, E. Dalcanale, A. Du vosel, and S. Spera, *J. Org. Chem.*, 1988, **53**, 5475.
7 A. G. S. Högberg, *J. Am. Chem. Soc.*, 1980, **102**, 6046.
8 A. G. S. Högberg, *J. Org. Chem.*, 1980, **45**, 4498.
9 L. M. Tunstad, J. A. Tucker, E. Dalcanale, J. Weiser, J. A. Bryant, J. C. Sherman, R. C. Hegelson, C. B. Knobler, and D. J. Cram, *J. Org. Chem.*, 1989, **54**, 1305.
10 (*a*) J. R. Moran, S. Karback, and D. J. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 5826; (*b*) E. Dalcanale, P. Soncini, G. Bacchilega, and F. Ugozzoli, *J. Chem. Soc., Chem. Commun.*, 1989, 500.
11 M. L. Martin, J.-J. Delpuech, and G. J. Martin, 'Practical NMR Spectroscopy,' Heyden, London, 1980, pp. 297–340.

Paper 0/00811G
Received 22*nd February* 1990
Accepted 20*th June* 1990