The Complexation of Estrogens and Tetralins in the Cavities of Azoniacyclophanes. A ^1H and ^{13}C Nuclear Magnetic Resonance Spectroscopic Study[1]

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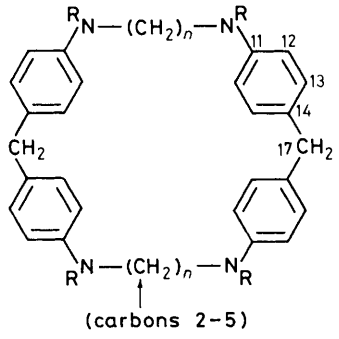
^1H N.m.r. shift titrations of *e.g.* estradiol (**2**), 2-tetralol (**6**), and the corresponding phenoxides (**3**) and (**4**) with an azoniacyclophane (**CP6**), containing diphenylmethane and n-hexane chains, in aqueous methanol shows association constants K between 20 and 250 l mol^{-1}, corresponding to 10^2—10^5 l mol^{-1} in neat water (by extrapolation). The binding constants are approximately double for the steroid compared with the tetralin derivatives, although the cavity can encompass only the A and B rings of the estrogen. The enlarged cavity in a cyclophane containing n-octane chains (**CP8**) does not lead to increased binding of the steroid, but to a decrease by a factor of 2.5. ^1H N.m.r. complexation-induced shifts (c.i.s.) indicate the insertion of tetralin derivatives and of the corresponding A and B steroid rings inside the cyclophanes. The corresponding ^{13}C c.i.s. values, although relatively large, are shown to give no reliable information about the geometries of the inclusion complexes in solution.

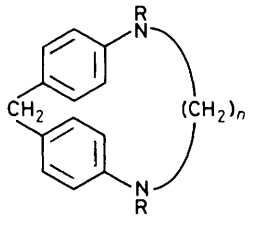
Macrocyclic compounds with large endolipophilic cavities can be made water soluble by the presence of, *e.g.*, positively charged nitrogen atoms. They can then act as simple receptor models complexing a variety of organic substrates preferentially by hydrophobic forces, but also by electrostatic attraction if the substrate carries complementary charges.[2] We wanted to see to what degree azoniacyclophanes of the type (**CP6**) can complex very large substrates such as steroids, which can only be partially inserted into the host cavity, and also how an enlarged host ring size affects the binding.

Estratriene derivatives (**1**)—(**3**) were chosen in view of their sufficient solubility in aqueous media and the possibility of investigating the influence of charge in the form of the 3-phenoxy anion; for comparison the corresponding tetralin compounds (**5**) and (**6**) were also studied. The only reliable method to prove the existence of intracavity inclusion in solution has been shown to be n.m.r. spectroscopy[2,3] which until now has largely been restricted to ^1H n.m.r. observations. In this paper we also investigated whether ^{13}C n.m.r. shifts can be used as these have been so successful in structural studies of steroids.[4]

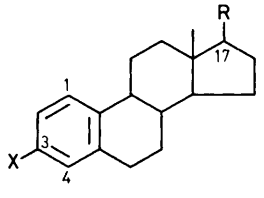
Synthesis of Hosts.—The one-step preparation of large heterocycles from suitable diphenylmethane derivatives and α,ω-dihalogenoalkanes has been performed by Lüttringhaus, who also discovered the simultaneous formation of smaller rings containing two instead of four heteroatoms.[5,6] Whereas the reaction of ditosylated *p,p'*-dianilinomethane[2a] with 1,6-dibromohexane furnishes only the tetra-azacyclophane (**CP6**)[7a] treatment with 1,8-dibromo-octane also yielded 25% of the smaller diaza-ring (**CP8D**), which could be removed after detosylation to (**CP8b**). The macrocycles, including the permethylated derivative (**CP8-c**), which was obtained by treatment of (**CP8-b**) with methyl iodide and then with hydrochloric acid, showed only the expected signals in the ^1H and ^{13}C spectra; signal integration by comparison with an internal reference of known concentration, however, indicated that after several attempts of purification the (**CP8**) compounds reached sufficient purity (>90%) for the complexation studies but not for elemental analysis. A similar situation has been found[7b] for many macrocycles which often contain other rings as well as oligo- and poly-mers not visible in the n.m.r. spectra.



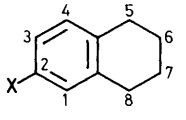
(**CP6**) (n = 6)
(**CP8**) (n = 8)
a; R = p-$SO_2C_6H_4CH_3$
b; R = H
c; 2R = 2 · $CH_3(^+N,Cl^-)$



(**CP8D**) (n = 8)



(**1**) X = OH, R = =O
(**2**) X = OH, R = β-OH, α-H
(**3**) X = O^-, R = β-OH, α-H
(**4**) X = NH_2, R = =O



(**5**) X = OH
(**6**) X = O^-

N.m.r. Spectral Analysis of the Steroids and their Tetralin Analogues.—Although ^{13}C n.m.r. signals of common estrogens

Table 1. N.m.r. shifts of estra-1,3,5-triene derivatives[a]

Carbon atom	3-OH, 17-Oxo (1)		3-OH, 17β-OH (2)		3-O⁻, 17β-OH (3)		3-NH₂, 17-Oxo (4)	
	^{13}C[b]	^{1}H[b]	^{13}C[c]	^{1}H[c]	^{13}C[d]	^{1}H[d]	^{13}C[e]	^{1}H[e]
1	126.0	7.25	127.07	7.13	126.93	7.01	126.17	7.08
2	112.9	6.50	114.00	6.60	117.23	6.41	113.10	6.52
3	155.0		156.40		164.15		144.19	
4	115.0	6.44	116.33	6.55	119.22	6.36	115.36	6.44
5	137.1		138.81		138.57		137.37	
6α	29.1	2.74[f]	30.65	2.8[f]	30.35	2.7[f]	29.48	2.8[f]
6β								
7α	26.2	1.36	28.51	1.26	28.23	1.25	26.60	1.59
7β		1.89		1.89		1.83		1.98
8	38.0	1.44	40.57	1.35	40.27	1.34	38.55	1.58
9	43.5	2.11	45.35	2.11	44.81	2.07	43.98	2.20
10	130.0		132.45		127.63		130.08	
11α	25.5	2.28	27.60	2.28	27.23	2.26	25.93	2.36
11β		1.33		1.38		1.37		1.48
12α	31.4	1.34	38.07	1.23	37.50	1.21	31.82	1.47
12β		1.73		1.92		1.90		1.94
13	47.3		44.38		43.97		48.03	
14	49.6	1.43	51.41	1.18	50.63	1.18	50.46	1.49
15α	21.0	1.94	24.02	1.69	23.64	1.68	21.57	2.03
15β		1.55		1.33		1.31		1.60
16α	35.4	2.40	30.80	2.06	30.14	2.01	35.84	2.49
16β		2.03		1.50		1.49		2.13
17	221.04		82.54	3.68	82.47	3.67	220.83	
18	13.5	0.80	11.68	0.74	11.67	0.74	13.86	0.90

[a] In p.p.m. from internal Me_4Si, ambient temperature; [b] In [$^2H_6$]DMSO. [c] In CD_3OD. [d] In CD_3OD–D_2O 40:60 (v/v). [e] In $CDCl_3$. [f] α And β signals overlap in cross-sections.

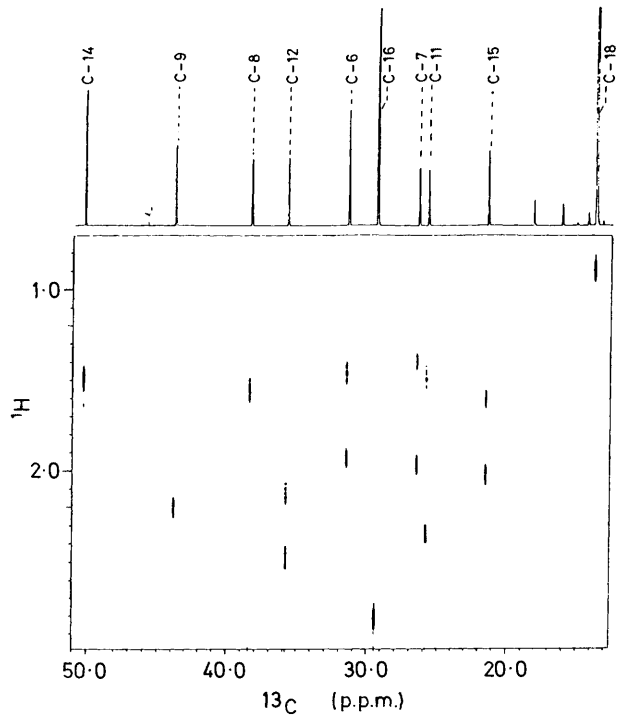


Figure 1. ^{13}C–^{1}H Shift-correlated 2D n.m.r. spectrum of 3-aminoestrone (**4**) (0.7M in $CDCl_3$, ambient temperature), contour plot; aromatic parts omitted

as (**1**)—(**4**) are well known,[4] some signals were not previously assigned unambiguously. Precise analysis was necessary for the present study in view of the small complexation-induced shifts

Table 2. N.m.r. shifts of 2-tetralol[a]

Carbon atom	Phenol (5)		Phenoxide (6)	
	^{13}C[b]	^{1}H[c]	^{13}C[c]	^{1}H[c]
1	115.48	6.61	117.76	6.35
2	153.31		160.09	
3	113.14	6.64	115.87	6.41
4	130.10	6.98	130.51	6.81
5	28.81†	2.67	29.35†	2.61
6	23.42*	1.72*	24.36*	1.69*
7	23.73*	1.72*	24.71*	1.69*
8	29.71†	2.64	30.39†	2.57
4a	138.04		138.66	
8a	128.97		126.77	

[a] See footnotes to Table 1; †, * represent interchangeable signals. [b] In CCl_4, shift differs from reported values by ±0.02 p.p.m. in carbons 1, 5, 6, 7, and 8, by −0.09 p.p.m. in carbons 3 and 4, and by −0.53 p.p.m. in carbons 2, 9, and 10. [c] In CD_3OD–D_2O 20:80 (v/v).

(c.i.s.), which also required new measurements, mostly in aqueous solution (Table 1).

The ^{1}H n.m.r. spectra of the estrogens (**1**)—(**4**) were analysed by the 2D-n.m.r. strategy and conditions described earlier.[8] Modern 2D techniques[9] have made the measurement and assignment of ^{1}H signals routine even for more complicated steroids.[10] Heteronuclear shift correlation spectroscopy between ^{13}C and ^{1}H (Figure 1) furnished the C–H connectivities for (**1**)—(**4**), which were supported by some COSY-45 ^{1}H–^{1}H shift-correlated spectra.

Inspection of cross-sections of the ^{13}C–^{1}H correlation spectra allowed the axial protons to be identified by their larger coupling, with the exception particularly of ring D signals. These were assigned by n.O.e. difference spectroscopy (Figure 2); irradiation at the C(18)H_3 signal showed signal enhancement for the β-protons in positions 8, 11, 12, 15, and 16. The

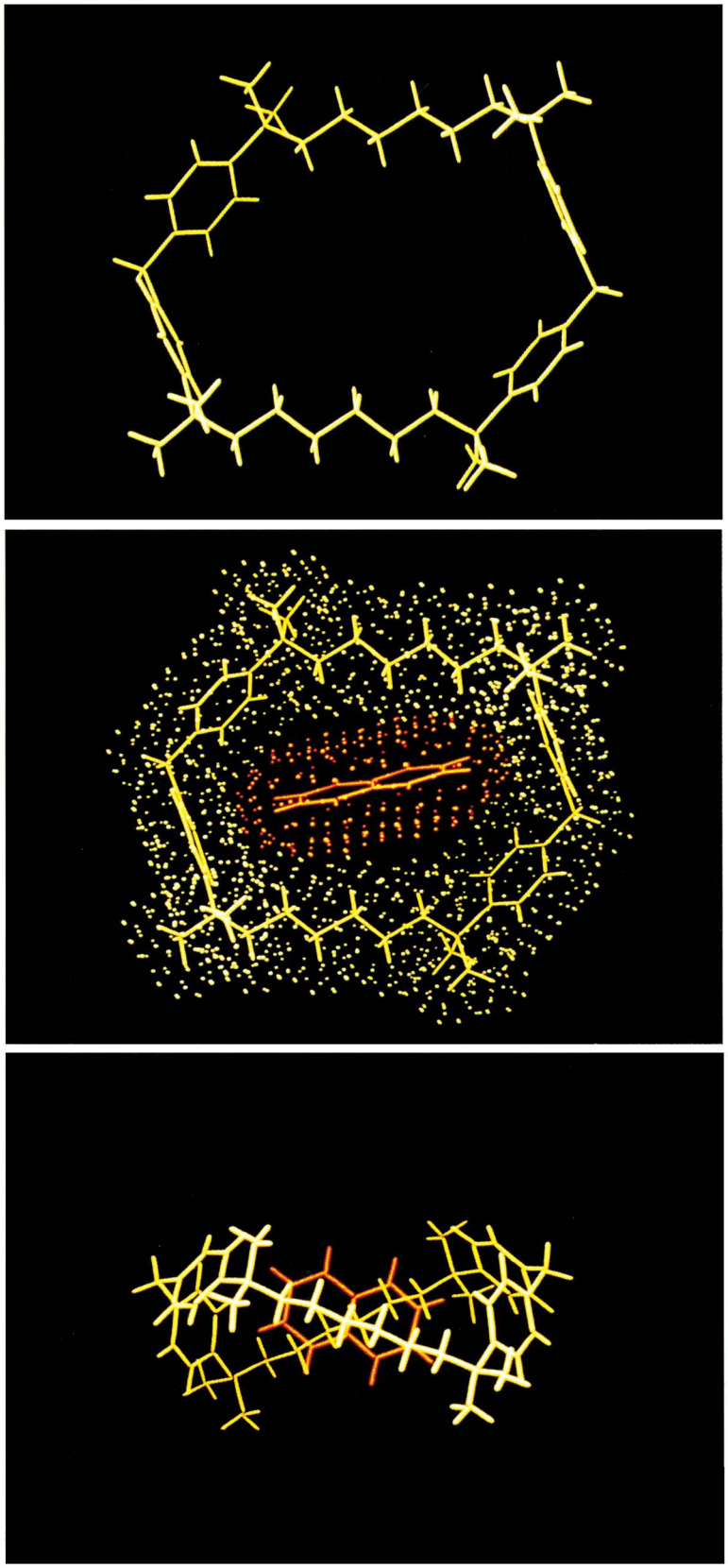


Figure 4. Computer-optimized structure (a) of the cyclophane (**CP6**) and most probable inclusion complex geometry (b), (c) with naphthalene as representative substrate for pseudoequatorial inclusion

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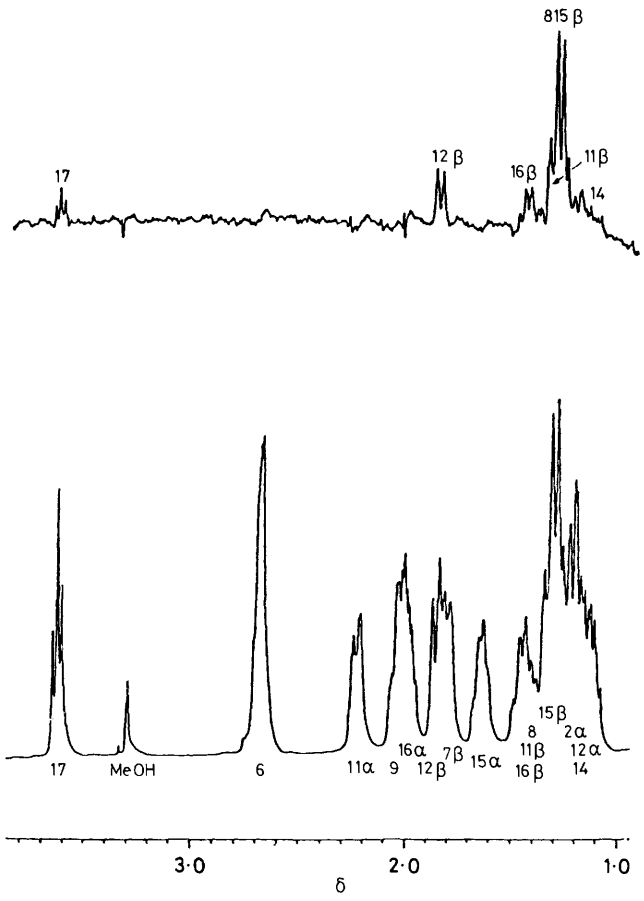

Figure 2. N.O.e. difference spectrum of estradiol (**2**) (0.2M in CD_3OD, ambient temperature), lower trace: undecoupled, upper trace: difference spectrum with irradiation at the $C(18)H_3$ signal

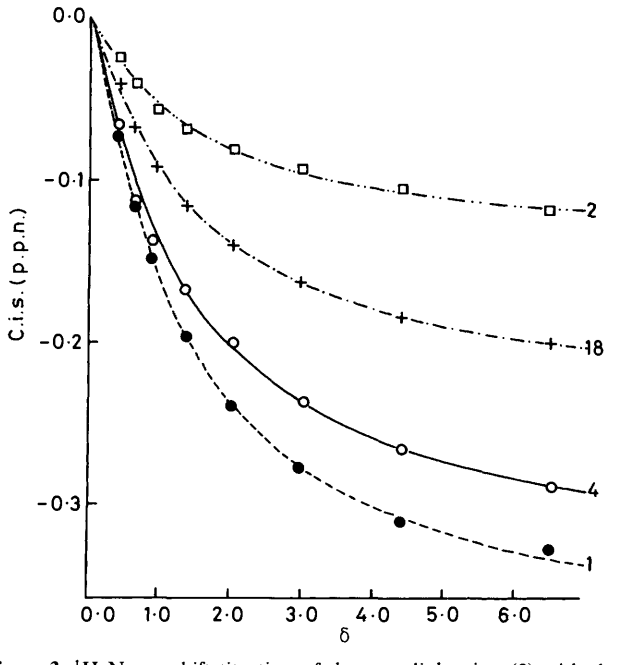

Figure 3. ^1H N.m.r. shift titration of the estradiol anion (**3**) with the cyclophane (**CP8**); experimental points and computer-simulated curve for H-1, -2, -4, and -18

assignments are also supported by shift comparison between different compounds (Table 1) as well as by literature data,[10] which, however, were of limited use in view of the very different solvents employed.[10d] Help in assignments also came from the regular deprotonation-induced shifts[11] (d.i.s.) between the phenols and phenoxides such as (**2**)–(**3**) or (**5**)–(**6**). Ambiguities in the ^{13}C signal assignments of the steroids between C-7 and C-11 and C-6/C-8 and C-16 could thus be removed. This could also be achieved for C-13 and C-14 or C-9 and C-13 on the basis of multiplicity determination *via* DEPT experiments.

The unambiguous analysis of the tetralol (**5**) and (**6**) signals[12] is hindered by some aliphatic carbon and hydrogen atoms which show only small shielding differences for exchangeable signals (< 1 p.p.m. for ^{13}C, < 0.04 p.p.m. for ^1H; Table 2). The host compound (**CP6**) could be used as a shift reagent for (**5**), as the benzylic H-5 and -8 are shifted by complexation to a different degree. An n.O.e. difference experiment showed enhancement of the H-1/H-4 signals upon irradiation of H-8/H-5, respectively (not shown). These proton assignments could not be used for analysing the corresponding ^{13}C signals in view of sensitivity and dynamic range problems with a ^{13}C–^1H shift correlation experiment for samples containing little substrate and much host compound.

Complexation Studies with Azoniacyclophanes.—Equilibrium constants K were determined by ^1H n.mr. shift titrations using non-linear least-squares curve fitting and measuring procedures described earlier.[13] A typical titration is shown in Figure 3. One advantage of n.m.r. as opposed to optical methods is the availability of several independent K determinations from each observable signal (Tables 3 and 4); the deviation between the K values was usually $\pm 5\%$ for the steroids and $\pm 18\%$ for the tetralols. The limited solubility of the steroids restricted the investigation to estradiol and its anion and to the use of solvents with a higher methanol content.

The most important results (Tables 3 and 4) are the doubling of K observed for the estradiol anion compared with the tetralol anion, and the weaker steroid binding in the larger ring (**CP8**) compared with (**CP6**). On the basis of recently studied solvent dependencies of K[13] one can estimate the K in pure water for estradiol (**2**) to be 10^2 l mol^{-1} and for its anion (**3**) 10^4—10^5 l mol^{-1}, whereas the values for the tetralol guests in water should be around half those of the steroids. The *ca.* 10-fold stronger binding of the anion compared with the phenol in the case of the steroid reflects the predominant electrostatic contribution in the much less hydrophilic solvent used here (40–50% methanol) which strongly decreases the hydrophobic binding effect.[13] The difference between anion and phenol is correspondingly much smaller in the case of the tetralol, which was measured in 20% methanol.

The complexation-induced ^1H n.m.r. shifts (c.i.s. values at 100% complexation; Tables 3 and 4), which are obtained simultaneously with K from the curve-fitting procedure,[13] show clearly that the steroid A and B rings are inserted in the cavity of the cyclophane. The distinct shielding effects for the observable protons resemble those found earlier with other naphthalene-like substrates,[2g,14] which can be accommodated without any geometrical distortion[2g] inside the (**CP6**) macrocycle (Figure 4); the torsion angles remain constant within $\pm 2°$ after full minimization of the complex with naphthalene. The c.i.s. values have been shown by calculations of ring current and electrical field effects[3b] to be compatible with a pseudoequatorial orientation of the substrate; this is supported for the steroids by the small shifts observed for ring D signals upon complexation with (**CP6**). The larger c.i.s. found here in the (**CP8**) inclusion complex and the simultaneously smaller effects for rings A and B indicate the presence of other substrate orientations in this

Table 3. ^{1}H N.m.r. complexation-induced shifts (c.i.s.) and equilibrium constants K^a for the steroids[a]

		1-H	2-H	4-H	6-H	17-H_2	18-H_3	CD_3OD (%)	K_{av}	ΔK (%)
β-Estradiol–(**CP6**)	C.i.s.	−1.74	−0.99	−1.00	−1.53	−0.01	−0.14	50	21	5
	K	21	21	22	20	*b*	25			
β-Estradiol anion–(**CP6**)	C.i.s.	−1.52	−0.57	−0.65	−1.34	−0.06	−0.16	40	253	6
	K	237	241	269	*b*	*b*	265			
β-Estradiol anion–(**CP8**)	C.i.s.	−0.53	−0.19	−0.46	−0.51	−0.12	−0.33	40	108	5
	K	112	109	109	*b*	*b*	101			

[a] See footnotes to Table 1; *K* in l mol^{-1}; error in *K* (%). [b] Signal mostly enveloped by host signals; c.i.s. from single measurement and correction for complexation.

Table 4. N.m.r. complexation-induced shifts (c.i.s.) and equilibrium constants *K* for 2-tetralol[a] with (**CP6**)

		1-H	3-H	4-H	CD_3OD (%)	K_{av}	ΔK (%)
2-Tetralol	C.i.s.	−1.14	−1.09	−1.29	20	100	25
	K	89	78	134			
2-Tetralol anion	C.i.s.	−0.58	−0.46	−1.19	20	225	10
	K	198	271	205			
2-Tetralol anion	C.i.s.	−0.54	−0.50	−1.21	40	126	17
	K	152	106	120			

[a] See footnotes to Table 1; *K* in l mol^{-1}.

Table 5. Complexation- and deprotonation-induced ^{13}C n.m.r. shifts (c.i.s., d.i.s.) for β-estradiol[a]

Carbon atom	C.i.s.[b] β-estradiol with (**CP6**)	C.i.s.[c] β-estradiol anion with (**CP6**)	C.i.s.[d] β-estradiol anion with (**CP8**)	D.i.s.[e]
1	−0.26	−0.18	−0.11	0.14
2	−0.19	−0.26	−0.19	+3.23
3	*f*	−0.20	−0.17	+7.75
4	−0.06	−0.34	−0.30	+2.89
5	−0.59	−0.86	−0.43	−0.24
6	−0.17	−0.49	*f*	−0.30
7	−0.06	−0.26	−0.26	−0.28
8	−0.06	−0.30	−0.26	−0.30
9	−0.20	−0.47	−0.31	−0.54
10	−0.83	−0.79	−0.51	−4.82
11	−0.06	−0.17	−0.19	−0.37
12	−0.09	−0.33	−0.26	−0.57
13	−0.09	−0.17	−0.31	−0.41
14	−0.17	−0.48	−0.69	−0.78
15	*f*	−0.08	*f*	−0.38
16	−0.02	−0.21	*f*	−0.66
17	−0.31	−0.27	−0.71	−0.07
18	+0.22	+0.23	+0.33	−0.01

[a] See footnotes to Table 1. [b] In CD_3OD–D_2O 50:50 (v/v), from measurement with [Host] 0.06, [Guest] 0.01M, 54% complexation. [c] CD_3OD–D_2O 40:60 (v/v), average value from three measurements (see Table 6). [d] CD_3OD–D_2O 40:60 (v/v), from measurement with [Host] 2.62×10^{-2}M, [Guest] 7.17×10^{-3}M, 70% complexation. [e] CD_3OD–D_2O 40:60 (v/v). [f] Enveloped under receptor signals.

Table 6. Single measurements of ^{13}C n.m.r. shifts (p.p.m.) induced by (**CP6**) on estradiol anion[a]

[(**CP6**)]/M	0.012	0.025	0.050
[(**3**)]/M	0.010	0.010	0.010
CD_3OD (%)	40	40	40
Complex (%)	60	81	91
C-1	−0.18	−0.17	−0.19
C-2	−0.23	−0.25	−0.31
C-3	−0.08	−0.12	−0.40
C-4	−0.33	−0.32	−0.37
C-5	−0.87	−0.83	−0.87
C-6	−0.50	−0.48	−0.50
C-7	−0.28	−0.24	−0.26
C-8	−0.33	−0.27	−0.30
C-9	−0.48	−0.40	−0.54
C-10	−0.88	−0.77	−0.71
C-11	−0.20	−0.16	−0.15
C-12	−0.35	−0.30	−0.33
C-13	−0.20	−0.15	−0.16
C-14	−0.53	−0.44	−0.47
C-15	+0.12	+0.09	+0.03
C-16	−0.23	−0.19	−0.20
C-17	−0.28	−0.26	−0.27
C-18	+0.25	+0.22	+0.23

[a] In p.p.m. relative to uncomplexed substrate; for conditions see Table 5.

Table 7. Complexation- (**CP6**) and deprotonation-induced ^{13}C n.m.r. shifts (c.i.s., d.i.s.) for 2-tetralol[a]

Carbon atom	C.i.s. phenol[b] I[c]	C.i.s. phenol[b] II[d]	C.i.s. phenoxide III[e]	C.i.s. phenoxide IV[b]	D.i.s.[b]
1	+0.70	+0.62	+1.82	+1.69	+2.26
2	+1.12	+1.06	+6.41	+6.01	+6.78
3	+0.85	+0.75	+2.27	+2.08	+2.73
4	+1.15	+1.03	−0.15	−0.08	+0.41
4a	+1.95	+1.72	−0.85	−0.85	+0.62
8a	+1.27	+1.05	−4.65	−4.54	−2.20

[a] See footnotes to Table 1. [b] In CD_3OD–D_2O 20:80 (v/v). [c] Calculated from measurement at 60% complexation. [d] From 65% complexation. [e] In CD_3OD–D_2O 40:60 (v/v).

wider cavity. The similarity in c.i.s. of the steroid and tetralol in complexes (**CP6**) indicated a similar insertion geometry which allows optimal approach between the phenoxide ions and one of the positively charged azoniacyclophane nitrogens.

^{13}C N.m.r. shifts could be observed for all steroid atoms (Table 5) in contrast to the protons, which due to sensitivity and dynamic range problems from the necessary presence of large host signals could not be analysed by 2D n.m.r. techniques. The shift titration used for the more sensitive proton spectrum is impractical for following ^{13}C shifts, which were therefore obtained from single measurements at known degrees of complexation: the agreement found, *e.g.* with experiments at 60, 81, and 91% substrate complexation (Table 6), validates this procedure, which was also used for the tetralol derivatives (Table 7). The resulting ^{13}C c.i.s. values, however, give a confusing picture, showing the expected shielding at the A and B carbon of the steroids, but strong deshielding for the tetralols as well as for C-18 of the steroid, which is fairly remote from the complexation site. The observed irregular ^{13}C shifts are not

Table 8. N.m.r. shifts of (**CP8**) derivatives[a]

	$NSO_2C_6H_4CH_3$-*p*		NH		$\overset{+}{N}Me_2 \cdot Cl^-$	
Atom	^{13}C[b]	^1H[b]	^{13}C[c]	^1H[c]	^{13}C[d]	^1H[d]
2	50.34	3.43	44.22	2.98	70.22	3.79
3	28.72	1.32	29.60	1.51	28.68	1.33
4	27.99	1.25	29.34 }	1.15—1.40	25.99 }	0.85—1.20
5	26.05	1.12	27.08 }		23.68 }	
11	140.02		146.60		143.91	
12, 16	128.64	7.24—7.26	112.79	6.44—6.46	121.71	7.47—7.49
13, 15	129.34	7.41—7.43	129.51	6.88—6.90	131.64	7.68—7.70
14	135.31		130.68		143.53	
17	40.67	3.95	44.22	3.68	40.37	4.04
NCH_3					55.19	3.54

[a] See footnotes to Table 1. [b] In $CDCl_3$–Me_2SO 80:20 (v/v); n.m.r. shifts of tosyl group: 137.16 (C-2′ *), 129.34 (C-3′ †), 127.56 (C-4′ †), 143.22 (C-5′ *), 21.43 (C-1′); † and * represent interchangeable signals. [c] In $CDCl_3$. [d] In D_2O. δ_H: 2.86 (s, 3 H, tosyl CH_3) and 6.89—7.08 (dd, 4 H, ArH).

directly related to d.i.s. (or to corresponding charge accumulation) effects as seen by comparing the corresponding shielding variations (Tables 5 and 7). In consequence, ^{13}C n.m.r. shifts, which due to the relative ease of measurement in complicated spin systems have been used, *e.g.* for cyclodextrin complexes,[15] cannot yet be used to obtain information on the complex geometries involved. This is not quite unexpected in view of the ^{13}C shielding mechanisms, which besides anisotropy effects of the same magnitude as for protons, are characterized by large paramagnetic contributions due to electron density redistribution by field effects, and in particular for the aromatic substrates, also by mesomeric contributions as well as by enhanced reaction field or medium effects.[16] Proton c.i.s. values are much more useful due to the absence of paramagnetic contributions, the simplification of field effects by the presence of only one polarized bond, and finally due to their unique exposure to anisotropy effects, *etc.* at the surface of the substrate, whereas the 'inside' carbon atoms are much more influenced by intramolecular interactions.

Conclusions.—The results demonstrate for the first time that steroids can be complexed effectively in aqueous solution by a simple receptor model which provides essentially a polyethylene chain surrounding the A and B rings and N^+ changes, particularly if one complementary charge is present. The binding is, in comparison with the corresponding tetralols, significantly increased by substrate parts such as rings C and D in the steroid which are *not* in contact with the host surface. It is also shown that complexation-induced n.m.r. shifts can be used to distinguish possible complex conformations on the basis of ^1H, but not of ^{13}C n.m.r. shielding variations. The results should contribute towards an understanding of the binding mechanisms of host–guest complexes in aqueous solution and also of steroid binding to natural receptors.

Experimental

N.m.r. Measurements.—These were performed with a Bruker AM 400 system at 400 MHz for ^1H and at 100 MHz for ^{13}C in the Fourier transform mode under conditions given in the footnotes to the tables. The digital resolution was usually ± 0.001 p.p.m. for ^1H, ± 0.005 p.p.m. for ^{13}C, $\pm 2 \times 10^{-5}$ p.p.m. for n.O.e., and ± 0.002 p.p.m. (^1H) to ± 0.01 p.p.m. (^{13}C) for ^{13}C–^1H shift correlation spectra. N.O.e. difference, ^{13}C–^1H-2D, COSY-45, as well as DEPT experiments were performed as described in the literature[9] and more specifically in our earlier publication.[8]

Equilibrium constants *K* and complexation-induced ^1H n.m.r. shifts (c.i.s.) were obtained by n.m.r. shift titration as described earlier,[13] usually with 10 measurements at substrate and guest concentrations optimized by suitable computer programs.[13]

Compounds.—These were commercially available or prepared according to the literature (**CP6**),[7] with the exception of the new cyclophanes (**CP8**).

1,10,24,33-*Tetrakis*-(p-*tolylsulphonyl*)-1,10,24,33-*tetra-aza*[10.1.10.1]*paracyclophane* (**CP8a**). A suspension of *N*,*N*′-bis-(*p*-tolysulphonyl)-4,4′-diaminodiphenylmethane[7] (50.0 g, 0.098 mol), 1,8-dibromo-octane (27.3 g, 0.1 mol), and anhydrous potassium carbonate (70.0 g, 0.5 mol) in distilled dimethylformamide (1.2 l) was stirred at room temperature for 3 days. The solution was concentrated to 200 ml under reduced pressure and then acidified with 50% hydrochloric acid (100 ml). The residue was filtered, washed with excess of water to neutral pH, and dried after washing with methanol and ether. The ratio of diaza- and tetra-aza ring in this mixture was 1:3, by ^1H n.m.r. signal integration; the amount of cyclized product was 70%, as calculated from ^1H n.m.r. using an internal reference of known concentration (^1H n.m.r. data, Table 8).

1,10,24,33-*Tetra-aza*[10.1.10.1]*paracyclophane* (**CP8b**). A solution of the *N*-tosylcyclophane (52 g, 4.2×10^{-2} mol) and phenol (100 g, 1.1 mol) in 48% distilled hydrobromic acid (520 ml) was refluxed under stirring for 4 h. The aqueous phase was decanted and the organic layer was treated with excess of ether (*ca.* 750 ml) with stirring. The residue was filtered, washed with ether, and then stirred with 40% KOH solution for 1 h. The residue thus obtained was filtered and washed with excess of water to neutral pH. The dried mass was again washed with acetone to remove polymeric impurities and the diazacyclophane. After drying, the material was found to contain <2% diaza ring; the purity was 70% by ^1H n.m.r. internal standard comparison. It was chromatographed on a silica gel column using methanol–propan-2-ol (1:99) as eluant to give 95% pure tetra-aza ring product (1.0 g) (^1H n.m.r. data, Table 8).

1,1,10,10,24,24,33,33-*Octamethyl*-1,10,24,33-*tetra-azonia*-[10.1.10.1]*paracyclophane Tetrachloride* (**CP8c**). A mixture of the amine (1.0 g, 1.62 mmol), calcium carbonate (2.5 g, 2.5×10^{-2} mol), methanol (100 ml), methyl iodide (5 ml; excess), and water (20 ml) was refluxed under stirring for 12 h. After evaporation the residue was acidified with dilute hydrochloric acid (*ca.* 25 ml) and filtered. The dried mass was refluxed with methanol saturated with hydrochloric acid (20 ml) for 2 h. It was then concentrated and the residue together with water (20 ml) was washed with dichloromethane (3 × 15 ml). To the aqueous phase acetone (*ca.* 100 ml) was added and the resulting amorphous residue was filtered and dried to yield (**CP8c**) (100 mg) which was found to be 72% pure. All attempts at further purification failed. ^1H N.m.r. data (Table 8), however, showed only signals for the desired compound.

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