SYNTHESIS AND PROPERTIES OF WATER-SOLUBLE BIS-PARACYCLOPHANES

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Summary: Novel water-soluble bis-paracyclophanes (5, 6, 7) were synthesized and their proper-
ties as hosts having two independent binding sites were studied. Examples are presented in
which a guest molecule having two aromatic rings forms a complex by binding at two sites
cooperatively, when host and guest are complementary.

Host molecules with multiple independent binding sites, capable of forming complexes with
multiple guest molecules simultaneously, or with a single guest molecule at multiple sites
cooperatively, are of particular interests in relation to assembling and recognizing molecules
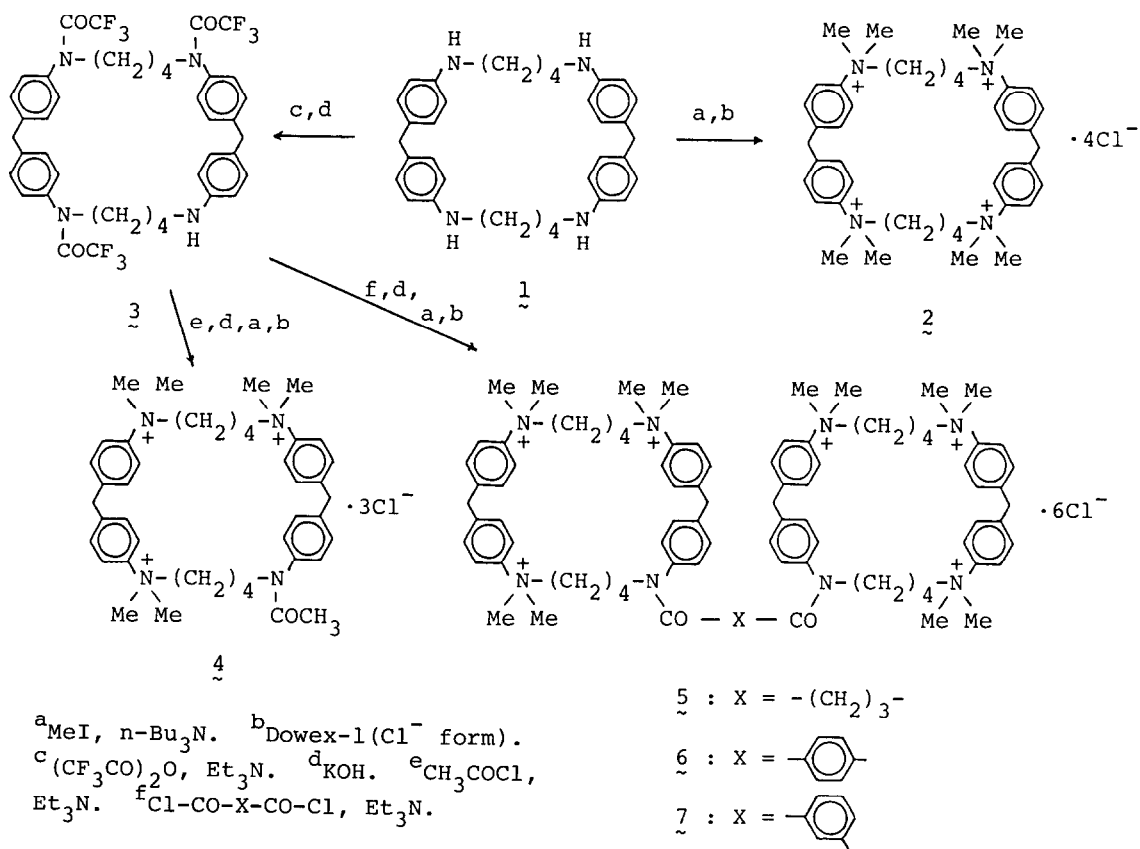and/or ions by complexation.

We have previously reported that water-soluble paracyclophanes (such as 1 and 2) having
diphenylmethane skeletons form inclusion complexes with aromatic guest molecules in aqueous
solution in particular geometries and with remarkable selectivities.[1] The present paper
describes the synthesis of novel hosts (5, 6, 7) having two paracyclophane units bridged by
glutaryl, terephthaloyl, or isophthaloyl residue, and their properties as hosts having two
independent binding sites.

The hosts ($2,^{2,3}$ $4,^{2)}$ $5,^{2)}$ $6,^{2)}$ $7^{2)}$) were synthesized from 1 as shown in Scheme I.

Complex formation between hosts (2, 4, 5, 6, 7) and guests (8, 9, 10, 11, 12) was investi-
gated by ^{1}H NMR in D_2O.[4] Upon complexation, proton signals of the guests and hosts moved
upfield.[1,5] Maximum shifts ($\Delta\delta_{max}$[6]) of H_2- and H_3-protons of the guest (8) were found to be
-1.66 and -2.01 ppm for 2·8 complex, and -1.37 and -1.79 ppm for 4·8 complex, respectively.
Stability constants (Ks) of the 1:1 complexes by the Benesi-Hildebrand method[7] using ^{1}H NMR
chemical shift changes were calculated to be 3.3 ×10^3 M^{-1} for 2·8 complex,[8] and 7.7 ×10^2 M^{-1}
for 4·8 complex. These data show that the mono-paracyclophane (4), having one amide nitrogen
and three quaternary ammonium nitrogens, exhibits similar but somewhat smaller stability
constant with 8, compared with that of the mono-paracyclophane (2), having four quaternary
ammonium nitrogens.

In agreement with this observation, bis-paracyclophanes (5, 6, 7), made by connecting
two paracyclophane units with two amide bonds, were also found to work as hosts. Thus, $\Delta\delta_{max}$
values of H_2- and H_3-protons of the guest (8) were found to be around -1.6 and -2.0 ppm upon
complexation with these hosts. By using excess 8, $\Delta\delta_{max}$ values of the protons of the inner

Scheme I

^{a}MeI, n-Bu$_3$N. ^{b}Dowex-1(Cl$^-$ form).
^{c}(CF$_3$CO)$_2$O, Et$_3$N. ^{d}KOH. ^{e}CH$_3$COCl,
Et$_3$N. ^{f}Cl-CO-X-CO-Cl, Et$_3$N.

$\underset{\sim}{5}$: X = -(CH$_2$)$_3$-

$\underset{\sim}{6}$: X = ◯

$\underset{\sim}{7}$: X = ◯

-CH$_2$CH$_2$- groups of the bridging moieties of the hosts were found to be around -0.6 ppm, which agrees with -0.63 ppm observed for 4·8 complex. This result shows that the two cavities of these bis-paracyclophanes can accommodate two molecules of 8 simultaneously.
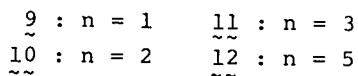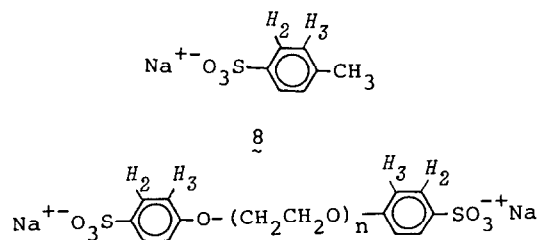
Complexation of the guests (9, 10, 11, 12) with mono-paracyclophane (4) and bis-paracyclo-phanes (5, 6, 7) was also examined by ^{1}H NMR as shown in Figure I and Table I. The concentrations of the paracyclophane unit of the hosts are equal to or higher than those of the aromatic group of the guests. Using 9 as a guest, Δδ values are found to be moderate, i.e., -1.1 ~ -1.2 ppm, and are independent of the concentration of the hosts in all cases examined. In cases where 12 is a guest, however, Δδ values are moderate, but increase gradually by the increase in the concentration

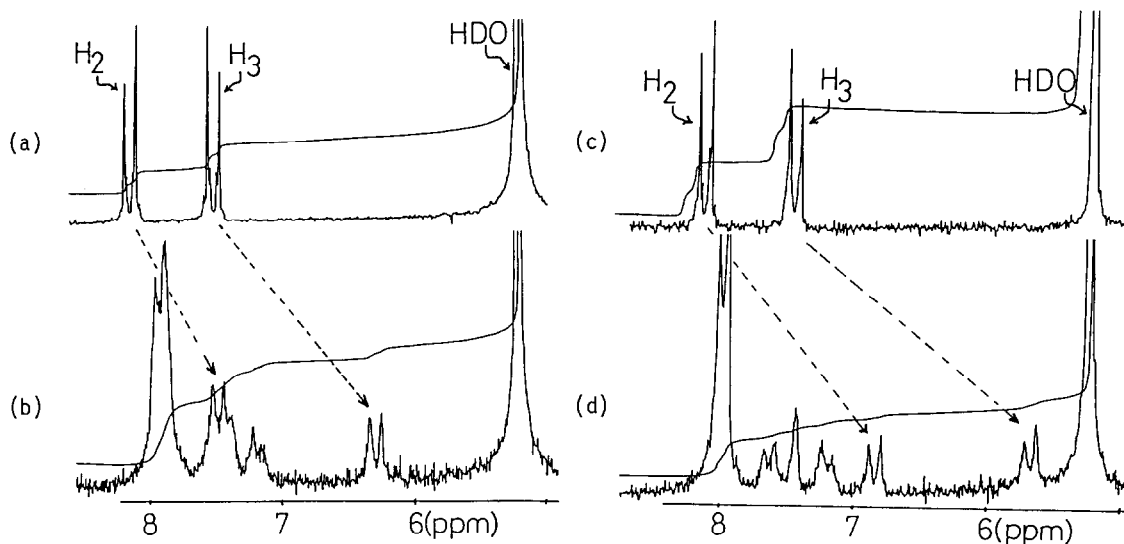Figure I. ^{1}H NMR spectra (100 MHz) of (a) 9(1mM), (b) 9(1mM) + 6(1mM), (c) 12(1mM), and (d) 12(1mM) + 6(1mM) in D_2O[4)]

Table I. Δδ Values of the Protons of Guests in the Presence of Hosts in D_2O[4)]

Host	Guest mM	9(1mM) H_2	9(1mM) H_3	10(1mM) H_2	10(1mM) H_3	11(1mM) H_2	11(1mM) H_3	12(1mM) H_2	12(1mM) H_3
4	2	a	-1.11	-0.64	-0.96	-0.71	-0.97	-0.70	-0.94
	10	a	-1.14	a	-0.99	a	-1.06	a	-1.12
	20	a	-1.14	b	b	b	b	a	-1.23
5	1	-0.72	-1.23	-1.03	-1.38	a	-1.5[c]	-1.21	-1.67
	5	a	-1.25	-1.16	-1.52	-1.22	-1.66	-1.30	-1.78
6	1	-0.69	-1.24	-0.77	-1.14	a	-1.36	-1.30	-1.80
	5	a	-1.24	a	-1.18	a	-1.44	-1.38	-1.90
7	1	-0.71	-1.24	a	-1.42	a	-1.5[c]	-1.36	-1.81
	5	a	-1.24	-1.32	-1.68	-1.39	-1.93	-1.46	-1.95

[a]The signals are buried in those of the host. [b]Not measured. [c]Broad.

of the host (4), while they are reasonably high even under the same concentration of bis-paracyclophanes (5, 6, 7), and are considered to be close to $\Delta\delta_{max}$. In cases where 10 and 11 are used as guests, the results are between those of the above two cases where 9 and 12 are used.

These data may be rationalized as shown in Scheme II. Thus, using guest A having two aromatic groups connected by a shorter bridge (such as 9), the structures of the predominant complexes are C-type with mono-paracyclophane, and G-type with bis-paracyclophanes. In these complexes, one of the aromatic groups of the guest is bound, while the other is free.[5)]

Scheme II
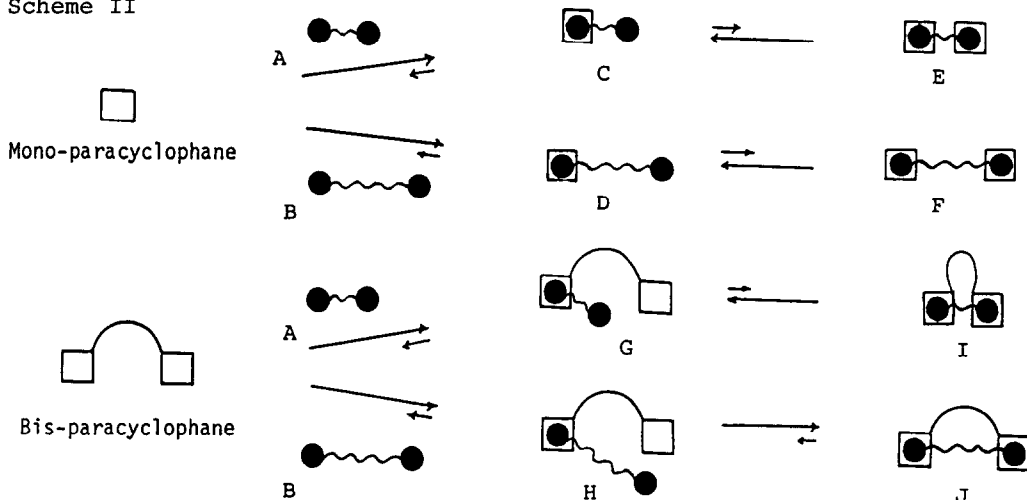
Further complexation to give E-type and I-type seems to be difficult even under higher concentration of the hosts, probably due to steric and electronic repulsions.[9]

When guest B having two aromatic groups connected by a longer bridge (such as 12) is used, the structure of the predominant complex with mono-paracyclophane seems to be D-type. In this case, increase in the concentration of the host shows a tendency to form F-type complex, but this process is minor. However, in the presence of bis-paracyclophanes, guest B forms J-type complexes predominantly, in which the two aromatic groups of the guest are both bound cooperatively to the two binding sites of the hosts.[10]

The present results clearly show that the host molecule having two independent binding sites can form complex at two sites cooperatively with a guest molecule having two aromatic groups, when they are complementary. This further suggests the possibility of highly efficient multiple binding by rigid host molecules having multiple binding sites.

References and Notes

1) K. Odashima and K. Koga, "Cyclophanes," Vol. 2, ed. by P. M. Keehn and S. M. Rosenfeld, Academic Press, New York, 1983, Chapter 11, and references cited therein.

2) Elemental analyses (C, H, N, Cl)($C_{42}H_{60}N_4Cl_4 \cdot 7H_2O$ for 2, $C_{42}H_{57}N_4O_1Cl_3 \cdot 9H_2O$ for 4, $C_{85}H_{114}N_8O_2Cl_6 \cdot 15H_2O$ for 5, $C_{88}H_{112}N_8O_2Cl_6 \cdot 23H_2O$ for 6, and $C_{88}H_{112}N_8O_2Cl_6 \cdot 20H_2O$ for 7) and spectral data are consistent with the assigned structures.

3) We warmly thank Mr. A. Miwa for the preparation of this compound.

4) Measured at ambient temperature of 28 ± 2°C using TMS(neat) as an external reference.

5) Since the system is in the NMR chemical shift fast-exchange limit, the proton signals appear at the weighed averages of the chemical shifts of the free and the complexed forms.

6) $\Delta\delta = \delta$(Host + Guest) - δ(Guest). Negative values of $\Delta\delta$ indicate upfield shifts.

7) H. A. Benesi and J. H. Hildebrand, J. Am. Chem. Soc., 71, 2703(1949).

8) We warmly thank Mr. H. Kawakami for this measurement.

9) This is based on the CPK molecular model studies.

10) Formation of polymeric complexes is unlikely, because F-type complex is proved to be minor.

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