Tetrahedron Letters Vol. 21, pp 4347 - 4350
0040-4039/80/1101-4347$02.00/0

INCLUSION COMPLEX FORMATION IN A PARTICULAR GEOMETRY BY A WATER-SOLUBLE PARACYCLOPHANE IN AQUEOUS SOLUTION

—— NMR STUDIES ——

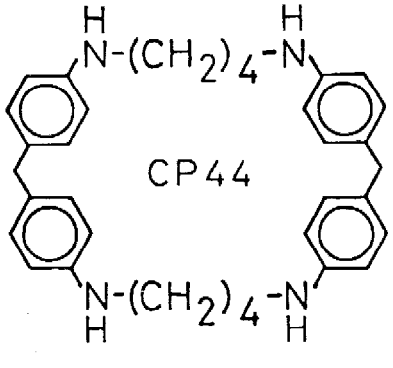
Kazunori Odashima,[a] Akiko Itai,[a] Yoichi Iitaka,[a] Yoji Arata[b] and Kenji Koga*[a]

(a) Faculty of Pharmaceutical Sciences, (b) Faculty of Science, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: NMR studies (^{1}H and ^{13}C) demonstrating an inclusion complex formation in a particular geometry between a water-soluble paracyclophane, CP44, and hydrophobic substrates in acidic aqueous solution are described.

Water-soluble paracyclophanes[1] are a group of artificial host compounds which enable us to design hydrophobic cavities of definite shape and size. Recently we have reported the first direct evidence (X-ray) that this type of host compound forms an inclusion host-guest complex with a hydrophobic substrate (CP44·4HCl—durene complex).[2] We have also reported the spectral evidences (fluorescence, ^{1}H NMR) that strongly support an inclusion host-guest complex formation between CP44 and hydrophobic substrates in acidic aqueous solution.[2,3] Whether the inclusion complex formation occurs in a random manner or in a particular geometry is of great interest in relation to substrate selective binding and fixation. Now we wish to report the NMR studies (^{1}H and ^{13}C)[4] demonstrating that in acidic aqueous solution CP44 forms an inclusion complex with appropriate hydrophobic substrates in a particular geometry, which is characteristic of host-guest complex formation and difficult to expect in mobile systems (micelle, synthetic polymer).

The NMR studies were carried out in DCl-D_2O solution of pD 1.2.[5] ^{1}H NMR spectra (100 MHz) of (a) 2,7-dihydroxynaphthalene (2,7-DHN; 1), (b) CP44, and (c) their mixture are shown in Figure 1. Chemical shift changes ($\Delta\delta$; ppm) of the proton signals of the host (substrate) induced by the substrate (host) are shown in Figure 2a. Marked upfield shifts were observed with all the three proton signals of the substrate and also with the tetramethylene proton signals of the host. In ^{1}H NMR these marked upfield shifts can be ascribed to a strong intermolecular shielding effect due to the aromatic ring(s) of the other component of the complex. In addition each proton signals of CP44 and the substrate shifted to a different degree. These marked and individual upfield shifts indicate an intimate complex formation in a particular geometry[6] between CP44 and the hydrophobic substrate.[7]



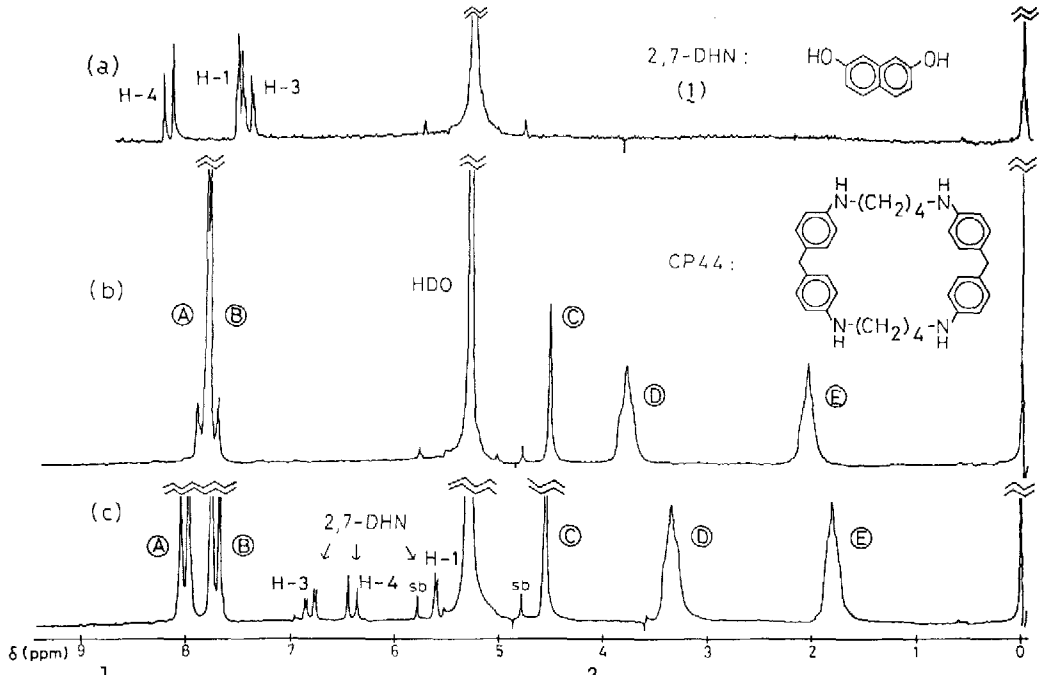


Figure 1 ^{1}H NMR spectra (100 MHz) of (a) 2.5×10^{-2} M 2,7-dihydroxynaphthalene (2,7-DHN), (b) 5.0×10^{-2} M CP44, and (c) 2.5×10^{-2} M 2,7-DHN and 5.0×10^{-2} M CP44 in DCl-D_2O solution of pD 1.2 at ambient temperature of 28 ± 2°C. TMS(neat) was used as external reference.

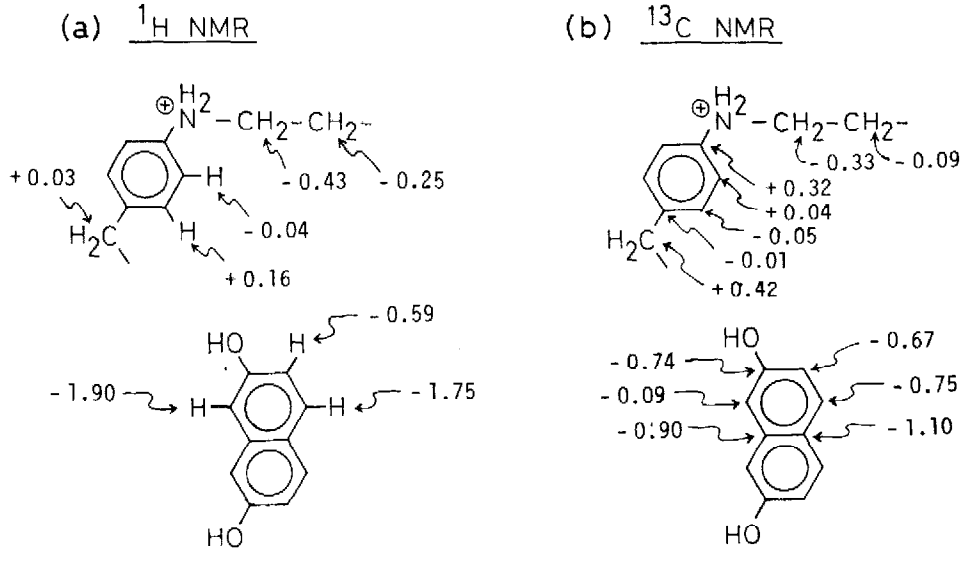


Figure 2 Chemical shift changes in NMR spectra. The negative values indicate upfield shifts ($\Delta\delta$ = δ(host + substrate) - δ(host or substrate only); ppm)

The following observations are important to consider the preferred geometry of the complex. (i) H-1 and H-4 signals of the substrate shifted upfield remarkably and to a similar extent (1.90 and 1.75 ppm, respectively) while H-3 signal shifted upfield to a much smaller, but still remarkable extent (0.59 ppm). (ii) The two tetramethylene proton signals of the host (Ⓓ and Ⓔ), especially that of N-$\underline{CH_2}$ (Ⓓ), shifted upfield remarkably (0.43 and 0.25 ppm, respectively), while the methylene proton signal of the diphenylmethane skeletons (Ⓒ) shifted very little (0.03 ppm). From these observations the inclusion geometry such as shown in Figure 3a can be presumed, in which the host molecule takes a similar conformation to that in the crystalline complex with durene[2] and the substrate molecule is included with the long axis of its naphthalene ring penetrating the cavity obliquely. ("pseudoaxial" inclusion[8])

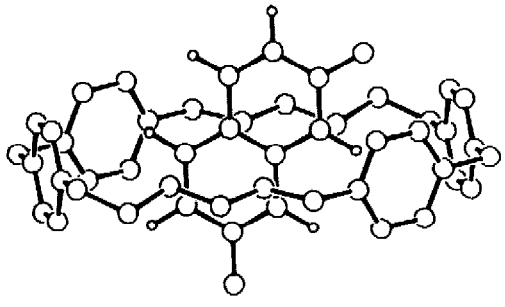
Among several possible geometries of the complex (Figure 3a-c),[9] the inclusion geometry 3a affords the best agreement between the calculated[10] and observed chemical shift changes of the substrate protons. (Table 1)[12] In addition, marked and individual chemical shift changes were also observed in ^{13}C NMR (25 MHz) under the same conditions, and the above inclusion geometry was further supported, since among the substrate carbons C-9 and C-10 which are presumed to contact most intimately with the host molecule showed the largest chemical shift changes (-0.90 and -1.10 ppm, respectively; Figure 2b).[13,14]

On the basis of these NMR studies, it seems reasonable to conclude that the inclusion complex formation by CP44 in acidic aqueous solution occurs <u>in a particular geometry</u>[7] and not in a random manner, and this fundamental nature of CP44 is obviously an important factor for binding and fixation of appropriate substrates in aqueous solution.

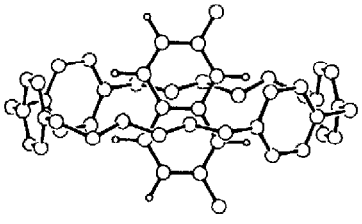
Table 1 The calculated chemical shift changes ($\Delta\delta$; ppm)

Geometry	H-1	H-3	H-4
3a	-2.43 (1.3)	-0.74 (1.3)	-2.16 (1.2)
3b	-2.44 (1.3)	-0.41 (0.7)	-2.43 (1.4)
3c	-0.16 (0.08)	-3.06 (5.2)	-1.70 (1.0)
(observed)	-1.90	-0.59	-1.75

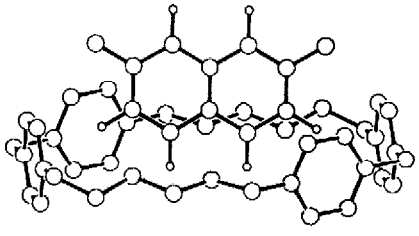
* $\Delta\delta$(calcd.) / $\Delta\delta$(obsd.) are shown in the parentheses.[10]



(a) "pseudoaxial" inclusion



(b) "axial" inclusion



(c) "equatorial" contact

Figure 3 The presumed geometries of the complex. The smaller circles indicate hydrogen atoms. The hydrogen atoms of the host molecule are not shown.

References and Notes

1) (a) I. Tabushi, Y. Kimura and K. Yamamura, J. Am. Chem. Soc., 100, 1304 (1978), and references cited therein; (b) Y. Murakami, A. Nakano, R. Miyata and Y. Matsuda, J. C. S. Perkin Trans. I, 1669 (1979), and references cited therein.

2) K. Odashima, A. Itai, Y. Iitaka and K. Koga, J. Am. Chem. Soc., 102, 2504 (1980).

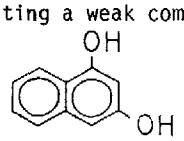
3) CP44 is soluble in water as an amine salt below pH 2.

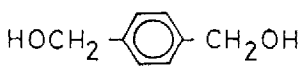
4) To our knowledge this NMR study is the first example concerning the geometry of host-guest complex formation by a water-soluble paracyclophane in aqueous solution. For the related studies with cycloamyloses, see for example: (a) P. V. Demarco and A. L. Thakkar, Chem. Comm., 2 (1970); (b) R. Bergeron and R. Rowan, III, Bioorg. Chem., 5, 425 (1976).

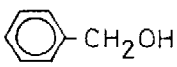
5) pD was adjusted according to P. K. Glasoe and F. A. Long, J. Phys. Chem., 64, 188 (1960).

6) In a statistical sense. (Since the system is in the NMR chemical shift fast-exchange limit, the proton signals of the substrate (host) appear at the average of the chemical shift of the free substrate (host) and the chemical shift of the substrate (host) bound in each possible orientation to the host (substrate), weighed by the fractional population of the substrate (host) molecules in each environment.)

7) Similar ^{1}H NMR spectral changes were also observed with other hydrophobic substrates having a benzene or a naphthalene ring (2 - 4), which are expected to fit well with the cavity of the host. In all cases an addition of the acyclic reference compound, AC11, instead of CP44 did not induce such marked and individual shifts on the proton signals of either component, suggesting a weak complex formation. (See ref. 2)

2: 

3: 

4: 

8) For the term "axial" inclusion, see: F. Cramer and W. Kampe, J. Am. Chem. Soc., 87, 1115 (1965). In the CP44·4HCl—durene complex the host molecule forms a cavity that fits well with the benzene ring of durene.[2] Considering from this X-ray result, it seems reasonable to presume "axial" or "pseudoaxial" inclusion for the substrate having a naphthalene ring.

9) There are no overshort contact between the host and the substrate in any of these three presumed geometries.

10) An approximate calculation employing the procedure of Johnson and Bovey,[11] based on the assumption that the host molecule takes the same conformation as that in the crystalline complex with durene.[2] Under the experimental condition 98 % of the substrate is estimated to be complexed with the host. ($K_d = 3.5 \times 10^{-4}$ M)

11) C. E. Johnson, Jr., and F. A. Bovey, J. Chem. Phys., 29, 1012 (1958).

12) The agreement of $\Delta\delta$(calcd.) / $\Delta\delta$(obsd.) values of all the substrate protons in Geometry 3a, and the disagreement of those in Geometries 3b and 3c may also support Geometry 3a.

13) As in ^{1}H NMR (Footnote 7), an addition of the acyclic reference compound, AC11, did not induce such marked and individual shifts on the carbon signals of either component.

14) For the related study with cyclohexaamylose, see: R. Bergeron and M. A. Channing, Bioorg. Chem., 5, 437 (1976).

(Received in Japan 9 July 1980)