DESIGN AND SYNTHESES OF PARACYCLOPHANES HAVING CHARGED SIDE CHAINS
THAT ARE SOLUBLE IN NEUTRAL AQUEOUS SOLUTION

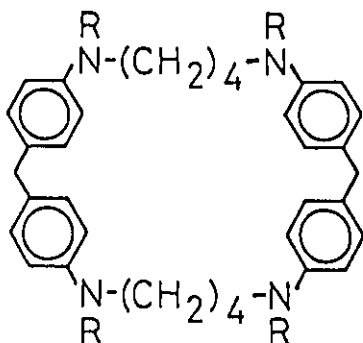Kazunori Odashima and Kenji Koga*

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Abstract: A series of water-soluble paracyclophanes having charged side chains
(2a,b,3a,b) were synthesized, and their complexation properties toward organic
guest molecules in neutral aqueous solution were examined.

We have recently designed and synthesized a series of novel water-soluble paracyclophanes
having diphenylmethane skeletons, represented by CP44 (1) shown below, as host compounds to trap
organic guest molecules by hydrophobic interaction in aqueous solution.[1] Both crystallographic[1a]
and NMR spectral[1b] studies have strongly supported an inclusion complex formation in a particular
geometry. In addition, substrate selective complex formation was observed in aqueous solution,
which was based upon host-guest recognition of mutual structure and charge.[1c,d] Although this
artificial system may afford a primitive, but promising model for molecular recognition in aqueous
solution, the acidic condition (pH < 2) required to solubilize these host compounds[1a] should
severely limit their application. Therefore it is highly desirable to make them soluble in neutral
aqueous solution.

We wish to report here the modification of CP44 (1) by introducing side chains having a charge
at neutral pH. The modified hosts (2a,b,3a,b) were synthesized as shown in Scheme 1,[2] starting
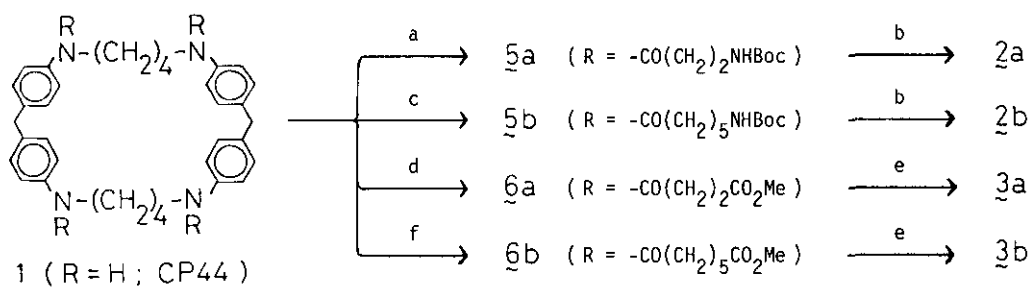from CP44 (1).[1a] All the modified hosts were freely soluble in neutral aqueous solution.

1 :   R = -H (CP44)

2a: R = $-CO(CH_2)_2NH_2$

2b: R = $-CO(CH_2)_5NH_2$

3a: R = $-CO(CH_2)_2CO_2H$

3b: R = $-CO(CH_2)_5CO_2H$

In addition, the following two points differ from the parent host, which might affect the stability of the host-guest complex. (i) The modified hosts have positive (2a,b) or negative (3a,b) charges at neutral pH. (ii) The state of their nitrogens is amide (2a,b,3a,b) whereas that of CP44 is ammonium (at acidic pH).

Complex formation by the modified hosts was investigated using TNS (2-toluidinonaphthalene-6-sulfonate) as the substrate. All the modified hosts induced fluorescence enhancement and blue shift in the fluorescence spectrum of TNS (Figure 1), suggesting that the substrate was included within the hydrophobic cavity of the modified hosts.[3] Dissociation constants (K_d) of the 1:1 complexes are listed in Table 1,[4] from which the effects of charge on inclusion complex formation

Scheme 1

1 (R = H ; CP44)

5a (R = -CO(CH$_2$)$_2$NHBoc) →^{b} 2a

5b (R = -CO(CH$_2$)$_5$NHBoc) →^{b} 2b

6a (R = -CO(CH$_2$)$_2$CO$_2$Me) →^{e} 3a

6b (R = -CO(CH$_2$)$_5$CO$_2$Me) →^{e} 3b

a) Boc NH(CH$_2$)$_2$CO$_2$H, DCC, in CH$_2$Cl$_2$; b) HCl, in EtOH; c) Boc NH(CH$_2$)$_5$CO$_2$H, DCC, in CH$_2$Cl$_2$; d) MeO$_2$C(CH$_2$)$_2$COCl, Et$_3$N, in CH$_2$Cl$_2$; e) NaOH, in MeOH / H$_2$O (10:1); f) MeO$_2$C(CH$_2$)$_5$CO$_2$H, CH$_3$CH$_2$N = C = N(CH$_2$)$_3$N(CH$_3$)$_2$·HCl (water-soluble DCC), in CH$_2$Cl$_2$.

2a· R = -CO(CH$_2$)$_2$NH$_3^{\oplus}$
3a   R = -CO(CH$_2$)$_2$CO$_2^{\ominus}$

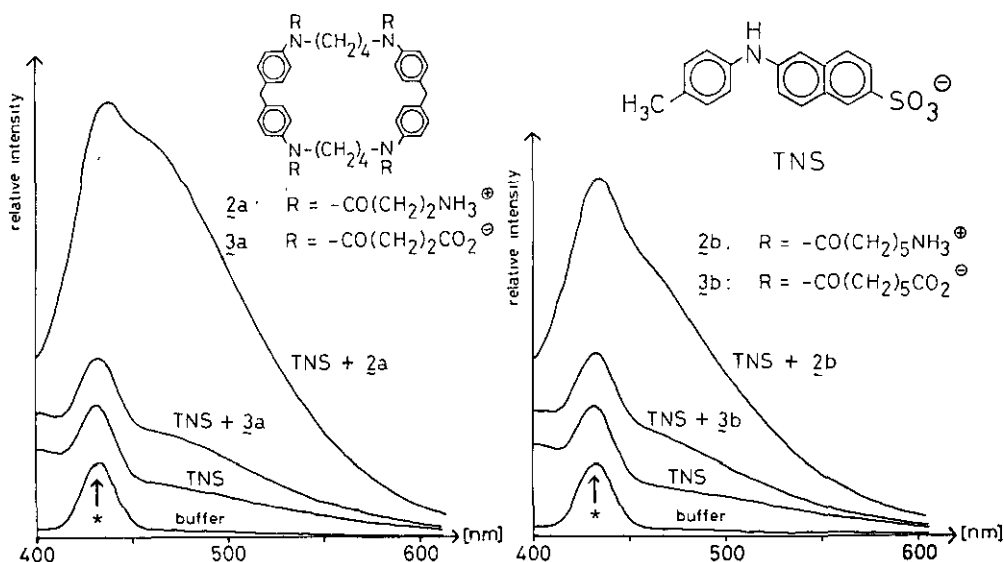2b. R = -CO(CH$_2$)$_5$NH$_3^{\oplus}$
3b: R = -CO(CH$_2$)$_5$CO$_2^{\ominus}$

Figure 1 Fluorescence spectra of TNS in the presence and absence of the modified hosts. pH 7.07; [TNS] = 4×10^{-6} M; [Host] = 5×10^{-5} M. * Raman scattering of water.

are considered as follows:

(1) All the modified hosts showed complex formation with TNS in neutral aqueous solution.[5] Especially the strong complex formation by host 2a was comparable with that by the known water-soluble host compounds.[6]

(2) The hosts having positive charges (2a,b) showed stronger complex formation than the corresponding hosts having negative charges (3a and 3b, respectively). Since the substrate has a negative charge ($Ar-SO_3^-$), the stronger complex formation by hosts 2a and 2b can be ascribed to a favorable electrostatic interaction. Thus a simple charge proximity effect have resulted in molecular recognition by a factor of as high as 22 ($K_d = 8.6 \times 10^{-5}$ M by 2a vs. $K_d = 1.9 \times 10^{-3}$ M by 3a), which indicates the importance of electrostatic interaction in aqueous solution.[7]

(3) Destabilization of the host-guest complexes in the order of $1 \rightarrow 2a \rightarrow 2b$[8] may be explained by the increasing separation of positive charges and hydrophobic cavity (Figure 2), thus the importance of the electrostatic interaction between host and substrate is indicated from a different angle.

Although complex formation has been weakened by the present modification, a host compound (2a) exhibiting K_d value of $\sim 10^{-4}$ M with an organic guest molecule in <u>neutral</u> aqueous solution[6] was successfully obtained. Therefore it may be concluded that this type of host compounds have found wider possibilities of their future applications.

<u>Table 1</u> Dissociation constants (K_d) of the 1:1 complexes between TNS and the modified hosts.[4,8]

Host		K_d [M]
2a	(R = $-CO(CH_2)_2 NH_3^+$)	8.6×10^{-5} (1.0)[a]
2b	(R = $-CO(CH_2)_5 NH_3^+$)	3.1×10^{-3} (0.028)[a]
3a	(R = $-CO(CH_2)_2 CO_2^-$)	1.9×10^{-3} (0.045)[a]
1	(R = H_2^+; CP44)	9.7×10^{-6} (8.9)[b]

25.0 ± 0.1°C; excited at 375 nm; measured at 495 nm; [TNS] = $2-10 \times 10^{-6}$ M.   (a) KH_2PO_4 - Na_2HPO_4 buffer (pH 7.07). (b) KCl - HCl buffer (pH 1.95).   The values in the parentheses are the relative <u>stabilities</u> ($1 / K_d$) of the complexes.

1 (R = H_2^+; CP44)   2a (R = $-CO(CH_2)_2 NH_3^+$)   2b (R = $-CO(CH_2)_5 NH_3^+$)
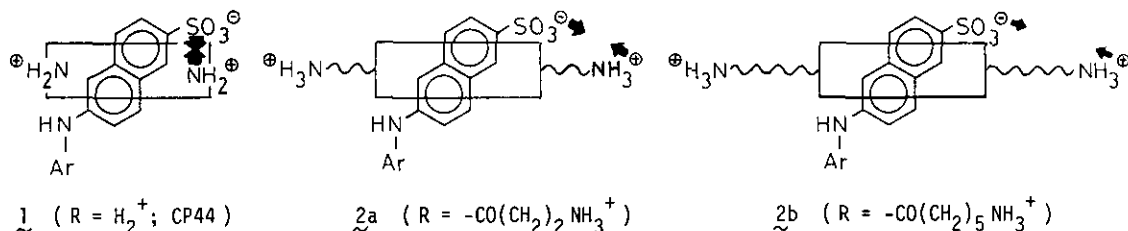
<u>Figure 2</u> Schematic drawings of attractive electrostatic interaction between host and substrate.

REFERENCES AND NOTES

1. (a) K. Odashima, A. Itai, Y. Iitaka, and K. Koga, J. Am. Chem. Soc., 1980, 102, 2504; (b) K. Odashima, A. Itai, Y. Iitaka, Y. Arata, and K. Koga, Tetrahedron Lett., in press; (c) T. Soga, K. Odashima, and K. Koga, ibid., in press; (d) K. Odashima, T. Soga, and K. Koga, submitted to publication.

2. 5a: dec pt 120.5-122°C;[a,b] 5b: mp 106.5-107°C (dec.);[a,b] 6a: mp 208-208.5°C (dec.);[a,b] 6b: mp 125-125.5°C (dec.);[a,b] 3a: dec pt 238-239°C;[a,b] 3b: mp 196.5-197.5°C (dec.).[a,b] 2a[a,b] and 2b[a] did not show distinct decompositing points. (a) Satisfactory ^{1}H NMR spectra were obtained. (b) Satisfactory elemental analyses (C,H,N) were obtained.

3. For the similar fluorescent changes by native or modified cycloamyloses, see: (a) H. Kondo, H. Nakatani, and K. Hiromi, J. Biochem., 1976, 79, 393; (b) I. Tabushi, Y. Kuroda, and K. Shimokawa, J. Am. Chem. Soc., 1979, 101, 1614.

4. The dissociation constants were determined by Benesi-Hildebrand plot. (H. A. Benesi and J. H. Hildebrand, J. Am. Chem. Soc., 1949, 71, 2703.) The complex formation by host 3b was not strong enough to determine accurate dissociation constant.

5. ^{1}H NMR spectral study using benzyl alcohol as the substrate has also demonstrated complex formation by the modified hosts. Upfield shifts of the aromatic proton signal of the substrate induced by the host were as follows. 2a: 0.26 ppm;[a] 3a: 0.14 ppm;[a] 1: 0.65-0.87 ppm.[b,c] (See ref. 1b.) Substrate concentration was 2.5×10^{-2} M throughout. (a) [Host] = 2.1×10^{-2} M, pD 7.1. (b) [Host] = 2.5×10^{-2} M, pD 1.2. (c) Splitted into several signals.

6. For comparison, see for example: (a) Ref. 3a; (b) I. Tabushi, Y. Kuroda, and Y. Kimura, Tetrahedron Lett., 1976, 3327; (c) I. Tabushi, H. Sasaki, and Y. Kuroda, J. Am. Chem. Soc., 1976, 98, 5727; (d) Y. Murakami, Y. Aoyama, M. Kida, and A. Nakano, Bull. Chem. Soc. Jpn., 1977, 50, 3365.

7. For the related studies by modified cycloamyloses, see: (a) I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, and K. Yamamura, J. Am. Chem. Soc., 1977, 99, 7100; (b) Y. Matsui and A. Okimoto, Bull, Chem. Soc. Jpn., 1978, 51, 3030; (c) J. Boger, D. G. Brenner, and J. R. Knowles, J. Am. Chem. Soc., 1979, 101, 7630; J. Boger and J. R. Knowles, ibid., 1979, 101, 7631.

8. Rough comparison of the dissociation constants determined under different pH's (pH 7.07 and 1.95) may be allowed in this case, because the predominant form of TNS is considered to be Ar-NH-SO_3^- at either pH.