USE OF ELECTROSTATIC INTERACTION FOR CHIRAL RECOGNITION. ENANTIOSELECTIVE COMPLEXATION OF ANIONIC BINAPHTHYLS WITH PROTONATED AMINO-β-CYCLODEXTRIN

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ABSTRACT

The studies using NMR and capillary zone electrophoresis clearly reveal that protonated 6^A-amino-6^A-deoxy-β-cyclodextrin recognizes the chirality of anionic binaphthyl derivatives such as 1,1'-binaphthyl-2,2'-diyl phosphate and 1,1'-binaphthyl-2,2'-dicarboxylate through electrostatic interaction between the host and the guest and simultaneous inclusion.

1. INTRODUCTION

Chiral recognition is one of the recent topics in cyclodextrin (CDx) chemistry [1]. Three-point attachment model has been accepted as a mechanism which explains chirality-recognizing host-guest complexation [2]. Hydrogen-bonding interaction has widely been used to achieve chiral discrimination through this mechanism [3]. In general, however, hydrogen bond is hardly formed in water because of strong hydration to hydrogen-bonding sites of both host and guest molecules. Electrostatic force is expected to act as a point interaction in place of hydrogen bonding. The present study deals with the chiral recognition of anionic, chiral guests by a cationic CDx. We used protonated 6^A-amino-6^A-deoxy-β-CDx (6-Amino-β-CDx) as the cationic host and 1,1'-binaphthyl-2,2'-diyl phosphate (BNP) and 1,1'-binaphthyl-2,2'-dicarboxylate (BNC) as the anionic guests having the axial chirality. To the best of our knowledge, there are three examples with the chiral recognition by aminated CDxs. Nardi et al. [4] reported that the enantiomers of mandelic acid and its related compounds are separated by capillary zone electrophoresis (CZE) using 6^A-*N*-methylamino-6^A-deoxy-β-CDx and 6^A,6^D-di-*N*-methylamino-6^A,6^D-dideoxy-β-CDx as the chiral separators. Brown et al. [5] found a weak ability of protonated 6-Amino-β-CDx to discriminate between the enantiomers of 2-phenylpronionate. Kano et al. [6] demonstrated that the conformational enantiomerism of bilirubin induced by heptakis(6-amino-6-deoxy)-β-CDx is

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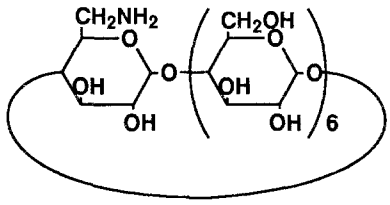
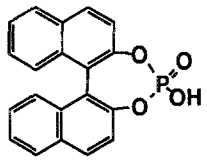
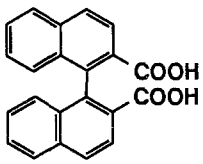
achieved by a hydrogen-bonding interaction between the NH_3^+ groups of the cyclodextrin and the CO_2^- groups of bilirubin.



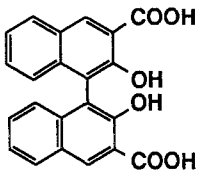
6-Amino-β-CDx



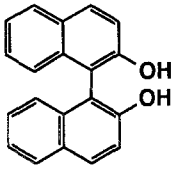
BNP



BNC



HBNC



BN

The present study reveals that protonated 6-Amino-β-CDx is a good host for recognizing the axial chilarities of the binaphthyl derivatives. The cooperative effect of the electrostatic and van der Waals and/or hydrophobic interactions seems to be very important to form stable inclusion complexes of 6-Amino-β-CDx.

2. EXPERIMENTAL

6-Amino-β-CDx was prepared according to the procedures described in the literature [7]. β-CDxs (Nacalai) commercially obtained was washed with THF using a Soxhlet extractor to remove an antioxidant. Optically active and racemic BNP and 1,1'-bi-2-naphthol (BN, Aldrich) were commercially obtained. The preparation of (±)-, (*S*)- and (*R*)-2,2'-dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylic acids (HBNC) were described before [8]. 1,1'-Binaphthyl-2,2'-dicarboxylic acid (BNC) was the same as previous one [9].

The CZE experiments were carried out by using a Jasco capillary electropherograph system CE-800 having a 50 μm (I.D.) x 300 mm fused silica capillary cartridge (non-coated). The capillary was filled with a buffer solution with CDx and the sample in the same buffer solution was introduced into the capillary by applying the potential for 10 s. The electropherogram was taken at the same potential using a Jasco 875-CE UV-Vis detector. The NMR spectra were taken with a JEOL JNM A-400 (400 MHz) in D_2O using sodium 3-(trimethylsilyl)propionate-d_4 (Aldrich) as an external standard.

The molecular mechanics-molecular dynamics (MM-MD) calculations were carried out as described previously [9].

3. RESULTS AND DISCUSSION

3.1. CZE of Binaphthyl Derivatives Using 6-Amino-β-CDx as Separator

CZE is very convenient tool to know the system where chiral host enantioselectively complexes with chiral guest [9, 10]. The electropherogram of a mixture of (±)-BNC and (±)-BNP is shown in Fig. 1. The migration time (t) of BNP is shorter than that of BNC, indicating that the binding constant (K) for the BNP complex is larger than that for the BNC complex (*vide infra*). At the same time, it can be predicted that protonated 6-Amino-β-CDx prefers the anionic forms of (*S*)-BNP and (*R*)-BNC as the guests. The results of CZE of other binaphthyl derivatives are summarized in Table 1. The enantiomers of BNC can be separated by β-CDx in the pH 3.08 to 5.50 range. Of course, no separation occurs for undissociated BNC at lower pH range. At pH above 5.50, dissociated BNC is not included in the β-CDx cavity leading to unification of the peaks of the BNC enantiomers. In the case of 6-Amino-β-CDx, however, the separation

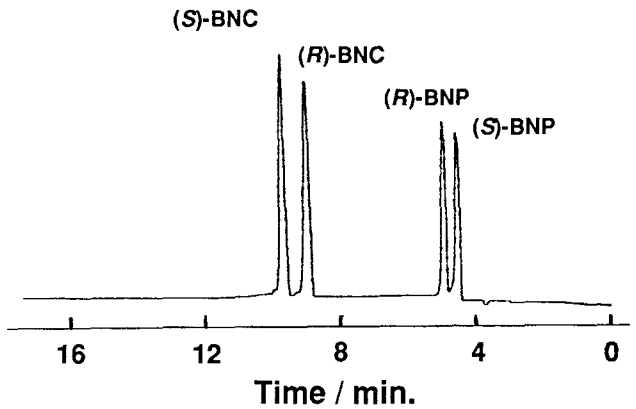


Fig. 1 Electropherogram of a mixture of (±)-BNP and BNC (4×10^{-4} M).
Separation solution: 6-Amino-β-CDx (0.01 M)
Buffer: 0.033 M phosphate buffer at pH 7.21
Applied voltage: 13.1 kV (30.1 μA)

can be achieved at wider pH range. Even at higher pH range, the BNC anion can be bound to protonated 6-Amino-β-CDx through electrostatic interaction. Therefore, the enantiomers of BNC are separated each other by CZE up to pH 7.70. At pH above 7.70, the amounts of protonated 6-Amino-β-CDx become small resulting in the disappearance of electrostatic interaction between the host and the guest. Although it

was very difficult to separate the optical isomers of HBNC by CZE using β-CDx, 6-Amino-β-CDx makes it possible. Since BN has no charge, no separation occurs in CZE

TABLE 1. Chiral separation of the binaphthyl derivatives (4 x 10^{-4} M) by CZE using 6-Amino-β-CDx (0.01 M) as a chiral separator

Sample	CDx	pH	Voltage/kV	Current/μA	t_S/min	t_R/min	α
BNP	β-CDx	5.40	12	13	12.2	13.0	1.12
	6-Amino-β-CDx	5.54	12	26	6.80	8.20	1.18
BNC	β-CDx	4.15	21	10	7.40	6.20	1.20
	6-Amino-β-CDx	6.33	21	10	7.40	6.20	1.20
HBNC	6-Amino-β-CDx	8.35	8	6	12.3	13.0	1.05
BN	6-Amino-β-CDx	2.40	12	21	8.20	10.6	1.29

using β-CDx. The enantiomeric separation of BN, however, is realized by CZE using 6-Amino-β-CDx at the low pH range, where the electroosmotic flow is negligible.

3.2 NMR Study on Chiral Recognition of BNP by 6-Amino-β-CDx

Figure 2 shows the 6-Amino-β-CDx-induced shifts in the ^{1}H NMR signals due to (*R*)- and (*S*)-BNPs in D_2O at pD 6.0. Although it is very difficult to deduce the structure of

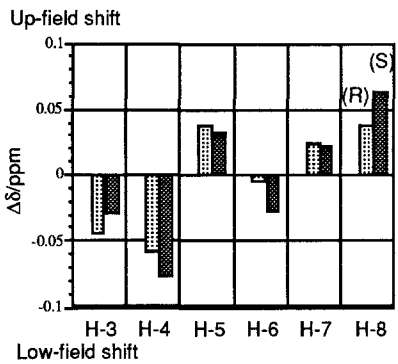


Fig. 2 6-Amino-β-CDx-induced shifts in the ^{1}H NMR signals of BNP in D_2O ([BNP] = 0.001 M, [6-Amino-β-CDx] = 0.01 M)

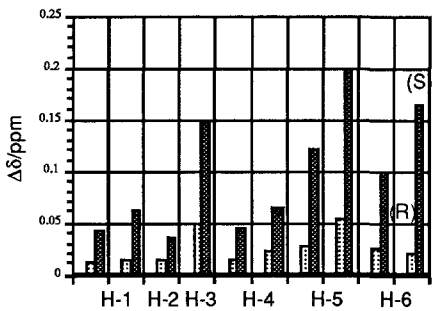


Fig. 3 BNP-induced shifts in the ^{1}H NMR signals of 6-Amino-β-CDx in D_2O ([BNP] = 0.001 M, [6-Amino-β-CDx] = 0.01 M)

the complex from the results exhibited in Fig. 2, it can be assumed that the structure of the (*S*)-enantiomer is similar to that of the (*R*)-enantiomer. The BNP-induced shifts of the ^{1}H NMR signals due to 6-Amino-β-CDx is shown in Fig. 3. The signals of the protons at the 3-, 5-, and 6-positions remarkably shift to higher magnetic fields due to the ring-current effect by the aromatic ring of the guest, suggesting that BNP is bound to both sides of the cyclodextrin. Namely, it seems that the BNP-6-Amino-β-CDx complex is not so simple as to be shown by a sole structure.

The binding constants for complexation of the enantiomers of BNP and BNC with 6-Amino-β-CDx were determined from the ^{1}H NMR-titration curves. The results are

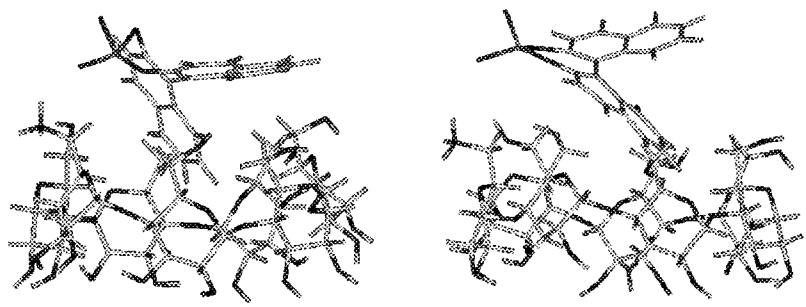
TABLE 2. Binding constants for complexation of 6-Amino-β-CDx with BNP and BNC in D_2O at pD 6

Sample	K/M^{-1}	R/S
(*S*)-BNP	3474	3.5
(*R*)-BNP	998	
(*S*)-BNC	214	0.52
(*R*)-BNC	415	

revealed in Table 2. The order of the K values is in good agreement with that predicted from the results of CZE (*vide supra*). Although dissociated BNC cannot be bound to β-CDx, it forms the complex with protonated 6-Amino-β-CDx. This is one of the advantages of the use of electrostatic interaction in the host-guest chemistry in water.

3.3 Structures of Complexes

The plausible structures of the complexes of (*S*)- and (*R*)-BNPs and 6-Amino-β-CDx are obtained from molecular dynamics and molecular mechanics calculations. The information on the charges was obtained from the MOPAC calculations and the effects of water molecules were considered in calculations. The results are shown in Fig. 4.



(*S*)-BNP (*R*)-BNP

Fig. 4 Calculated structures of the complexes of the (*S*)- and (*R*)-BNP anions and protonated 6-Amino-β-CDx

In both complexes, the electrostatic attraction is observed between the NH_3^+ group of 6-Amino-β-CDx and the phosphate anion group of BNP. In the case of (*S*)-BNP, a naphthalene moiety of BNP penetrates somewhat deeply into the cyclodextrin cavity.

Meanwhile, more shallow binding is observed for the (*R*)-enantiomer. The ROESY spectra indicated the correlation between the protons at the 3-, 5-, 7-, and 8-positions of (*S*)-BNP and the protons at the 5- and 6-positions of 6-Amino-β-CDx. In contrast with this, only the protons at the 7- and 8-positions of (*R*)-BNP correlate with the protons at the 5- and 6-positions of the host. Such difference may be interpreted in terms of that (*S*)-BNP penetrates more deeply into the CDx cavity compared with (*R*)-BNP.

Of course, the chiral recognition cannot be achieved only by an electrostatic interaction between host and guest. In the present study, the electrostatic binding occurs only at one position. Therefore, the simultaneous inclusion of the guest into the host cavity is essential for the chiral recognition.

ACKNOWLEDGMENT

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References

[1] Kano, K. *Selectivities in cyclodextrin chemistry*, in Bioorganic Chemistry Frontiers, (Ed. Dugas, H., Schmidtchen, F. P.) Springer-Verlag, Berlin, 1993, Vol. 3, Pp. 1-23

[2] Daffe, V., Fastrez, J., Cyclodextrin-catalysed hydrolysis of oxazol-5(4H)-ones. Enantioselectivity of the acid-base and ring-opening reactions, *J. Chem. Soc., Perkin Trans. 2*, 789-796 (1983); Boehm, R. E., Martire, D. E.; Armstrong, D. W., Theoretical considerations concerning the separation of enantiomeric solute by liquid chromatography, *Anal. Chem.*, **60**, 522-528 (1988)

[3] Rebek, Jr., J. *Recent progress in molecular recognition*, in Topics in Current Chemistry, (Ed. Weber, E.) Springer-Verlag, Berlin, 1988, Vol. 149, Pp. 189-210.

[4] Nardi, A., Eliseev, A., Bocek, P., Fanali, S., Use of charged and neutral cyclodextrins in capillary zone electrophoresis: enantiomeric resolution of some 2-hydroxy acids, *J. Chromatogr.*, **638**, 247-253, (1993)

[5] Brown, S. E., Coates, J. H., Duckworth, P. A., Lincoln, S. F., Easton, C. J., May, B. L., Substituent effects and chiral discrimination in the complexation of benzoic, 4-methylbenzoic and (RS)-2-phenylpropanoic acids and their conjugate base by β-cyclodextrin and 6^A-amino-6^A-deoxy-β-cyclodextrin in aqueous solution: Potentiometric titration and ^{1}H nuclear magnetic resonance spectroscopic study, *J. Chem. Soc., Faraday Trans.*, **89**, 1035-1040 (1993)

[6] Kano, K., Arimoto, A., Ishimura, Conformational enantiomerism of bilirubin and pamoic acid inducd by protonated aminocyclodextrins, T., *J. Chem. Soc., Perkin Trans. 2*, 1661-1666 (1995)

[7] Melton, L. D., Slessor, K. N., Synthesis of monosubstituted cyclohexaamyloses, *Carbohydr. Res.*, **18**, 29-37 (1971)

[8] Kano, K., Tamiya, Y., Otsuki, C., Shimomura, T., Ohno, T., Hayashida, O., Murakami, Y., Chiral recognition by cyclic oligosaccharides. Enantioselective complexation of binaphthyl derivatives with cyclodextrins, *Supramol. Chem.*, **2**, 137-143 (1993)

[9] Kano, K., Minami, K., Horiguchi, K. Ishimura, T., Kodera, M. Ability of non-cyclic oligosaccharides to form molecular complexes and its use for chiral separation by capillary zone electrophoresis, *J. Chromatogr. A*, **694**, 307-313 (1995)

[10] Li, S. F. Capillary Electrophoresis, Principles, Practice and Applications, Elsevier, Amsterdam, 1992