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Extraction of Catecholamines by Calixarene Carboxylic Acid Derivatives

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Abstract

Extraction behaviors of catecholamines with a series of calixarene carboxylic acid derivatives were investigated. Relatively large calix[6]arene and calix[8]arene extract catecholamines into the organic solution, while smaller calix[4]arene and the monomer analog do not. The calix[6]arene, which has a cavity that fits a protonated amino group well, selectively extracts a primary amino compound dopamine over other catecholamines. Slope analysis and Job's method confirmed formation of a 1:1 complex between the calix[6]arene and dopamine. On the other hand, the calix[8]arene extracts both dopamine and adrenaline, due to the large cavity for induced-fit recognition. Dopamine extracted with the calixarene is quantitatively stripped by contacting the organic solution with a fresh acidic solution.

Abbreviations: ^{t}Oct[4]CH_2COOH: *p*-tert-octylcalix[4]arene tetracarboxylic acid derivative; ^{t}Oct[1]CH_2COOH: *p*-tert-octylphenoxyacetic acid (as a monomer analog); D2EHPA: bis(2-ethylhexyl) hydrogen phosphate; ^{t}Oct[1]CH_2COOH: *p*-tert-octylphenoxyacetic acid; ^{t}Oct[6]CH_2COOH and H6R: *p*-tert-octylcalix[6]arene hexacarboxylic acid derivative; ^{t}Oct[8]CH_2COOH and H8R: *p*-tert-octylcalix[8]arene octacarboxylic acid derivative; DA: dopamine; Ad: adrenaline; NA: noradrenaline; E: degree of extraction of catecholamine; D: distribution ratio of catecholamine

Introduction

Recognition of amines by macrocycles has been one of the most important subjects in macrocyclic chemistry, and is studied in order to understand biological molecular recognition and to apply it to separation technology for biomolecules [1]. Various calixarene derivatives have been synthesized to interact with amino compounds [2, 3]. In particular, calix[6]arene and homooxacalix[3]arene derivatives are attractive as receptors of amines due to their suitable cavity size and C_3 symmetry. Chang *et al.* reported liquid membrane transport of amino acids with a calix[6]arene ester derivative as a carrier [4]. Odashima *et al.* and Chen *et al.* have developed poly(vinyl chloride) membranes containing calix[6]arene ester derivatives as sensory elements to respond to primary amines [5]. Shinkai *et al.* synthesized several homooxacalix[3]arene derivatives as receptors for primary amines [6]. Tsubaki and coworkers recently reported a chromogenic homocalix[3]arene for naked-eye discrimination of various amines [7].

We have developed a calix[6]arene carboxylic acid derivative (abbreviated as ^{t}Oct[6]CH_2COOH) as an extractant for biorelevant amino compounds. The calix[6]arene, which has a strong affinity to a protonated amino group, displays extractability for amino acids, nucleotide bases such as adenine, and other organic ammonium ions [8]. Even a cationic protein cytochrome *c* is transferred into an organic solution with ^{t}Oct[6]CH_2COOH, through interactions between ϵ-amino groups of lysine residues and ^{t}Oct[6]CH_2COOH molecules [9]. The present study examines liquid–liquid extraction of catecholamines with calix[*n*]arene carboxylic acid derivatives ($n = 4, 6, 8$), in order to elucidate the extractabilities of and selectivities for the biologically important amines.

Some researchers have synthesized receptors prepared from calixarenes and investigated their recognition selectivity for catecholamines. Odashima *et al.* investigated selectivities of membrane potential changes for catecholamines with calix[6]arene derivatives and related host molecules incorporated in poly(vinyl chloride) (PVC) matrix liquid membrane [10]. The calix[6]arene esters and homooxacalix[3]arene triether show selectivities for dopamine over noradrenaline and

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adrenaline. Nakano *et al.* prepared a self-assembled monolayer electrode with a calix[6]arene thioether derivative as a dopamine sensor [11]. Recently, Jeon *et al.* developed PVC polymeric membrane electrodes incorporating lipophilic 1,3-bisbridged cofacial-calix[6]-crowns as catecholamine selective ionophores [12]. A lipophilic 1,3-bisbridged cofacial-calix[6]crown-5-ether shows a selective response towards a secondary amine adrenaline over other catecholamines.

In the 1990s, solvent extraction of catecholamines was studied from the viewpoint of large-scale separation processing of the biologically important molecules. Mirkovic *et al.* described extraction of catecholamines using a liquid cationic exchanger from various rat tissues [13]. We also reported liquid–liquid extraction of catecholamines with bis(2-ethylhexyl) hydrogen phosphate (D2EHPA) [14]. The organophosphorus extractant extracts dopamine by forming a 4:1 complex. Furthermore, the quantitative structure-property relationship (QSPR) of extractability trends of catecholamines was provided using molecular modeling with semi-empirical molecular orbital calculations.

A combinatorial investigation in this study relating to complexation between the host calixarenes and the guest catecholamines provides valuable information for designing a host molecule that can recognize biomolecules. The mechanism for the extraction of dopamine by the calix[6]arene was confirmed by slope analysis and Job's method. Stripping of the extracted dopamine into an aqueous solution was also demonstrated.

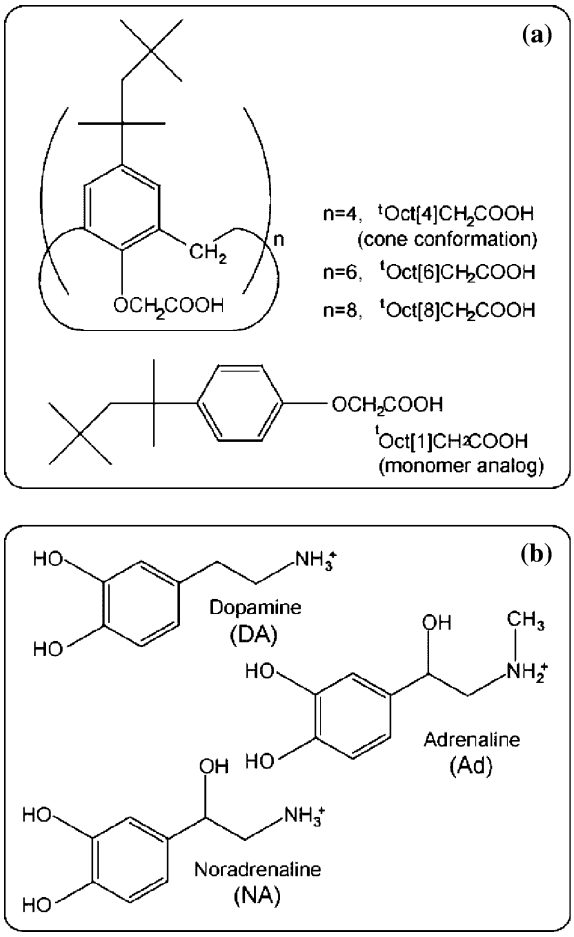

Figure 1. Molecular structures and abbreviations of (a) extractants and (b) guest catecholamines in this study.

Experimental

Reagents

Figure 1 shows the molecular structures and abbreviations of extractants (a) and guest catecholamines (b) used in the present study. The extractants *p*-tert-octylcalix[4]arene tetracarboxylic acid derivative (abbreviated as ^{t}Oct[4]CH_2COOH), *p*-tert-octylcalix[6]arene hexacarboxylic acid derivative (^{t}Oct[6]CH_2COOH), *p*-tert-octylcalix[8]arene octacarboxylic acid derivative (abbreviated as ^{t}Oct[8]CH_2COOH), and *p*-tert-octylphenoxyacetic acid as a monomer analog (abbreviated as ^{t}Oct[1]CH_2COOH), were synthesized according to the procedures described in previous papers [8a, 15]. These final products were purified by recrystallization and then identified by means of FT-IR, ^{1}H-NMR, and elemental analysis.

Analytical grade dopamine (DA), adrenaline (Ad) and noradrenaline (NA) were purchased from Tokyo Kasei Co. Ltd (Tokyo, Japan). DA purchased as the hydrochloride was used as received. Ad and NA were treated with hydrochloric acid in 2-propanol, in order to obtain the hydrochloride. After washing with diethyl ether, the products were identified by means of FT-IR, ^{1}H-NMR, and elemental analysis.

Extraction equilibrium of catecholamines in liquid–liquid extraction

Two aqueous solutions were separately prepared by dissolving 0.3 mmol/dm^3 of a catecholamine (DA, Ad, or NA) hydrochloride into either 100 mmol/dm^3 hydrochloric acid or glycine solution. The pH of the aqueous solution was adjusted by mixing the above two aqueous solutions. An organic solution was prepared by dissolving an extractant in chloroform. The initial concentration of ^{t}Oct[4]CH_2COOH, ^{t}Oct[6]CH_2COOH or ^{t}Oct[8]CH_2COOH was 3.0 mmol/dm^3 (corresponding to 10 equivalents of the guest catecholamine), while the concentration of the monomer analog ^{t}Oct[1]CH_2COOH was 18.0 mmol/dm^3, to adjust the number of functional carboxyl groups to be the same as that of ^{t}Oct[6]CH_2COOH. Equal volumes (5 cm^3) of the aqueous and the organic solutions were mixed in a stoppered glass tube (volume 10 cm^3) and gently shaken in a thermostatted water bath at 30 °C. After 20 h the extraction had reached equilibrium and the phases were separated. The catecholamine concentration in aqueous solution was determined by a UV–Vis spectrometer (PerkinElmer LAMBDA 190) to determine the degree of extraction (E [–], $E = [\text{catecholamine}]_{org,eq}/[\text{catecholamine}]_{aq,ini} =$

$1-[\text{catecholamine}]_{aq,eq}/[\text{catecholamine}]_{aq,ini}$) and the distribution ratio {D [–], $D = [\text{catecholamine}]_{org,eq}/[\text{catecholamine}]_{aq,eq} = ([\text{catecholamine}]_{aq,ini} - [\text{catecholamine}]_{aq,eq})/[\text{catecholamine}]_{aq,eq}$}.

Stripping test

The forward extraction of DA with ^{t}Oct[6]CH_2COOH was performed from the aqueous to the organic phase (25 cm^3/25 cm^3) in a similar manner to that described in the above section. The organic phase containing DA was divided into 5 cm^3 portions, and each solution was contacted with a fresh 5 cm^3 aqueous solution containing each mineral acid. Both phases were mixed and gently shaken at 30 °C for 20 h. The stripping solution was separated from the organic phase and the DA concentration was quantified to calculate the percent stripping ($= 100 \times [DA]_{aq,eq} / [DA]_{org,ini}$).

Results

*Extraction and stripping of catecholamines with calix[*n*]arene carboxylic acid derivatives (*n* = 4,6,8)*

Since the extraction experiments were carried out under acidic conditions, the catecholamines were present as the cationic species. Extraction profiles of DA with various extractants (^{t}Oct[*n*]CH_2COOH (*n* = 1, 4, 6, 8)) as a function of pH are displayed in Figure 2. As shown in the figure, DA is not self-distributed under the conditions examined. DA is extracted with the calix[6]arene and the calix[8]arene, which have larger cavities to include the guest cation. On the other hand, neither the calix[4]arene ^{t}Oct[4]CH_2COOH which has a smaller cavity nor the monomer ^{t}Oct[1]CH_2COOH show any extractability for DA. Namely, DA is effectively extracted by a macrocyclic host molecule that is large enough to include the target molecule into its cavity.

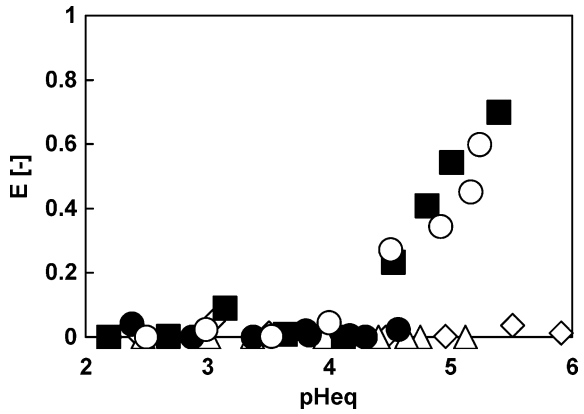

Figure 2. Extraction profiles of DA with ^{t}Oct[*n*]CH_2COOH (*n* = 1,4,6,8): extractant free (diamonds), ^{t}Oct[1]CH_2COOH (triangles), ^{t}Oct[4]CH_2COOH (filled circles), ^{t}Oct[6]CH_2COOH (squares), ^{t}Oct[8]CH_2COOH (open circles).

Extraction profiles of Ad with ^{t}Oct[*n*]CH_2COOH (*n* = 1, 4, 6, 8) are plotted in Figure 3. ^{t}Oct[8]CH_2COOH shows the highest extractability for Ad of the four extractants examined. Extractability with the calix[6]arene ^{t}Oct[6]CH_2COOH is the next highest. Furthermore, ^{t}Oct[4]CH_2COOH and ^{t}Oct[1]CH_2COOH do not show any extractability for Ad. Extraction profiles of NA with ^{t}Oct[6]CH_2COOH and ^{t}Oct[8]CH_2COOH are shown in Figure 4. The calix[6]arene and the calix[8]arene exhibit a small amount of extractability for NA. ^{t}Oct[4]CH_2COOH and ^{t}Oct[1]CH_2COOH do not show any extractability for NA (data not shown).

Extraction of DA with ^{t}Oct[*n*]CH_2COOH was compared to that with an organophosphorus extractant D2EHPA under the same conditions (data not shown) [13]. The macrocyclic extractant ^{t}Oct[6]CH_2COOH exhibits extractability comparable to a 60-fold equivalent of D2EHPA. That is, the calixarene carboxylic acid derivatives are one of the most powerful extractants for DA. Since the extraction with calixarene carboxylic acids proceeds via a proton-exchange reaction, catecholamines are extracted in a high pH region and the aqueous pH value decreases as the extraction progresses.

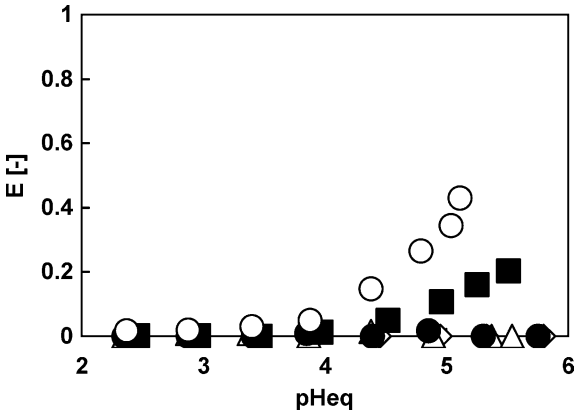

Figure 3. Extraction profiles of Ad with ^{t}Oct[*n*]CH_2COOH (*n* = 1,4,6,8): extractant free (diamonds), ^{t}Oct[1]CH_2COOH (triangles), ^{t}Oct[4]CH_2COOH (filled circles), ^{t}Oct[6]CH_2COOH (squares), ^{t}Oct[8]CH_2COOH (open circles).

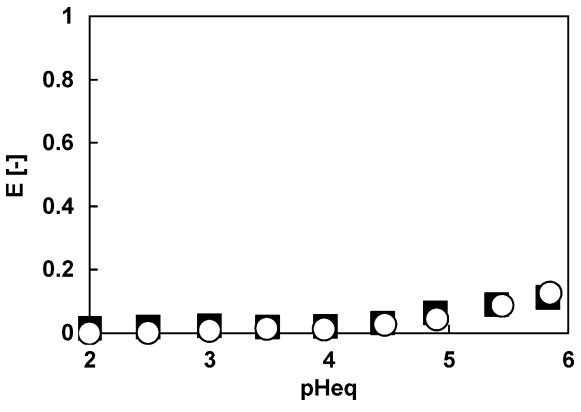

Figure 4. Extraction profiles of NA with ^{t}Oct[*n*]CH_2COOH (*n* = 6,8): ^{t}Oct[6]CH_2COOH (squares), ^{t}Oct[8]CH_2COOH (open circles).

Recovery of the extracted catecholamines also is important, in order to utilize the extraction system as a separation and purification method for catecholamines. A stripping test of DA extracted with ^{t}Oct[6]CH_2COOH into a fresh aqueous solution was performed, and the results are summarized in Table 1. DA is quantitatively stripped from an aqueous solution at a pH less than 3, through the back-extraction reaction. This result means that ^{t}Oct[6]CH_2COOH functions as a mobile carrier for transporting the catecholamine in a liquid membrane system [16].

Determination of complex species

In a previous paper, it was confirmed that an amino acid ester and the calix[6]arene ^{t}Oct[6]CH_2COOH form a 1:1 complex [8a]. The complexation mechanism between the catecholamine DA and ^{t}Oct[6]CH_2COOH in the present study was also investigated by Slope analysis and Job's method.

Figure 5 shows the effects of pH (open symbols) and extractant concentration (filled symbols) on the extraction of DA with ^{t}Oct[6]CH_2COOH. As shown in Figure 5(a), the slope for the relationship between the logarithmic distribution ratio of DA and the pH is unity, which means that one hydrogen ion is released from one ^{t}Oct[6]CH_2COOH molecule in the extraction reaction. In addition, the slope for the relationship between the logarithmic distribution ratio of DA and the logarithmic ^{t}Oct[6]CH_2COOH concentration is also unity (Figure 5(b)), which indicates that one ^{t}Oct[6]CH_2COOH molecule interacts with one DA molecule in the extraction. The effects of pH (open symbols) and the extractant concentration (filled symbols) on the extraction of DA with ^{t}Oct[8]CH_2COOH are also displayed in Figure 6. The slopes for the relationship between the logarithmic distribution ratio of DA and the pH, as well as the relationship between the logarithmic distribution ratio of DA and the logarithmic ^{t}Oct[8]CH_2COOH concentration are also unity. The results suggest that 1:1 complex is formed between ^{t}Oct[8]CH_2COOH and DA and one hydrogen ion is released from ^{t}Oct[8]CH_2COOH.

A Job's plot of the complexation between DA and ^{t}Oct[6]CH_2COOH is displayed in Figure 7, in order to confirm the stoichiometry of the extraction complex. As shown in the figure, the concentration of DA extracted in the organic solution ([DA]org. eq) reaches a maximum value when the molar ratio of ^{t}Oct[6]CH_2COOH/DA is unity. This result means that a 1:1 complex was formed on extraction.

On the basis of these results, the proton-exchange reaction for the extraction of DA with ^{t}Oct[6]CH_2COOH is expressed by the following equation:

Table 1. Stripping of DA extracted with ^{t}Oct[6]CH_2COOH

pH or acidity	% Stripping
1 mol/dm^3 HCl	100
1	90
2	100
3	100
4	38
4.5	26

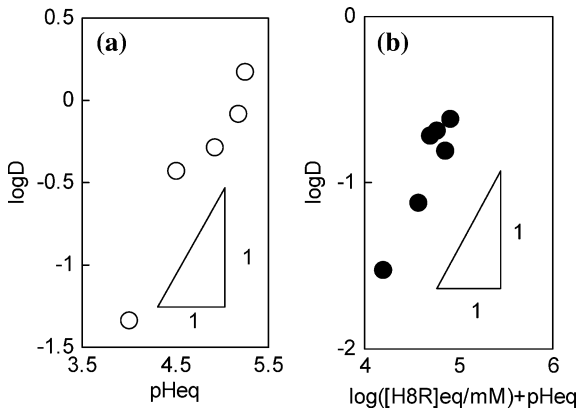

Figure 6. Slope analysis of DA with ^{t}Oct[8]CH_2COOH (H_8R). (a) Relationship between logD of DA and the pH. [H_8R] = 3mM (const.) (b) Relationship between logD of DA and log[H_8R]. pH = 4.6–4.8.

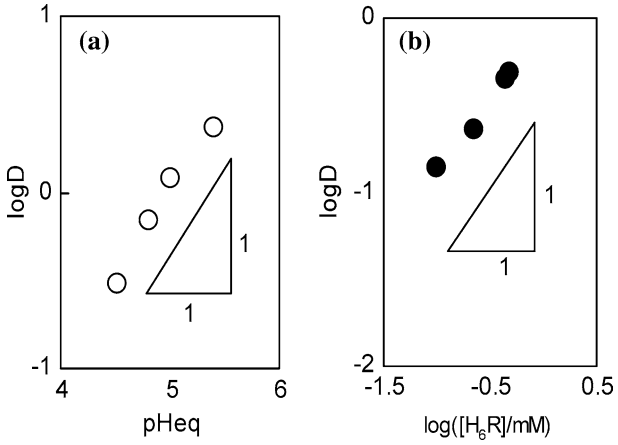

Figure 5. Slope analysis of DA with ^{t}Oct[6]CH_2COOH (H_6R). (a) Relationship between logD of DA and the pH. [H_6R] = 3mM (const.) (b) Relationship between logD of DA and log[H_6R]. pH = 6.0 (const.).

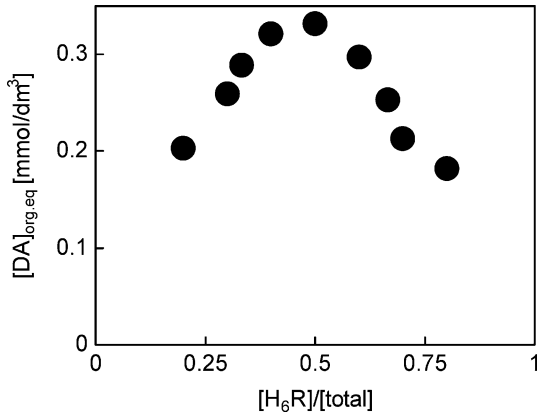

Figure 7. Job's plot of complexation between ^{t}Oct[6]CH_2COOH and DA.

$$(DA)H^+ + H_6R = \{(DA)H\}H_5R + H^+$$

where H_6R denotes a ^{t}Oct[6]CH_2COOH molecule and $(DA)H^+$ denotes a protonated DA molecule.

Discussion

Catecholamines DA, Ad, and NA are all prepared sequentially from tyrosine through the biosynthetic pathway. Because catecholamines are structurally similar to each other, they are interesting compounds to use as guest molecules for the calixarene derivatives in order to understand their inclusion characteristics.

Results from tests to determine catecholamine extraction by calixarenes are shown in Figures 2, 3, and 4 and are summarized in Figure 8, as a relationship between the extraction at pH 5.0 ($E_{pH5.0}$) and logarithmic *P*, which gives a quantitative indicator for the hydrophilic/lipophilic balance of organic compounds [14, 17]. From the viewpoint of the separation factor, the

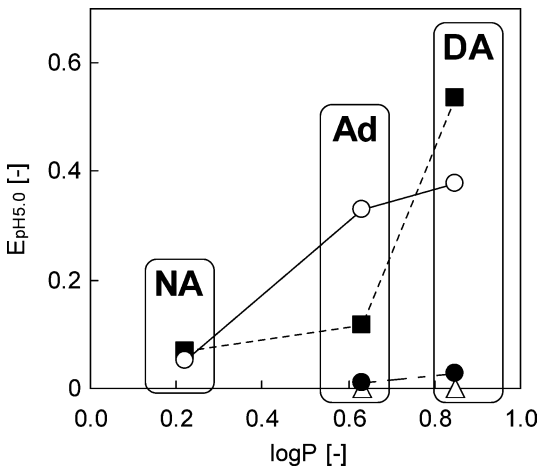

Figure 8. Relationship between extraction of catecholamines with ^{t}Oct[*n*]CH_2COOH (*n* = 1,4,6,8) at pH 5.0 ($E_{pH5.0}$) and log *P* of the catecholamines: extractant free (diamonds), ^{t}Oct[1]CH_2COOH (triangles), ^{t}Oct[4]CH_2COOH (filled circles), ^{t}Oct[6]CH_2COOH (squares), ^{t}Oct[8]CH_2COOH (open circles).

calix[6]arene ^{t}Oct[6]CH_2COOH selectively extracts a primary amine DA over a secondary amine Ad. On the other hand, the calix[8]arene ^{t}Oct[8]CH_2COOH exhibits similar extraction behaviors for DA and Ad. NA is hard to extract with all the extractants.

In our previous study, dominant host and guest parameters for the formation of stable host-guest complexes on the extraction of ammonium compounds by calixarenes were investigated [8b]. The important host parameters for amino acid extraction are the cavity structure, the cavity size, the functional carboxylic acid groups, and the length of the alkyl chains. The calix[6]arene ^{t}Oct[6]CH_2COOH has an ideal structure for entrapping a primary amino compound due to the suitability of the cavity size for inclusion, the complementary C_3 symmetry for an NH_3^+ group, and the preorganized carboxylic acid groups. On the basis of spectroscopic observations, it was confirmed that ^{t}Oct[6]CH_2COOH forms a 1:1 *endo* complex with an amino acid ester by including it into the cavity. Similarly to our expectations, the order of the extractabilities of the primary amino compound DA with ^{t}Oct[*n*]CH_2COOH is as follows: ^{t}Oct[6]CH_2COOH > ^{t}Oct[8]CH_2COOH >> ^{t}Oct[1]CH_2COOH, ^{t}Oct[4]CH_2COOH. Calixarenes which have a large cavity to include the guest cation show high extraction ability, while the smaller ^{t}Oct[4]CH_2COOH and the monomer analog ^{t}Oct[1]CH_2COOH do not. On the other hand, the order of the extractabilities for Ad with ^{t}Oct[*n*]CH_2COOH is different from that of DA: ^{t}Oct[8]CH_2COOH > ^{t}Oct[6]CH_2COOH >> ^{t}Oct[1]CH_2COOH, ^{t}Oct[4]CH_2COOH. The extractability of the secondary amino compound by the calix[6]arene is smaller than that of the primary amino compound DA, in contrast to the results for the calix[8]arene.

The important guest parameters for the extraction of ammonium compounds with ^{t}Oct[6]CH_2COOH are the hydrophobicity and the ionic property [8b]. Therefore, the orders of extraction for catecholamines using ^{t}Oct[6]CH_2COOH and ^{t}Oct[8]CH_2COOH are consistent with that of the log *P* values: DA (log *P* = 0.85) > Ad (log *P* = 0.63) > DA (log *P* = 0.22). An organophosphorus extractant D2EHPA also exhibits this selectivity for catecholamine [13]. It should be emphasized, however, that the selectivity for DA over Ad by ^{t}Oct[6]CH_2COOH is much higher than that by ^{t}Oct[8]CH_2COOH. These results suggest that the cavity size of the calixarene relates to the extraction selectivity between a primary and a secondary amine.

Figure 9 shows a conceptual illustration of the complexation reaction between ^{t}Oct[*n*]CH_2COOH (*n* = 6 or 8) and catecholamines. Since the macrocyclic structure of ^{t}Oct[6]CH_2COOH is well-suited for recognition of the primary amino compound DA, the complex is stable. On the contrary, the asymmetric structure of the secondary amino compound Ad is stereochemically unfavorable for recognition by ^{t}Oct[6]CH_2COOH. As a result, the complex between the calix[6]arene and Ad is unstable. On the other hand, ^{t}Oct[8]CH_2COOH

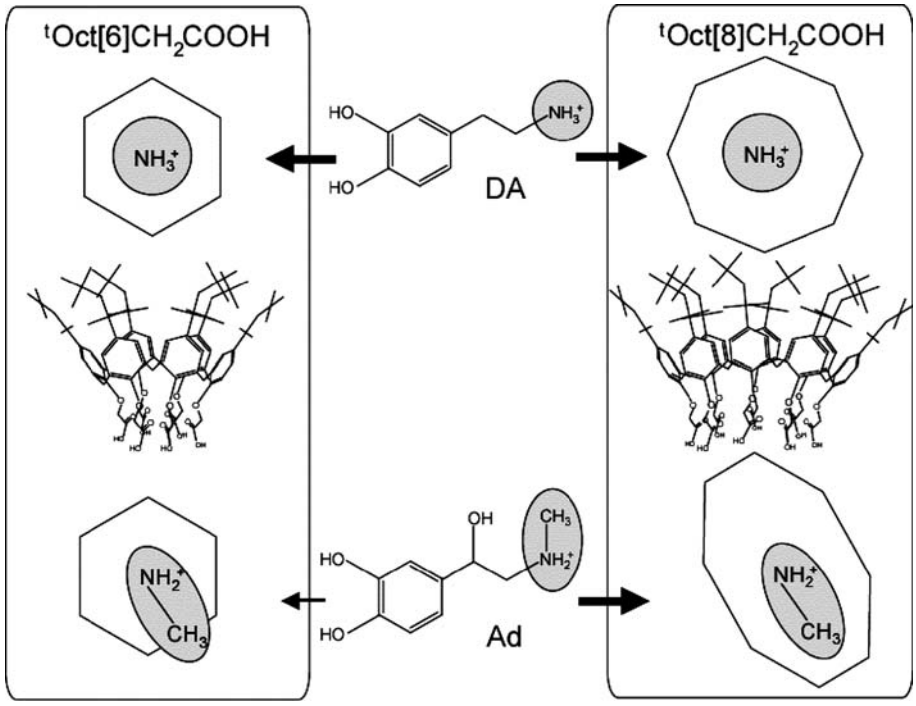

Figure 9. Conceptual illustration of complexation between ^{t}Oct[*n*]CH_2COOH ($n = 6,8$) and catecholamines (DA, Ad).

has a larger cavity and enough structural freedom to accept both the primary DA and the secondary Ad. Therefore, the selectivity by ^{t}Oct[8]CH_2COOH for catecholamines is dependent on simple chemical characteristics such as hydrophobicity and pK_a. In a previous paper [8b], the extractabilities of quaternary ammonium cations with ^{t}Oct[6]CH_2COOH were shown to be almost equivalent to that of the primary ammonium cation. These results mean that electrostatic interaction is a dominant factor in the extraction of ammonium cations with ^{t}Oct[6]CH_2COOH, while tripodal hydrogen bonding is a secondary factor. Further studies are required to investigate the effect of the symmetry of the ammonium group in a guest molecule on the complexation with ^{t}Oct[6]CH_2COOH, however, the results seem to confirm that ^{t}Oct[6]CH_2COOH functions as a tool for selective separation of DA over Ad and NA.

Conclusion

Extraction behaviors of catecholamines with a series of calixarene carboxylic acid derivatives were studied. A calix[6]arene carboxylic acid derivative functions as an extractant for selectively separating dopamine over other catecholamines adrenaline and noradrenaline. This selectivity probably originates from the formation of a stable *endo*-complex between the primary amino compound and the calix[6]arene. Comprehensive extraction experiments confirmed the extraction reaction to be a proton-exchange reaction that forms a 1:1 complex. Unfortunately, spectroscopic observation of the complex by ^{1}H-NMR and CD spectrometry was difficult [8a], because not all the calix[6]arene molecules in the organic solution are complexed with dopamine.

As described in this paper, the calix[6]arene carboxylic acid is available as a recognition and/or modification tool for various biomolecules bearing a primary amino group. Furthermore, functionalization at the upper rim might provide multi-functionality to the calixarene derivative as a functional receptor for biomolecules.

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