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A New Family of Indoaniline-Derived Calix[4]arenes: Synthesis and Optical Recognition Properties as a Chromogenic Receptor[1]

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A new family of indoaniline-derived calix[4]arenes has been synthesized for the purpose of developing a new chromogenic receptor. A condensing reaction of calix[4]arene (**1**) with 4-(diethylamino)-2-methylaniline hydrochloride (**2**) in the presence of an oxidizing agent under alkaline conditions affords mono- (**3**), 1,2-bis- (**4**), 1,3-bis- (**5**), and tetrakisindoaniline-derived (**6**) calix[4]arenes after careful column chromatography. Compound **3** is crystallized from a $CHCl_3$−MeOH solution, and the crystal structure was determined by X-ray analysis. The crystal is monoclinic, space group $P2_1/n$, $Z = 4$, $a = 19.507(6)$ Å, $b = 18.591(6)$ Å, $c = 8.524(2)$ Å, $\beta = 94.69(2)°$. The final R value for 2406 reflections of $F_o > 3\sigma(F_o)$ is 0.085. A unique intramolecular hydrogen-bonding network involving the carbonyl oxygen of indoaniline for **3** implied that the quinone carbonyl group as an acceptor of the chromophore can easily be subjected to an electrostatic interaction in the lower rim. Indeed, 1,3-bis(indoaniline)-derived 2,4-bis((ethoxycarbonyl)methoxy)calix[4]arene **7**, prepared by the reaction of **5** with ethyl bromoacetate in the presence of NaH, is capable of undergoing an efficient ion−dipole interaction between the binding cation and the two quinone carbonyl groups of the chromophores, so that a selective Ca^{2+}-induced pronounced color change (wavelength change > 100 nm) occurs with an association constant on the order of 10^6 in 99% EtOH, making **7** of potential use as an optical sensor for Ca^{2+} detection. The IR and NMR studies have indicated that Ca^{2+} is encapsulated in the cavity made by the distally located OCH_2CO_2 groups on the lower rim of the cone-shaped calix[4]arene segment. Interestingly, however, the shape of the cavity in which Ca^{2+} has been encapsulated does not have a C_2 axis of symmetry, as inferred from the $^1H-^1H$ COSY experiment. On the other hand, 1,2-bis(indoaniline)-derived analogue **8** shows no response with metal ions, which can be interpreted to mean the absence of a cavity for encapsulation on the lower rim.

Introduction

Our interest in the development of advanced functional molecules leads us to incorporate a biological function such as receptor, transporter, enzyme, and so on into materials for electrooptical applications because the cooperation of these functions produces new types of molecular devices. In this context, recently, we have been intrigued by the synthesis of chromogenic receptors that are defined dye molecules capable of binding a guest in the antenna segment. The binding of the guest induces a change in the physical properties of the chromophore as an optical sensory site. These artificial receptors have attracted considerable attention as efficient spectrophotometric analytical reagents for the detection of particular species,[2] as well as for fundamental aspects of molecular devices possessing recognition and signal sensing.[3] Particularly, in the former cases, the inherently sensitive nature of optical signaling makes it possible to perform the selective determination of biologically important species. Hence such molecules are extremely noteworthy for the development of optical fiber sensors to measure the concentration of desired species in clinical analysis.[4] Human blood plasma usually contains Na^+, K^+, Mg^{2+}, and Ca^{2+} ions.[5] While chromogenic receptors for Na^+ and K^+ are well-known,[6] studies on Ca^{2+} for such purposes are limited.[2a,7]

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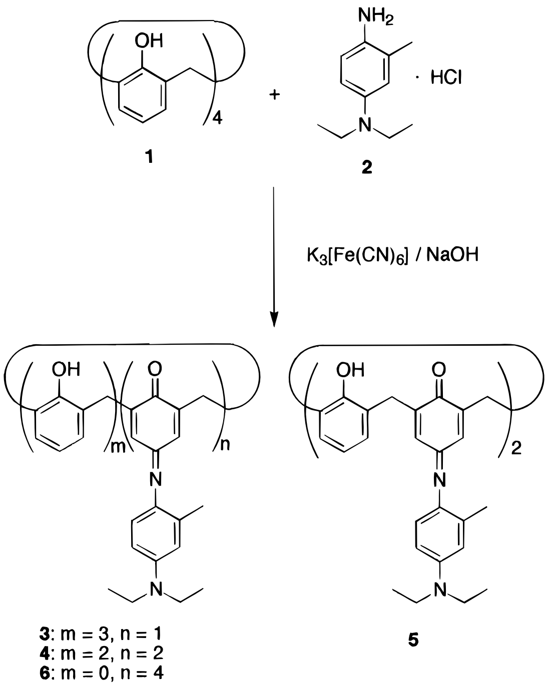
Calixarenes[8] are cyclic oligomers of varying ring size derived from *para*-substituted phenols and formaldehyde. The availability for chemical modification at the phenolic OH groups (lower rim) or at the aromatic nuclei (upper rim) has allowed the calixarenes to function as hosts for ions or small molecules.[8] Therefore, if one could introduce an appropriate optical sensory group into a calixarene bearing a preorganized guest-binding site, an encapsulated species would cause a physical change in the opto-functional site which can be monitored by spectroscopy. As such, there has been emphasis on the synthesis of "chromogenic" [6efhl,9] and "fluorogenic" [10] calix[4]arenes with the aim of developing new types of optical receptors. An indoaniline chromophore system, prepared by condensing phenol derivatives with (*N*,*N*-dialkylamino)anilines, may be important in this area because its optical properties can be perturbed significantly by chemical stimuli. Indeed, we found that the quinone carbonyl group of indoaniline-type ligands interacts with divalent metal ions to cause a pronounced color change.[11] Thus, the combined use of the chromophore constrained within a calixarene receptor framework would be of great interest in the design of chromogenic receptors; the inclusion of a positively charged species in the cavity would then, it was thought, cause a significant electrostatic perturbation of the chromophore. This paper describes the synthesis of several new types of indoaniline-derived calix[4]arene derivatives. Among them, compound **7**, containing two indoaniline chromophores designed to combine the specific complexation of the two ethyl acetate groups attached in a 1,3-fashion to oxygens on the lower rim, shows a large bathochromic shift induced by recognition of Ca^{2+}.

Results and Discussion

Scheme 1



Synthesis and Structure. The incorporation of an indoaniline chromophore with a calixarene was synthetically easy: condensing calix[4]arene **1**[12] with 4-(diethylamino)-2-methylaniline hydrochloride (**2**) under alkaline conditions in the presence of $K_3[Fe(CN)_6]$ as an oxidizing agent afforded four types of indoaniline-derived calix[4]arenes (**3**, **4**, **5**, and **6**) after chromatography (Scheme 1). The structures were identified by observed analytical data (see Experimental Section). In this case, bis(indoaniline)-derived analogues **4** and **5** are regioisomers. The assignments of the structure were, therefore, carefully conducted using NMR spectroscopy. In $CDCl_3$ solution, the compound exists as a mixture of conformers that interconvert slowly on the NMR time scale at room temperature. However, addition of CD_3OD into the solution results in the reduction of several intramolecular hydrogen bonds in the lower rim of the calix[4]arene ring, the equilibrium becomes fast on the NMR time scale, and averaged spectra have been obtained as shown in Figure 1. One can find that the signals from the $ArCH_2Ar$ are characteristic of the structure since a quinone group adjacent to the methylene is known to induce an upfield shift of the methylene resonance.[13] Actually, compound **4**, possessing proximally positioned indoaniline chromophores, displays in the ^1H NMR two singlets in a 3:1 ratio for the methylene protons (δ 3.72 and 3.85). These results indicate that one of bridging methylenes in the calix[4]arene skeleton binds to phenol residues on both sides (Figure 1; A). On the other hand, the $ArCH_2Ar$ bridging methylene resonance of compound **5** is a singlet at 3.70, in agreement with a 1,3-bis-substituted (distal) compound.

Table 1 summarized the results of the condensing reaction of **1** with **2**. It seemed likely that the number of indoaniline chromophores incorporated with the calix[4]arene increased as the [**2**]:[**1**] molar ratio and reaction time increased. In the case of run 2, the compounds **4** and **5** were obtained in 25% and 35% yields, respectively.

To obtain a better understanding of the conformation for indoaniline-derived calix[4]arene, it is important to elucidate the X-ray structure. After several trials, the crystal structure for **3** has been determined. The ORTEP

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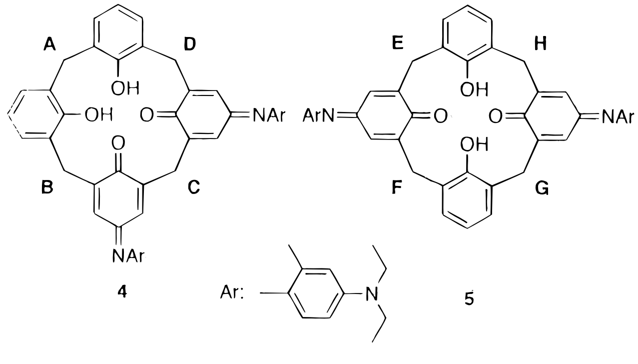

4

5

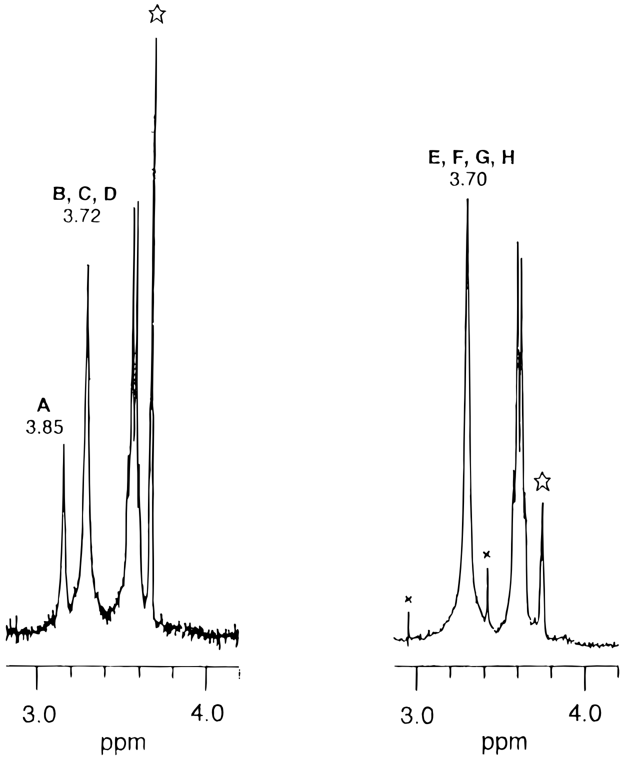

Figure 1. ^1H NMR spectra of **4** and **5** in $CD_3OD-CDCl_3$ at 300 MHz; * is signal of solvent.

Table 1. Synthesis of Indoaniline-Derived Calix[4]arenes[a]

	molar ratio			yield, %			
run	[**2**]/[**1**]	[ox][b]/[**1**]	RT,[c] min	**3**	**4**	**5**	**6**
1	4	8	120	50	11.5	8	trace
2	16	32	10	2	25	35	trace
3	16	32	240	–	3	1	37.5

[a] The procedure is similar to that described in ref 14. [b] $K_3[Fe(CN)_6]$. [c] Reaction time.

diagram is illustrated in Figure 2 with selected labeling. Compound **3** in a solid state exhibits the calix in a cone conformation; the dihedral angles between the aromatic units of the calix[4]arene skeleton through the methylene carbons are 112.4(8), 113. 1(8), 114.2 (7), and 110.1(7)°, respectively. These are slightly smaller than the corresponding values (123–126°) observed for the *p-tert*-butyl-[15] and the *p*-isopropylcalix[4]arene,[16] probably attributable to a unique intramolecular hydrogen-bonding network involving the carbonyl oxygen of indoaniline for **3**.

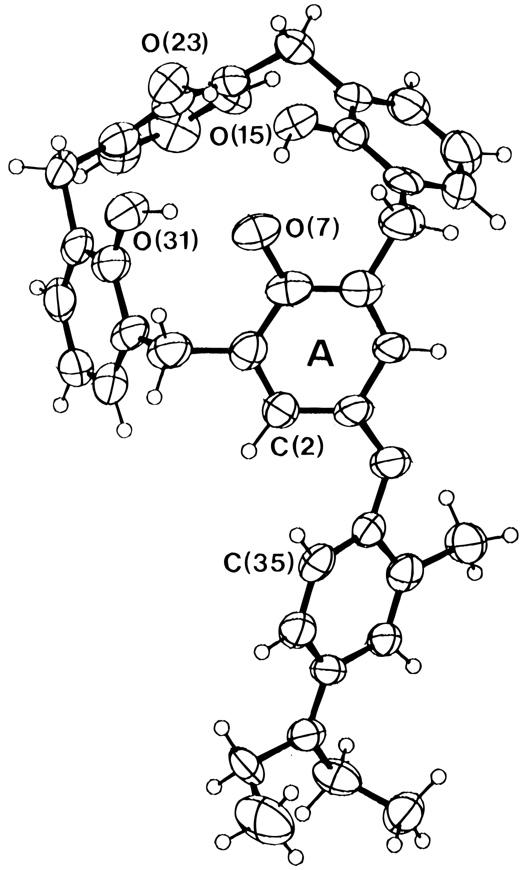

Figure 2. X-ray crystallographic structure of **3**.

Table 2. Intramolecular Hydrogen Bonding for the X-ray Structure of 3

O_a-H_a- -O_b	O_a-H_a (Å)	H_a-O_b (Å)	O_a- -O_b (Å)	O_a-H_a- -O_b (deg)
O_{15}-H_{15}- -O_7	1.0(1)	1.7(1)	2.60(1)	154(10)
O_{23}-H_{23}- -O_{15}	1.0(1)	1.8(1)	2.72(1)	158(9)
O_{31}-H_{31}- -O_7	1.0(1)	1.7(1)	2.65(1)	153(10)

Actually, dual intramolecular hydrogen bondings between the carbonyl oxygen (O_7) and H_{15} and H_{31} were observed with the interatomic distances of C_{15}- - -O_7 and O_{31}- - -O_7 being 2.60(1) and 2.65(1) Å, respectively (Table 2). These results implied that the quinone carbonyl group as an acceptor of the indoaniline chromophore can easily be subjected to an electrostatic interaction that takes place on the lower rim of calixarene and that functionalization of the lower rim would be profitable to produce a new type of chromogenic receptor. Looking at the chromophore, the aniline ring is tilted out of ring A by 31.4 (3)° because of steric repulsion between the hydrogens attached to C(2) and C(35). With the aim of developing the desired receptor, an anchoring functional group oriented in such a way that it delineates a suitable binding site is required; we decided to append ethyl acetate groups on the lower rim of the calix[4]arene platform for compounds **4** and **5** that possess *two* chromophores, depending on design as effective optical sensing sites, in the molecule. As shown in Scheme 2, the ethoxycarbonylmethylations of **4** and **5** were accomplished with ethyl bromoacetate in the presence of NaH to give the corresponding desired analogues **8** and **7** in 54% and 62% yields, respectively. An alternative route to **7** involves the reaction of 1,3-bis((ethoxycarbonyl)-methoxy)calix[4]arene (**9**)[10c] (Chart 1) with **2** in an MeOH–acetone solution. In spite of several trials, **7**

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[15] Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005.

[16] Perrin, M.; Oehler, D., in ref 8b.

Scheme 2

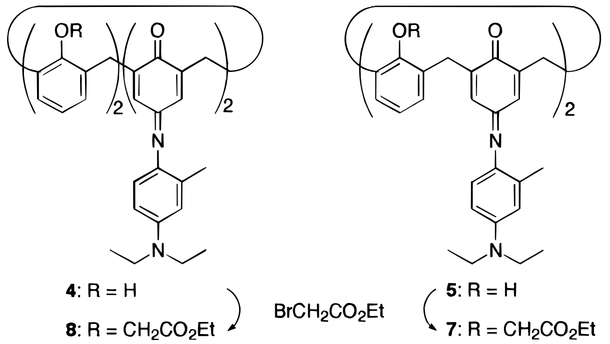
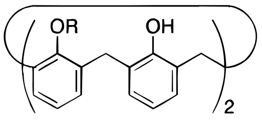


Chart 1

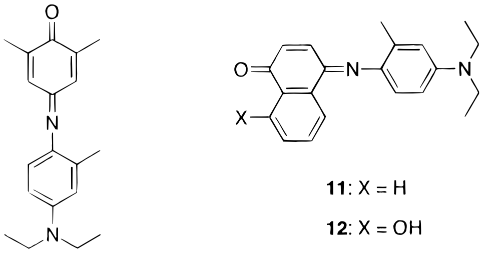


9: R = CH_2CO_2Et

Table 3. Absorption Spectra of Chromogenic Compounds in *n*-Butyl Acetate

compd	λ_{max}/nm (ϵ_{max}, $dm^3\ mol^{-1}\ cm^{-1}$)
3	661 (45 000)
4	643 (33 000)
5	634 (39 000)
6	617 (58 000)
7	583 (35 000)
8	605 (38 000)
10	589 (18 000)
11[18]	598 (16 000)
12[18]	646 (18 000)

Chart 2



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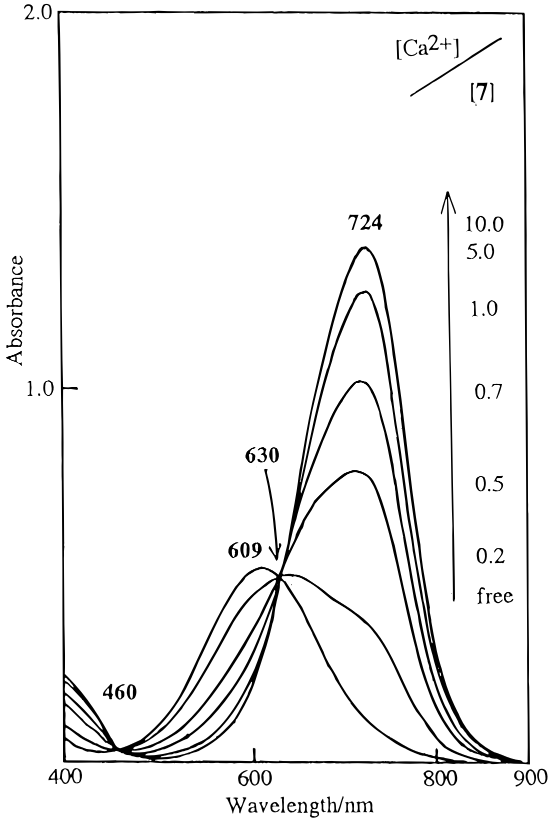

Figure 3. Spectral changes upon addition of $Ca(SCN)_2 \cdot 4H_2O$ to a solution of **7** in 99% EtOH; [**7**] = 1.5×10^{-5} mol dm^{-3}.

cannot be detected by the reaction using **9**, probably due to the fact that a hydrolysis reaction of the ethyl acetate segment takes place during the condensing reaction.

Spectral Characteristics of the Chromogenic Compounds. Wavelength maxima (λ_{max}) and the molecular extinction coefficients of the chromogenic calix[4]arenes as well as related compounds are summarized in Table 3. Mono(indoaniline)-derived **3** ($\lambda_{max} = 661$ nm) shows the largest bathochromic shift (72 nm) among the related compounds, compared to that of control **10** (Chart 2), which indicates that the indoaniline chromophore appears to be influenced by dual intramolecular hydrogen bonding between the carbonyl group of the chromophore and adjacent phenolic-OH groups. Consistent with this result is the X-ray crystal structure of **3**, which shows the calix in a cone conformation (*vide supra*). Compound **6**, the tetrakis(indoaniline)-derived calix[4]arene, absorbs visible light at 617 nm, the ϵ_{max} of which is 58 000 dm^3 mol^{-1} cm^{-1}, 3.2 times that of **10** because multiple chromophores exist in the structure. Regarding the bis(indoaniline)-derived compounds, compounds **5** and **7** absorb visible light at 634 nm (ϵ_{max} 39 000 dm^3 mol^{-1} cm^{-1}) and 583 nm (ϵ_{max} 35 000 dm^3 mol^{-1} cm^{-1}) in *n*-butyl acetate; the disappearance of an intramolecular hydrogen-bonding interaction between the carbonyl group of the chromophore and the adjacent phenolic-OH group by introducing the ethyl acetate group causes a hypsochromic shift of 51 nm,[17] in agreement with the difference in wavelengths (48 nm) between the related indoanilines **11** and **12** (Chart 2).[18] These findings, in turn, have led us to consider that a metal ion, which is encapsulated in the cavity constructed with OCH_2CO_2 groups for **7**, could cause a significant ion−dipole interaction with two quinone carbonyl groups of the chromophores and then would induce some intense spectral change in the absorption. A substantial difference, in fact, appears when we examine the effect of the optical response of the ligands to addition of Na^+, K^+, Mg^{2+}, and Ca^{2+} ions. As shown in Figure 3, compound **7** is blue and has a λ_{max} value of 609 nm (ϵ_{max} 35 000 dm^3 mol^{-1} cm^{-1}) in 99% EtOH; stepwise addition of $Ca(SCN)_2 \cdot 4H_2O$ to compound **7** in the solution causes a large bathochromic shift with an increase in absorption intensity with isosbestic points at 460 and 630 nm, respectively. At a [Ca^{2+}] to [**7**] ratio of 5:1, a new absorption band in the near-IR region at 724 nm was observed while the absorption band at 609 nm disappeared completely. The understanding of the binding profile came from a continuous variation method[19] using mixtures of **7** and Ca^{2+} in 99% EtOH under conditions of invariant total concentration. This ap-

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(17) Similarly, the λ_{max} values of **8** is shorter by 38 nm than that of **4**.

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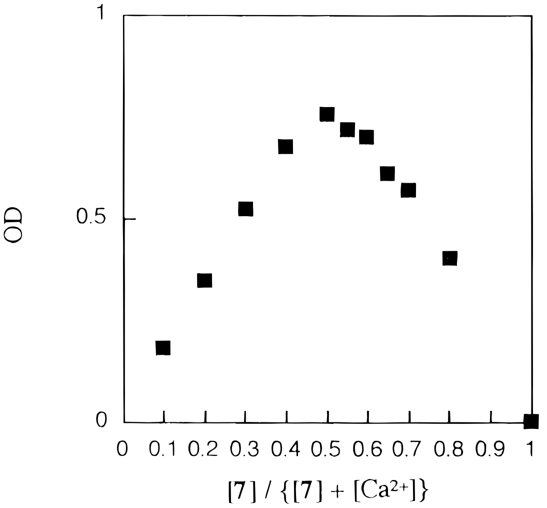

Figure 4. Continuous variation plot of the Ca^{2+}−**7** complex in 99% EtOH; [**7**] + [Ca^{2+}] = 2.0 × 10^{-5} mol dm^{-3}; o.d. 722 nm.

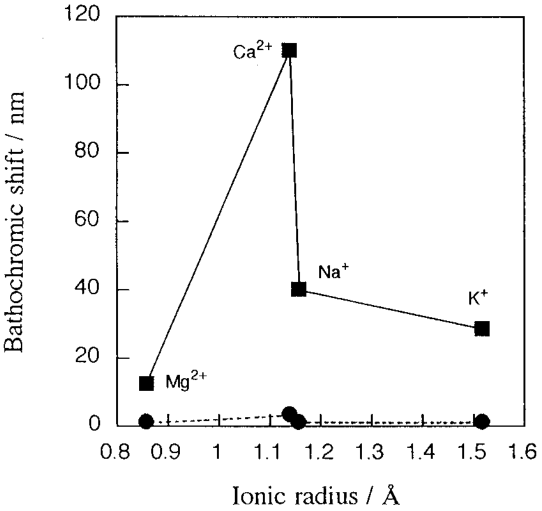

Figure 5. Influence of added NaSCN, KSCN, $Mg(ClO_4)_2$, and $Ca(SCN)_2{\cdot}4H_2O$ on the absorption spectra of **7** (■) and **8** (●).

proach, as illustrated in Figure 4, reveals that the relative **7**−Ca^{2+} complex concentration approaches a maximum when the molar fraction of **7** {[**7**]/([**7**] + [Ca^{2+}])} is approximately 0.5, as is expected for the formation of a 1:1 complex between **7** and Ca^{2+}.

We then tested compound **7** to see if it acted as a chromogenic receptor. Figure 5 shows spectral responses ($\Delta\lambda = \lambda$(complex) − λ(ligand)) in the presence (10^2 equiv) or absence of metal salts. A large bathochromic shift of 110 nm was observed in the presence of Ca^{2+}. In contrast, addition of NaSCN, KSCN, or $Mg(ClO_4)_2$ caused only minor changes ranging from 12 to 40 nm in the absorption spectra, suggesting that compound **7** exhibited a significant selectivity for Ca^{2+}. Alternatively, 1,2-bis-substituted analogue **8** was quite inefficient in the presence of those metal ions (*even in addition of* Ca^{2+}) as shown in Figure 5. The examination of CPK space-filling molecular models implies that compound **8** retains no cavity to encapsulate metal ions on the lower rim of the calix[4]arene segments. Thus, the lack of cation response of **8** is considered to be due to the unfavorable steric complementality between **8** and the cations. The spectroscopic study, in this way, reveals a significant difference between **7** and **8**; it is intriguing that distal- *vs* proximal-ethyl acetated derivatives provoke a drastic stereochemical dependence of cation complexation ability. Furthermore, the cyclic indoaniline tetramer **6** shows an unfavorable complexation property with Ca^{2+}, also indicating that disposition of ethyl acetate groups is significantly important. In recent years, a calixarenequinone derivative possessing a cavity shape similar to that of **7** has been reported with the aim of recognition of guest cations.[20]

Table 4. IR Spectral Data of C=O for the Ca^{2+}−7 Complex

	v, cm^{-1}	
compd	C=O (ester)	C=O (quinone)
7	1755	1628
Ca^{2+}−**7**	1721	1593

Selective Complexation Behavior for 7. IR spectroscopy was used to obtain insight into the coordination structure of the Ca^{2+}−**7** complex. The frequency of both C=O (ester) and C=O (quinone) absorptions for the complexes are lower by 34−35 cm^{-1} than those of the free ligand (Table 4). From these results, compound **7** could form an encapsulated complex with Ca^{2+} in the cavity made by the distally located OCH_2CO_2 groups on the lower rim. Hence, a rather specific Ca^{2+}-induced bathochromic shift could be explained on the basis of a well-tailored electrostatic interaction between the encapsulated cations and quinone carbonyl groups of the indoaniline chromophore. The excited state of the chromophore might be more stabilized by the cation than the ground state. This consideration is supported by the fact that compound **10** shows no color change with alkali and alkaline earth metal ions in a control experiment.

Some NMR studies were carried out in an effort to understand further details of the cation−receptor interactions. Figure 6 shows ^1H NMR spectra of ligand **7** and the Ca^{2+}−complex after solid [$Ca(SCN)_2{\cdot}4H_2O$]−liquid [$CDCl_3$] two-phase solvent extraction. At 24 °C in $CDCl_3$, ligand **7** exhibited a relatively broadened spectral pattern, which indicated that conformational interconversion is somewhat slow on the NMR time scale. However, upon interaction with Ca^{2+}, the spectra changed from the broad signal to split patterns in $CDCl_3$ with a downfield shift of 0.24 and 0.41 ppm, respectively, for the resonances of $CO_2CH_2CH_3$ (Figure 6b). This result can be explained on the basis of a restriction of the interconversion by complexation with Ca^{2+}, the process of which involves an arrangement for the cavity in order to accommodate the Ca^{2+} appropriately and the encapsulated cation- - -carbonyl oxygens (host) ion−dipole interaction. In a further attempt to assign the intricate signals of the complex using a ^1H−^1H COSY experiment (see Figure 7), the bridging methylene resonances could be assigned as four pairs of doublets in 1:1:1:1 integral intensity proportions, as substantiated by appropriate cross-peaks in the spectra. The chemical shifts for H_{exo} are δ 3.07, 3.10, 3.17, and 3.20 ppm, whereas those for H_{endo} are δ 4.19, 4.33, 4.06, and 4.19 ppm. Such findings indicate that the complex has been frozen out in a cone conformation according to the fact that $\Delta\delta$ values between H_{exo} and H_{endo} are ca. 1 ppm.[8a] Another interesting feature is that methylene resonances of the ethyl acetate groups displayed singlet (4.06 ppm) and AB patterns [4.53, 4.81 ppm (J = 15.6 Hz)], each integrating for two protons and undergoing an upfield shift of 1.08, 0.61, and 0.33 ppm,

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(20) Beer, P. D., Chen, Z.; Gale, P. A. *Tetrahedron* **1994**, *50*, 931.

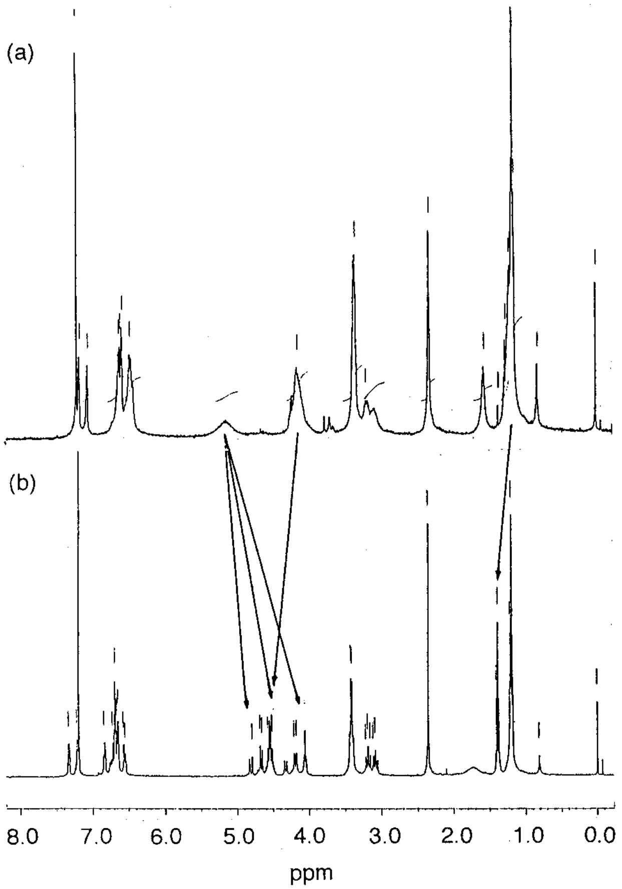


Figure 6. ^1H NMR spectra (400 MHz, $CDCl_3$, 24 °C) of **7** (a) and $Ca^{2+}-$**7** complex (b).

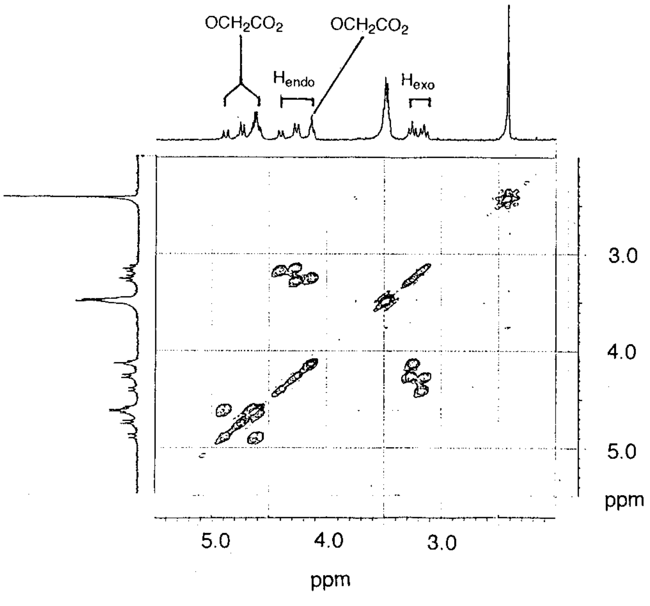


Figure 7. $^1H-^1H$ NMR spectrum of the $Ca^{2+}-$**7** complex in $CDCl_3$ at 400 MHz.

Chart 3

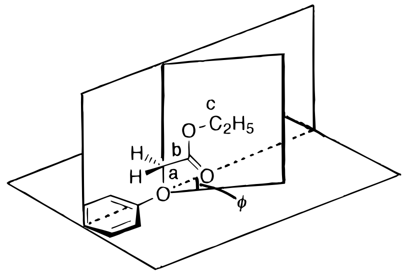
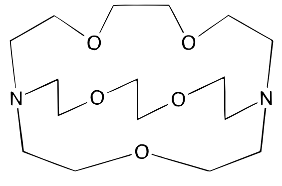


Table 5. Association Constants (K^a) and Binding Free Energies ($-\Delta G°$) in 99% EtOH at 25 °C

	K, $dm^3\ mol^{-1}$ [$-\Delta G°$, kcal mol^{-1}]^b			
host	Na^+	K^+	Mg^{2+}	Ca^{2+}
7	3.7×10^4 [6.23]	$3.2 \times 10^{5\,c}$ [7.51]	100 [2.73]	$7.6 \times 10^{6\,c}$ [9.39]
13	$2.5 \times 10^{5\,d}$	$8.9 \times 10^{3\,d}$	$< 100^d$	$8.9 \times 10^{6\,d}$

^{a} Determined from a Benesi–Hildebrand plot.[22] ^{b} 1 cal = 4.184 J. ^{c} Determined by the Rose–Drago method.[23] ^{d} In water.

Chart 4



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respectively, in comparison with that of free ligand **7** (Figure 6). Taken together, these results suggest that the shape of the cavity in which Ca^{2+} has been encapsulated does not have a C_2 axis of symmetry. The upfield shift-experienced OCH_2CO_2 protons of the side chain can be explained by assuming that Ca^{2+}-induced conformational change brings the methylene protons above the aromatic rings where they experience a ring current effect. Hence, the most upfield-shifted methylene protons (4.06 ppm; singlet) might be held in a magnetically equivalent "exo position" to the cavity constructed by ether and ester oxygens; namely, if one assumes that the orientation of the OCH_2CO_2Et side chain relative to its benzene ring is described by the $C_aC_b-O_bC_c$ torsion angle (ϕ) for a plane perpendicular to the ring (see Chart 3), the value would be 0°. Whereas the ϕ of the other side chain, in which the methylene resonance appears at 4.53 and 4.81 ppm (AB pattern), might be an acute angle. Consequently, the methylene bridge of the calix[4]arene segment is considered to result in a split pattern upon complexation. This finding is quite new because a diester–calix[4]arene–diquinone[20] and a tetraester-derived calix[4]arene derivative[21] usually exhibit two pairs of doublets for the methylene bridge and one singlet for OCH_2COR upon complexation with cations. Presently, we are attempting to obtain an X-ray structure of the complex to clarify such a result. The association constants and binding free energies ($-\Delta G°$) are summarized in Table 5. Compound **7** showed peak selectivity for Ca^{2+} with a $\Delta G°$ value of -9.39 kcal mol^{-1}, comparable to that of the cryptand **13**[24] (Chart 4). It is noteworthy that high Ca^{2+} selectivity over Na^+ ($\Delta\Delta G° = -3.16$ kcal mol^{-1}) is obtained, in spite of their similar ionic radii. This result can be interpreted in terms of ion–dipole interaction; because Ca^{2+} has a higher charge density than Na^+, it should interact more strongly with polar donor groups.[25] As a competitive experiment, treatment of compound **7** in 99% EtOH with a mixture

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(21) Arudini, A.; Pochini, A; Reverberi, S; Ungaro, R. *Tetrahedron* **1986**, *42*, 2089.

(22) Benesi, H. A.; Hidebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.

(23) Rose, N. J.; Drago, R. S. *J. Am. Chem. Soc.* **1959**, *81*, 6138.

(24) Lehn, J.-M.; Sauvage, J.-P. *Chem. Commun.* **1971**, 440.

(25) Gatto, V. J.; Gokel, G. W. *J. Am. Chem. Soc.* **1984**, *106*, 8240.

of Na^+, K^+, Mg^{2+}, and Ca^{2+} caused a bathochromic shift as if only Ca^{2+} was added to the solution of **7**. The high preference of ligand **7** for Ca^{2+} can be attributed to the better fitting of Ca^{2+} inside the pocket formed by the quinone carbonyl groups of the chromophores and (ethoxycarbonyl)methoxy groups and to the enhanced electrostatic interactions between Ca^{2+} and oxygens involved in complexation.

Summary

A new type of 1,3-bis(indoaniline)-derived 2,4-bis((ethoxycarbonyl)methoxy)calix[4]arene (**7**), prepared by **1** with **2** and followed by ethoxycarbonylmethylation, is the first rationally designed chromogenic calixarene-type receptor for Ca^{2+} and is more sensitive to Ca^{2+} than to Na^+, K^+, and Mg^{2+}, making it of potential use as an optical sensor for Ca^{2+} detection. The IR and NMR studies indicate that Ca^{2+} can be encapsulated in the cavity made by the distally located OCH_2CO_2 groups on the lower rim of cone-shaped calix[4]arene segment. On the other hand, 1,2-bis-substituted analogue **8** shows no response with those metal ions, which may be interpreted by no cavity on the lower rim of calixarene. We believe that this type of chromogenic receptor possessing a calixarene unit as a recognition site and indoaniline chromophore as an optical sensing site is of great value because it has synthetic advantage as follows: (1) the introduction of the chromophore into a calixarene skeleton is convenient; (2) several chemical modifications by some functional groups on the calixarene framework lead to change the shape of cavity, so that it would encapsulate various guest species. In our laboratory, the design, development, and elucidation of other types of chromogenic receptors according to this concept are in progress.[6e,9f,h]

Experimental Section

General Methods. Melting points were determined on a Mitamurariken micromelting point apparatus or a Mac Science TG-DTA 2000 thermal analyzer and are uncorrected. Absorption spectra were measured using a JASCO Ubest-30 spectrophotometer. NMR spectra were taken on General Electronics QE-300 (300 MHz) and Bruker AC200 (200 MHz) or AM400 or ARX (400 MHz) spectrometers. IR spectra were recorded by using a JASCO FT/IR-5000 spectrophotometer, and Perkin-Elmer System 2000. Mass spectra were run on a Hitachi M-80A spectrometer and elemental analyses were obtained using a Perkin-Elmer 240C C, H, N analyzer.

Materials. Unless specified otherwise, reagent-grade reactants and solvents were used as received from chemical suppliers. Calix[4]arene **1** was synthesized by the method described previously.[12] Compound **9**,[10c] 25,27-bis((ethoxycarbonyl)methoxy)-26,28-dihydroxypentacyclo[19.3.1.1.^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene, was prepared by the reaction of **1** with 2 equiv of ethyl bromoacetate in the presence of K_2CO_3 in dry acetone (37% yield): ^{1}H NMR ($CDCl_3$) δ 1.34 (t, $J = 7.2$ Hz, 6H), 3.38 and 4.48 (d, $J = 13.2$ Hz, 4H), 4.31 (q, $J = 7.2$ Hz, 4H), 4.72 (s, 4H), 6.70 (t, $J = 7.5$ Hz, 2H), 6.74 (t, $J = 7.6$ Hz, 2H), 6.89 (d, $J = 7.4$ Hz, 4H), 7.04 (d, $J = 7.4$ Hz, 4H), 7.56 (s, 2H).

Condensing Calix[4]arene 1 with 4-(Diethylamino)-2-methylaniline Hydrochloride (2). Typical procedure is as follows (Table1, run 4): to an aqueous acetone solution of **1** (500 mg, 1.18 mmol), **2** (4.05g, 18.9 mmol), and NaOH (1.25 g, 29.6 mmol) at room temperature was added dropwise an aqueous solution of $K_3[Fe(CN)_6]$ (12.4 g, 32.7 mmol). The resulting mixture was stirred for 10 min at room temperature. It was then poured into water (100 mL). After the acetone solvent was removed under reduced pressure, the crude materials obtained were filtered, dried *in vacuo*, and chromatographed on silica gel (Wakogel C-300) using $CHCl_3-(CH_3)_2CO$ (50:1 v/v) as eluent to provide 17 mg of mono(indoaniline)-derived **3** (2% yield), 228 mg of 1,2-bis(indoaniline)-derived **4** (25% yield), 316 mg of 1,3-bis(indoaniline)-derived **5** (35% yield), and a small amount of tetrakis(indoaniline)-derived calix[4]arene **6** (trace), respectively.

23-((4′-(Diethylamino)-2′-methylphenyl)imino)-26,27,28-trihydroxypentacyclo[19.3.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3,5,7(28),9,11,13(27),15,17,19(26),21-undecaen-25-one (3): mp 231−233 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, $J =$ 7.0 Hz, 6H), 2.28 (s, 3H), 3.39 (q, $J = 7.0$ Hz, 4H), 3.52−4.00 (brd, 8H), 6.47 (dd, $J = 2.7$, 9.6 Hz, 1H), 6.53 (s, 1H), 6.56−6.65 (m, 4H), 6.78 (d, $J = 6.9$ Hz, 1H), 6.91−6.98 (m, 5H), 7.19 (s, 2H), 9.38−9.68 (brd, 2H), 9.68−9.91 (brd, 1H); FTIR (KBr) 1595; mass spectrum *m/z* 600 ($M^+ + 2$). Anal. Calcd for $C_{39}H_{38}N_2O_4$: C, 78.24; H, 6.40; N, 4.68. Found: C, 78.09; H, 6.44, N; 4.61.

17,23-Bis((4′-(diethylamino)-2′-methylphenyl)imino)-27,28-dihydroxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3,5,7(28),9,11,13(27),15,18,21-decaene-25,26-dione (4): mp 178.2 °C (determined by TG-DTA); ^{1}H NMR ($CD_3OD-CDCl_3$) δ 1.21 (t, d = 7.0 Hz,12H), 2.20 (s, 6H), 3.44 (q, $J = 7.0$ Hz, 8H), 3.72 (s, 6H), 3.85 (s, 2H), 6.43−6.52 (m, 4H), 6.58−6.65 (m, 4H), 6.92 (dd, $J = 0.9$, 5.1 Hz, 2H), 7.01 (dd, $J = 0.9$, 7.1 Hz, 2H), 7.07 (s, 4H); FTIR (KBr) 1599; mass spectrum *m/z* 773 ($M^+ + 1$). Anal. Calcd for $C_{50}H_{52}N_4O_4$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.38; H, 6.91; N, 6.88.

11,23-Bis((4′-(diethylamino)-2′-methylphenyl)imino)-26,28-dihydroxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3,5,7(28),9,12,15,17,19(26),21-decaene-25,27-dione (5): mp 161−167 °C (determined by TG-DTA); ^{1}H NMR ($CD_3OD-CDCl_3$) δ 1.16 (t, $J = 6.8$ Hz, 12H), 2.23 (s, 6H), 3.39 (q, $J = 7.0$ Hz, 8H), 3.70 (s, 8H), 6.52−6.64 (m, 8H), 6.88 (d, J $= 7.3$ Hz, 4H), 7.15 (s, 4H); FTIR (KBr) 1596; mass spectrum *m/z* 776 ($M^+ + 4$). Anal. Calcd for $C_{50}H_{52}N_4O_4$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.32; H, 6.87; N, 7.09.

5,11,17,23-Tetrakis((4′-(diethylamino)-2′-methylphenyl)imino)pentacyclo[19.3.1.1$^{3.7}$.1$^{9.13}$.1$^{15.19}$]octacosa-1(24),3,6,9,12,15,18,21-octaene-25,26,27,28-tetraone (6): mp 157−160 °C; ^{1}H NMR (DMSO-d_6; 425 K) δ 1.16 (t, $J = 7.0$ Hz, 24H), 2.08 (s, 12H), 3.37 (q, $J = 6.9$ Hz, 16H), 3.49 (s, 8H), 6.52 (s, 8H), 6.62 (s, 4H), 7.03 (s, 8H); FTIR (KBr) 1600; mass spectrum *m/z* 1121 ($M^+ + 1$). Anal. Calcd for $C_{72}H_{80}N_8O_4$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.06; H, 7.29; N, 9.82.

Preparation of 1,3-Bis(indoaniline)-Derived 2,4-Bis((ethylcarbonyl)methoxy)calix[4]arene 7. To an anhydrous dimethylformamide (DMF) solution (10 mL) of compound **5** (50 mg, 0.065 mmol) in the presence of NaH (12.56 mg, 0.31 mmol) at room temperature was added an anhydrous DMF solution (1 mL) of ethyl bromoacetate (0.05 mL, 0.41 mmol). The resulting mixture was stirred for 1 h at 80 °C. It was then poured into ice water (100 mL). The solution was made acidic (pH = 5) by adding acetic acid and then was extracted with $CHCl_3$ (200 mL). The $CHCl_3$ extract was taken to dryness under reduced pressure. The residue was then purified by column chromatography on silica gel (Wakogel C-300) using $CHCl_3$ as eluent to provide 38 mg of compound **7** (62% yield).

11,23-Bis((4′-(diethylamino)-2′-methylphenyl)imino)-26,28-bis((ethoxycarbonyl)methoxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(24),3,5,7(28),9,12,15,17,19(26),21-decaene-25,27-dione (7): mp 110−112 °C; ^{1}H NMR (DMSO-d_6; 373 K) δ 1.04−1.35 (m, 18H), 2.20 (s, 6H), 3.21−3.45 (m, 12H), 3.73−3.93 (brd, 4H), 3.98−4.29 (brd, 4H), 4.47−4.69 (brd, 4H), 6.47−6.82 (m, 12H), 7.10 (s, 2H), 7.19 (s, 2H); FTIR (KBr) 1755, 1628; mass spectrum *m/z* 945 ($M^+ +1$). Anal. Calcd for $C_{58}H_{64}N_4O_8$: C, 73.71; H, 6.83; N, 5.93. Found: C, 73.07; H, 6.82; N, 5.81.

Preparation of 1,2-Bis(indoaniline)-Derived 3,4-Bis((ethoxycarbonyl)methoxy)calix[4]arene 8. To an anhydrous DMF solution (13 mL) of compound **5** (200 mg, 0.26 mmol) in the presence of NaH (64 mg, 1.6 mmol) at room temperature was added an anhydrous DMF solution (3 mL) of ethyl bromoacetate (0.18 mL, 1.63 mmol). The resulting mixture was stirred at ca. 6.8 h at 80 °C; during stirring an anhydrous DMF solution (5 mL) containing NaH (25 mg, 0.63 mmol) and ethyl bromoacetate (0.1 mL, 0.91 mmol) was also added as a second portion. After the disappearance of starting material, the resulting solution was poured into ice water (100 mL). The solution was made acidic by adding acetic acid (pH = 5) and then was extracted with $CHCl_3$ (150 mL). The $CHCl_3$ extract was taken to dryness under reduced pressure. The residue was then purified by column chromatography on silica gel (Wakogel C-300) using a $CHCl_3-C_6H_6$ mixture (1:4 (v/v)) as eluent. In this way, 133 mg of **8** was obtained (54% yield).

17,23-Bis((4′-(diethyamino)-2′-methylphenyl)imino)-27,28-bis((ethoxycarbonyl)methoxy)pentacyclo-$[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]$octacosa-1(24),3,5,7(28),9,11,13(27),15,18,21-decaene-25,26-dione (8): mp 128−130 °C; ^{1}H NMR (DMSO-d_6; 373 K) δ 1.06−1.26 (m, 18H), 2.21 (s, 6H), 3.16−3.35 (m, 4H), 3.35−3.49(m, 12H), 4.00−4.24 (brd, 4H), 4.29−4.53 (brd, 4H), 6.33−6.89 (brd, 12H), 6.89−7.09 (brd, 4H); FTIR (KBr) 1761, 1622; mass spectrum *m/z* 945 ($M^+ + 1$). Anal. Calcd for $C_{58}H_{64}N_4O_8$: C, 73.71; H, 6.83; N, 5.93. Found: C, 72.75; H, 6.82; N, 5.39.

Preparation of 10. To an aqueous EtOH solution (ca. 40 mL) of 2,6-dimethylphenol (1g, 8.19 mmol), NaOH (327 mg, 8.19 mmol), and 4-(diethylamino)-2-methylaniline hydrochloride (3.52 g, 16.4 mmol) was added dropwise an aqueous solution of $K_3[Fe(CN)_6]$ (10.78 g, 32.7 mmol). The resulting mixture was stirred for 15 min at room temperature. It was then poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was taken to dryness under reduced pressure. The residue was then purified by column chromatography on silica gel (Wakogel C-300) using $CHCl_3$ as an eluent and recrystallized from MeOH to produce 1.34 g of **10** (55% yield).

4-((4-(Diethylamino)-*o*-tolyl)imino)-2,6-dimethylcyclohexa-2,5-dienone (10): mp 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 6H), 2.02 (d, J = 1.3 Hz, 3H), 2.09 (d, J = 1.5 Hz, 3H), 2.29 (s, 3H), 3.40 (q, J = 7.1 Hz, 4H), 6.50 (dd, J = 2.8, 8.7 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 7.05 (dd, J = 1.2, 2.6 Hz, 1H), 7.12 (dd, J = 1.5, 2.6 Hz, 1H); FTIR (KBr) 1640; mass spectrum *m/z* 296 (M^+), 281 ($M^+ - Me$). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.16; H, 8.23; N, 9.47.

X-ray Data. The crystal data and details of the experiment are reported in Table 6. The lattice constants were determined by a CAD4 indexing program and refined by a least-squares method with the angular setting of 15 reflections (32 ° < 2θ < 42 °). Data were collected on an ENRAF-Nonius CAD4 diffractometer using a crystal with dimension of 0.4 × 0.2 × 0.15 mm. The diffraction power of the crystal is rather poor so that the diffraction spot could hardly be observed at the higher region ($2\theta > 100$ °). A total of 6483 reflections were measured in the range $2\theta < 141°$, of which 3703 with $F_0 \geq 1\sigma(F_0)$ were considered as observed and used for the structure determination. Lorenz and polarization corrections were applied. The structure was solved by the direct method[26] and refined by full-matrix least-squares technique.[27] The function $\sum(F_o - F_c)^2$ was minimized. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms could be located on a difference Fourier map, but some of their positions were recalculated geometrically. All H-atoms were included in the refinement procedure with isotropic thermal parameters. The maximum and minimum residual electron densities (ρ, e/Å^3) on the final difference Fourier map were 0.26 and −0.31, respectively.[28]

Table 6. Experimental Data for X-ray Diffraction Studies of 3

formula	$C_{39}H_{38}N_2O_4$
cryst syst	monoclinic
space group	$P2_1/n$
cell parameters at 296 K	
a, Å	19.507(6)
b, Å	18.591(6)
c, Å	8.524(2)
β, deg	94.69(2)
V	3081(1)
Z	4
d_x, g cm^{-3}	1.281
$F(000)$	1264
mol wt	594
diffractometer	ENRAF-Nonius CAD 4
scan mode	$\omega-0.67\theta$
maximum of sin θ/λ (Å^{-1})	0.611
radiation	Cu K_α (λ = 1.5418 Å), 40 kV, 80 mA
h min and max	−24, 24
k	0, 23
l	−10,0
$\Delta\rho_{max}$ and $\Delta\rho_{min}$	0.26, −0.31
$(\Delta/\sigma)_{max}$	0.18
R	0.085

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(27) Sheldrick, G. M. SHELX-76. Program for crystal structure determination, University of Cambridge.

(28) The author has deposited atomic coordinates for structure **3** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.