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PAPER

Hexahomotrioxacalix[3]arene derivatives as ionophores for molecular recognition of dopamine, serotonin and phenylethylamine†

Xin-Long Ni,[a,b] Shofiur Rahman,[a] Shi Wang,[a] Cheng-Cheng Jin,[a] Xi Zeng,[b] David L. Hughes,[c] Carl Redshaw[c] and Takehiko Yamato*[a]

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The lower rim functionalized hexahomotrioxacalix[3]arene derivatives *cone*-**3** and *cone*-**5** bearing three benzyl and three *N*,*N*-diethyl-2-aminoethoxy groups, respectively, were synthesized from triol **1**. Their complexation with 2-(3,4-dihydroxyphenyl)ethylamine (dopamine), 5-hydroxytryptamine (serotonin), and 2-phenylethylamine (phenethylamine), which have biologically important activities, has been studied by ^{1}H-NMR spectroscopy. The chemical shifts of the aromatic protons of the host and guest molecules and the up-field shifts of the ethyl protons of the guest molecules strongly suggest the formation of inclusion complexes in solution. The formation of the host–guest complexes is assisted by a hydrogen bond and/or an electrostatic interaction between the host and ammonium ion (RNH_3^+) of the guest. The structures of receptors *cone*-**3** and *cone*-**5** have been determined by X-ray crystallography.

Introduction

Calixarene and hexahomotrioxacalix[3]arene derivatives with C_3 or C_6 symmetry are known to be selective in the recognition of primary organic ammonium ions.[1] Since these ions act as C_3 symmetrical proton donors, receptors bearing a C_3 symmetrically arranged proton acceptor site are predisposed to interact with them. Moreover, the hydrophobic cavities generated by the aromatic walls of the phenol residues of these derivatives are potentially useful for the inclusion of non-polar moieties of such ions. For example, hexahomotrioxacalix[3]arene triether was especially useful for the construction of an electrode selective for dopamine, one of the biogenic amines.[2]

Dopamine receptors (DRs), members of the super-family of G-protein coupled receptors, are known to play an important role in cellular signalling processes of the nervous system.[3] The dopamine receptors may be subdivided according to their pharmacological behavior into D1-like and D2-like subfamilies. They are ideal targets for treating Schizophrenia and Parkinson's disease. Despite the biological importance, their exact binding mechanisms in biological systems are yet to be fully understood.

Meanwhile, considerable efforts have been focused on the development of artificial DRs in order to unravel dopamine binding mechanisms at the molecular level in biological systems.[4] As a consequence, a sizeable number of artificial receptors have been developed to date. The structural features of most of these artificial DRs, however, are far removed from those found in bio-systems and provide only a single binding site either for the ammonium ion or the catechol hydroxy groups of dopamine in organic or aqueous solutions.[5,6] Cation–π electron interactions are known to play an important role in the recognition of positively charged guests by the electron-rich π-systems of natural and synthetic hosts. Calixarenes, when suitably functionalized, can provide rigid, three-dimensional, π-rich cavities for the selective inclusion of organic cations, neutral molecules and for enhancing the degree of polymerization of supramolecular aggregates[7] in non-polar media. Katsu and Odashima reported that calixarenes derivatives were useful for the construction of a serotonin-selective membrane electrode.[8] Recently, we reported the construction of C_3 symmetry functionalized hexahomotrioxacalix[3]arenes, which selectively recognize organic primary ammonium ions.[9] The organic ammonium ion binding affinity depended on the calix[*n*]arene ring size and the substituents, which suggested that the selective recognition of certain types of alkylammonium ions could be achieved by optimizing the steric and electronic influence of the substituents.

An efficient recognition system for alkylammonium ions such as *n*-butyl- and 2-phenethylammonium ions is valuable in clinical applications,[10d] because they are present as structural motifs in biologically important amines such as GABA (gamma-amino-

[a]*Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga-shi, Saga 840-8502, Japan. E-mail: yamatot@cc.saga-u.ac.jp; Fax: +81(0)952/28-8548*
[b]*Key Laboratory of Macrocyclic and Supramolecular Chemistry of Guizhou Province, Guizhou University, Guiyang, Guizhou 550025, China*
[c]*Energy Materials Laboratory, School of Chemistry, University of East Anglia, Norwich, NR4 7TJ, UK*

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butyric acid) and dopamine.[10] The selective recognition of isomeric butylammonium ions has been reported by Pappalardo[11] using calixarene-based receptors. A dramatic increase in selectivity was observed on going from calix[6]arene to calix[5]arene-based receptors, demonstrating that complementary interactions between a host and guest are needed for successful molecular recognition.

Introduction of larger alkyl groups on the phenolic oxygen atoms (the so-called lower rim) of calix[4]arenes led to a situation where the OR groups within the cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation.[12] Although four possible conformational isomers exist for calix[4]-arenes, *viz* cone, partial-cone, 1,2-alternate and 1,3-alternate, only two different conformational isomers, "cone" and "partial-cone", are expected in hexahomotrioxacalix[3]arene. As a consequence, the conformational isomerism is much simpler than that of *O*-alkylated calix[4]arenes.

Shinkai *et al.* reported on the influence of *O*-substituents on the conformational isomerism of hexahomotrioxacalix[3]arenes **1** in detail.[13] They have established that interconversion between conformers, which occurs by oxygen-through-the-annulus rotation, can be sterically allowed for methyl, ethyl, and propyl groups whereas it is inhibited for butyl groups.[13] In their studies on the conformer distribution of hexahomotrioxacalix[3]arenes, Shinkai *et al.* reported that the partial-cone is sterically less crowded than the cone and therefore formed preferentially, regardless of the *O*-alkylation conditions. On the other hand, the cone results only when a template metal is present in the reaction system; the metal ion interacts strongly with phenolic oxygen atoms substituted with groups such as ethoxycarbonylmethyl or *N*,*N*-diethylaminocarbonylmethyl groups. However, the selective introduction of benzyl groups on the lower-rim has not yet been reported.

In this paper, we describe the selective synthesis of tris(benzyloxy)hexahomotrioxacalix[3]arenes **3**, with cone and partial-cone conformations, by *O*-benzylation of hexahomotrioxacalix[3]-arene **1**, and the inclusion properties of **3** with alkylammonium ions.

Results and discussion

Hexahomotrioxacalix[3]arene **1** was *O*-alkylated with benzyl bromide **2** in the presence of Cs_2CO_3 to yield a single pure conformational isomer, *partial-cone*-**3**, as a major product, while the other possible isomer, *cone*-**3**, was not observed (Table 1). In contrast, a similar reaction was carried out in the presence of K_2CO_3 to yield a mixture of the two conformers of the tri-*O*-alkylated product **3** in a ratio of 4 : 96 (*cone*-**3** : *partial-cone*-**3**) in 70% yield. The conformation ratio of **3** increased in the presence of NaH to 75 : 25 (*cone*-**3** : *partial-cone*-**3**) during the *O*-substitution of triol **1**. However, the attempted *O*-benzylation of triol **1** with a large excess of benzyl bromide (20 equivalents) in the presence of Na_2CO_3 was unsuccessful; only the starting compound was recovered in near quantitative yield. When a stronger base was employed (*e.g.* NaH rather than Cs_2CO_3), the template metal can hold the benzyloxy groups on the same side of the hexahomotrioxacalix[3]arene ring through the cation–π interaction,[13] as shown in Fig. 1(A). Thus, the conformation is preferentially immobilized in the cone, despite the much more flexible structure of **1** due to the ether linkage (*cf.* calix[4]arene). Although the contribution to the template effect is expected to be larger for Cs^+ than Na^+, as reported by Harrowfield,[14] the larger Cs^+ might enlarge the cyclophane ring of triol **1** to form a sufficient space for ring inversion to afford the thermodynamically stable partial-cone conformer as shown in Fig. 1(B). Thus, the template effect of the alkali metal cations plays an important role in this *O*-benzylation reaction, in a similar way to *O*-alkylation with bromoethylacetate or *N*,*N*-diethylchloroacetamide.[13] However, the regioselective introduction of one or two benzyl groups at the phenolic oxygen atoms of triol **1** was unsuccessful despite alterations to the reaction conditions. Thus, the attempted *O*-benzylation of triol **1** with benzyl bromide under the various reaction conditions failed to make the partial *O*-benzylated products, such as monobenzyloxy and dibenzyloxy derivatives. Only the tri-*O*-benzylated product **3** was obtained with the recovery of the starting compound **1**.

The ^{1}H-NMR spectrum of *cone*-**3** shows a singlet for the *tert*-butyl protons at δ 1.09 and a singlet for ArOCH_2Ph and the aromatic protons at δ 4.59 and 6.97 ppm, respectively, indicating a C_{3v}-symmetric structure for *cone*-**3**. On the other hand, the ^{1}H-NMR spectrum of *partial-cone*-**3** shows two singlets for the *tert*-butyl protons at δ 0.93, 1.20 ppm (relative intensity 2 : 1). Furthermore, the resonances for the ArOCH_2Ph methylene protons appear as two singlets at δ 3.40 and 4.19 ppm (relative intensity 1 : 2). On the basis of the ^{1}H-NMR studies and the consideration of a CPK model of *partial-cone*-**3**, two benzyl groups in the compound point upwards and the third is folded into the π-cavity formed by two benzene rings; with greater shielding,

Table 1 *O*-Benzylation reaction of hexahomotrioxacalix[3]arene **1** with benzyl bromide **2**

			Distribution (%)[a,b]	
Run	Base	Solvent	Cone	Partial-cone
1	NaH	THF	75 (45)	25 (16)
2	Na_2CO_3	Acetone	0[c]	0
3	K_2CO_3	Acetone	4	96 (82)
4	Cs_2CO_3	Acetone	0	100 (86)

[a] Relative yields determined by HPLC. [b] Isolated yields are shown in parentheses. [c] Starting compound **1** was recovered in quantitative yield.

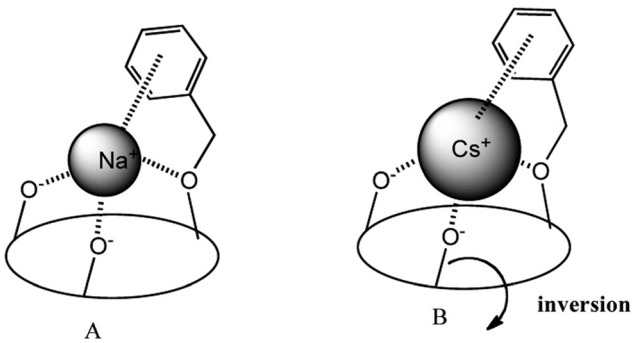


Fig. 1 Ring inversion of *O*-benzylation intermediate of triol **1** and immobilization by metal template.

there are upfield shifts to δ 3.40 ppm for the methylene protons and δ 6.72–6.78 ppm for the aromatic protons at the 2,6-positions. The remarkable shielding effect experienced by the *ortho* protons of the inverted benzene ring suggests that this benzene ring is tightly accommodated inside the hydrophobic cavity, *i.e.* a self-inclusion complex. Interestingly, two *tert*-butyl groups are located on the benzene ring of the inverted benzyl group in spite of the sterically crowded environment. Such findings might be attributed to C–H···π interactions[13] between the methyl groups of the *tert*-butyl group and the benzene ring. The same self-inclusion phenomenon was observed in the partial-cone structure for tris(benzyloxy)hexahomotrioxacalix[3]arene and in the tris[(2-pyridylmethyl)oxy] derivative.[9a]

Colourless, single crystals of compound *cone*-**3** suitable for X-ray crystallography were obtained by recrystallization from CH_2Cl_2. The molecule is shown in Fig. 2(a) and a projection on to the plane of the calix ring system is presented in Fig. 2(b).

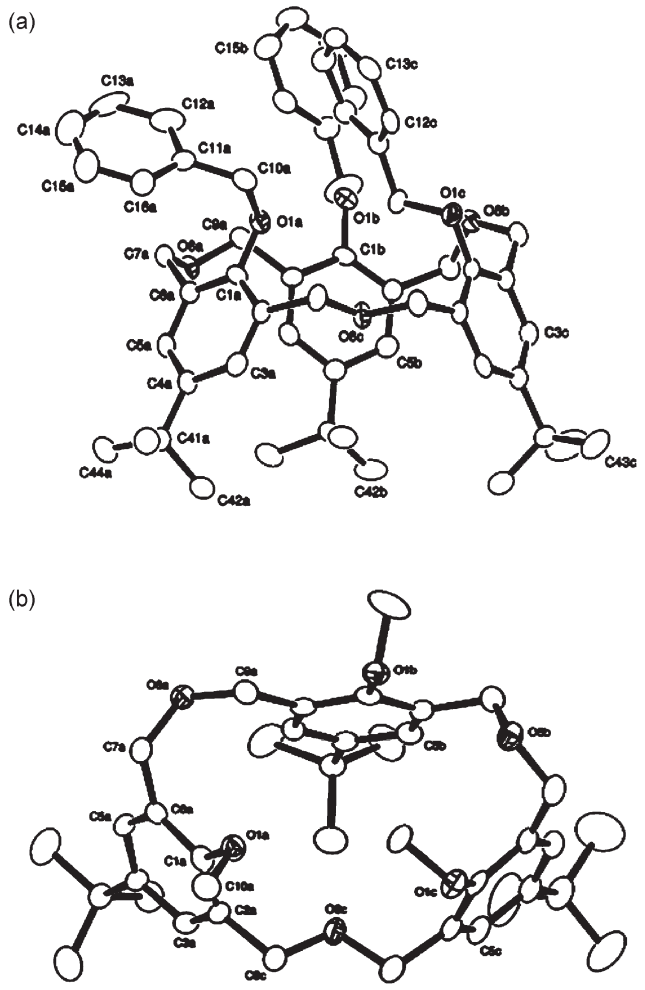
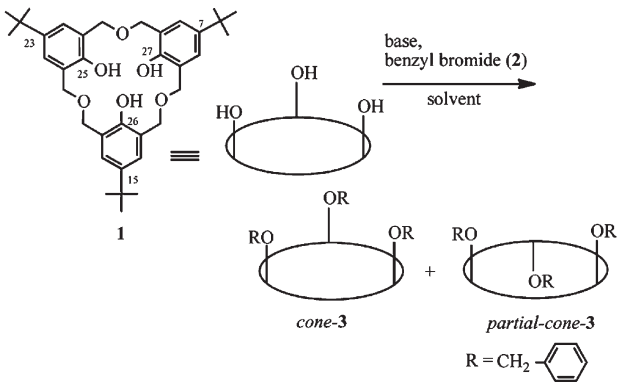
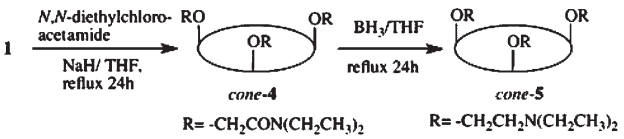


Fig. 2 Molecular structure of *cone*-**3**; (a) showing the whole molecule and indicating the atom numbering scheme, and (b) a projection of the calix ring on to the plane through C(1a), C(1b) and C(1c), with the lower rim benzyl groups omitted. The normals to the planes of the O(1a), O(1b) and O(1c) phenyl rings are 61.5(1), −70.4(1), and 72.0(1)° from the normal to the ring plane; the negative sign indicates the 'inwards' tilting of the ring. Ellipsoids are drawn at the 50% probability level.



Scheme 1



Scheme 2

The *cone* conformation is confirmed, as illustrated in Scheme 1, but there is much distortion of the ring from a C_3 symmetrical arrangement; two of the phenolic groups tilt outwards as in a normal calix cavity, but the third, of O(1b), folds into the cavity. At the lower rim, the benzyl groups of O(1a) and O(1b) are directed out from the centre of the molecule, whereas the benzyl group of O(1c) folds back to lie over the calix ring.

The synthesis of receptors *cone*-**4** and *cone*-**5** is depicted in Scheme 2. *cone*-Tris[(*N*,*N*-diethyl-2-amino)ethyl]hexahomotrioxacalix[3]arene, *cone*-**5**, was prepared by reduction of *cone*-Tris[*N*,*N*-diethylaminocarbonyl]methoxy]hexahomotrioxacalix-[3]arene, *cone*-**4**, in a refluxing mixture of BH_3/THF solution; *cone*-**4** was prepared by *O*-alkylation of hexahomotrioxacalix[3]-arene **1** with *N*,*N*-diethylchloroacetamide in the presence of NaH in refluxing THF according to the reported procedure.[1c] The ^{1}H-NMR spectrum of *cone*-**5** in $CDCl_3$ showed a single peak at δ 1.07 ppm for the *tert*-butyl protons and a single peak at δ 6.96 ppm for the aromatic protons, in agreement with its C_{3v}-symmetric structure.

Crystals were grown by slow evaporation of a solution of *cone*-**5** in dichloromethane and hexane at room temperature. A view of the molecule is shown in Fig. 3(a) and a projection of the calix ring system, omitting the lower rim groups, is given in Fig. 3(b). As for *cone*-**3**, the X-ray analysis confirmed the *cone* conformation, but with a much deformed cavity, crushed from a C_3 symmetrical shape. There are differences in the torsion angles around the 18-membered calix ring from those in *cone*-**3**, but again we find two phenolic rings tilting outwards and one, of O(1a), tilting into the cavity. At each of the three phenolic oxygen atoms, the substituent group is directed outwards (then upwards) from the central axis through the molecule. In this room-temperature study, we find disorder (resolved) in one of the ethyl groups and large thermal ellipsoids, suggesting atom oscillations (or maybe further disorder), in some of the other ethyl groups.

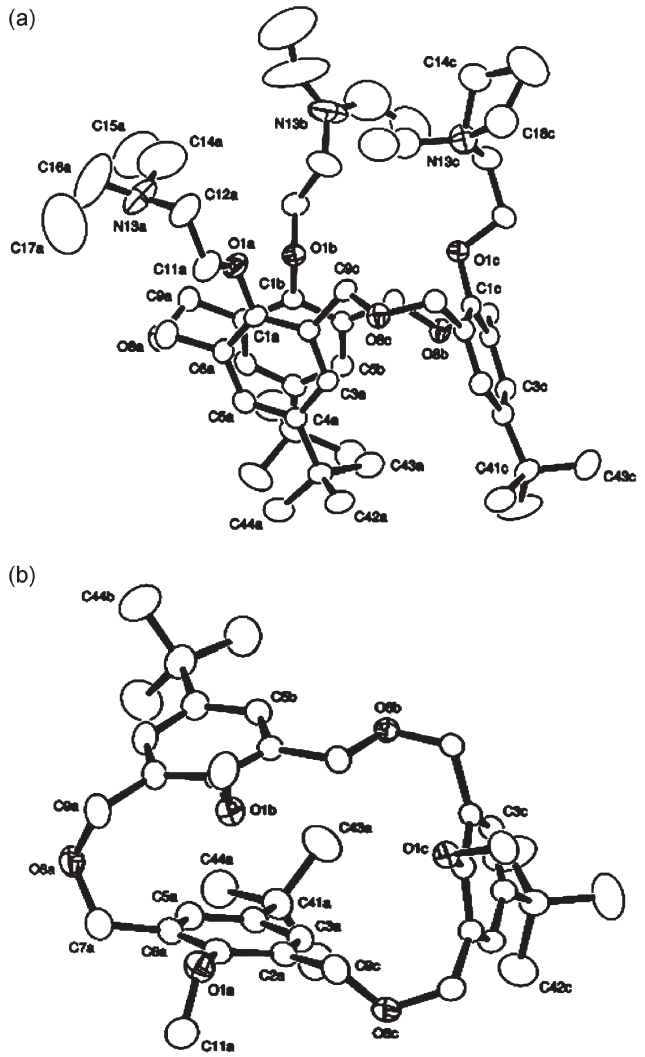


Fig. 3 Molecular structure of *cone*-**5**; (a) showing the whole molecule and indicating the atom numbering scheme, and (b) a projection of the calix ring on to the plane through C(1a), C(1b) and C(1c), with the lower rim (*N*,*N*-diethylamino)ethyl groups omitted. The normals to the planes of the O(1a), O(1b) and O(1c) phenyl rings are −74.3(1), 56.6(1), and 73.0(1)° from the normal to the ring plane; the negative sign indicates the 'inwards' tilting of the ring. Ellipsoids, for this room-temperature study, are drawn at the 30% probability level.

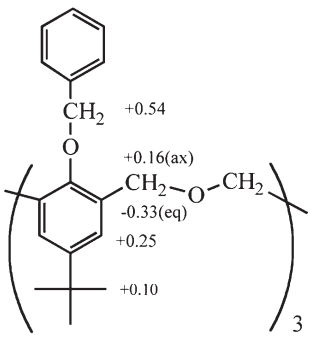
It is known that calixarenes can be modified and converted into neutral ligands by the introduction of ester or amide groups, and that the affinity and the selectivity depend on the calix[*n*]-arene ring size and the substituent groups.[1] To obtain quantitative insights into metal and alkylammonium ion affinity of *cone*-tris(benzyloxy)hexahomotrioxacalix[3]arene *cone*-**3**, we tried to determine the association constants by ^{1}H-NMR titration experiments according to literature methods.[16] The results are listed in Table 2.

The K_a values for alkali metals could not be evaluated since the addition of 5 equivalents of Li^+, Na^+, K^+ into solutions of *cone*-**3** did not cause any significant changes to the chemical shift. Thus, *cone*-**3** shows no complexation affinity for alkali metal ions. However, *cone*-**3** shows high affinity for

Table 2 Association constants[a] (K_{ass}, M^{-1}) of host *cone*-**3** with guest alkylammonium ions (host–guest, 1 : 1 ratio)

Ionophore	K_{ass} ($\times 10^3$) M^{-1}
$CH_3(CH_2)_3NH_3^+$	25.3
$CH_3(CH_2)_5NH_3^+$	4.55
$CH_3(CH_2)_7NH_3^+$	4.05
tBuNH$_3^+$	33.5

[a] Measured in $CDCl_3$–CD_3CN (10 : 1 v/v) at 27 °C by the ^{1}H-NMR titration method of the chemical shift change of the ArCH_2O protons, host concentration was 5×10^{-3} M.



cone-**3**

Fig. 4 Chemical shift changes of *cone*-**3** induced in the presence of *n*-BuNH$_3^+$Pic$^-$; + denotes a downfield and − denotes an up-field shift.

$CH_3(CH_2)_3NH_3^+$ and tBuNH$_3^+$, Interestingly, the same association constant was observed for *n*-butylammonium ion (K_a = 25.3 × 10^3 M^{-1}) as that of the corresponding tris[(*N*,*N*-diethylamino-carbonyl)methoxy] derivative *cone*-**4** (K_a = 23.5 × 10^3 M^{-1}), which also shows high association constants for alkali metal ions but not for tBuNH$_3^+$.

These results indicated that the association constants were affected by the size of the alkyl groups. Thus, *cone*-**3** binds both shorter chains and larger bulky alkylammonium ions. These findings might be attributable to the different complexation rates on entering the cavity.

After addition of one equivalent of *n*-butylammonium ion in deuterated chloroform, the peak signals of *cone*-**3** appeared separately from both those of the complex and of the free host. With increasing amounts of ammonium ion, the signals of *cone*-**3** decreased and finally only the complex signals were observed. In comparison with those in the free host, the axial protons in the bridge methylene groups in the complex were shifted to lower field ($\Delta\delta$ = +0.16 ppm), while the equatorial protons were shifted upfield ($\Delta\delta$ = −0.33 ppm). The ArOCH_2Ph methylene protons and the calix benzene protons were also shifted to lower field, $\Delta\delta$ = +0.54 and +0.25 ppm, respectively, as shown in Fig. 4. These phenomena also provided insight into the change of conformation of *cone*-**3** as the *n*-butylammonium ion, on complexation, was encapsulated into the cavity formed by the benzene rings.

The NH_3 protons interact with the three phenyl groups and phenolic oxygen atoms, and the *n*-butyl chain remains in the cavity of the calix benzene rings. The protons of the ammonium ion chain, encapsulated by the concave cavity, were shifted to

higher field (δ 5.76 ppm) compared to the signal of the 'free' protons (δ 8.79 ppm) because of the shielding of the calix benzene rings. The NH protons on the *n*-butylammonium ion were correspondingly shifted to higher field ($\Delta\delta$ = −3.03 ppm). The maximum up-field shift was observed among the protons of $CH_2CH_2NH_3^+$ ($\Delta\delta$ = −2.81 ppm) and the shifts then decreased along the length of the alkyl chain. The protons of $CH_2CH_2NH_3^+$ were shifted up-field by more than δ 2.0 ppm, while the CH_3CH_2 protons shifted up-field by only δ 0.72 ppm and δ 1.17 ppm, respectively. The calix cavity of the hexahomotrioxacalix[3]arene can include the whole *n*-butylammonium ion; the terminal $CH_2CH_2NH_3^+$ is located deep in the cavity, while CH_3CH_2 is located on the edge of the cavity. Very similar chemical shift values were observed for encapsulated NH protons in the longer alkylammonium ions, indicating that the $CH_2CH_2NH_3^+$ group is located in a similar position in the cavity of the calix benzene rings, and experiences a similar intensity of resonance shielding. It is reasonable to assume that the *n*-butylammonium chain is long enough to protrude from the calixarene cavity; similar results were also reported in the case of partial-cone calix[5]arene and its complex with ammonium ions.[11] Analogous up-field shifts of the NH and CH_3 protons of *t*-$BuNH_3^+$ were observed for the included *t*-butylammonium ion ($\Delta\delta$ = −3.84 and −1.85 ppm, respectively).

By contrast, the spectral pattern of the tris(benzyloxy) derivative of *partial-cone*-**3** did not show any significant change upon addition of 5 equivalents of *n*-butylammonium picrate. Only the original signals for *partial-cone*-**3** remained. This result

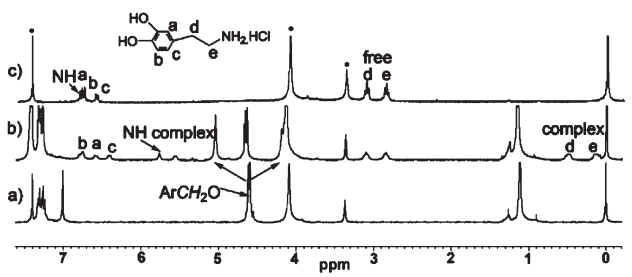


Fig. 5 ^{1}H-NMR spectra of the dopamine complex with host *cone*-**3** (host–guest; 1 : 1 ratio, 5×10^{-3} M) in ($CDCl_3$–CD_3OD = 4 : 1); (a) Free host *cone*-**3**; (b) *cone*-**3** ⊂ dopamine; (c) free dopamine. * Denotes the solvent peaks.

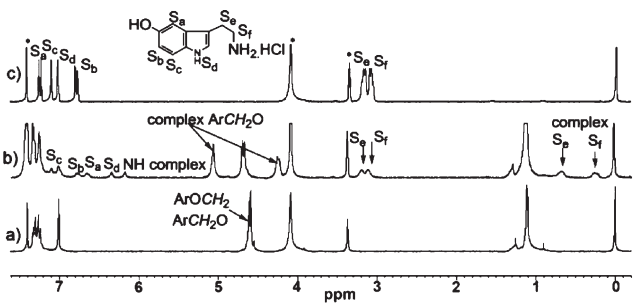


Fig. 6 ^{1}H-NMR spectra of the serotonin complex with host *cone*-**3** (host–guest; 1 : 1 ratio, 5×10^{-3} M) in ($CDCl_3$–CD_3OD = 4 : 1); (a) Free host *cone*-**3**; (b) *cone*-**3** ⊂ serotonin; (c) free serotonin. * Denotes the solvent peaks.

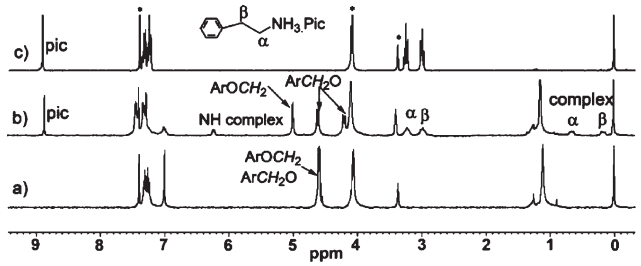


Fig. 7 ^{1}H-NMR spectra of 2-phenylethylamine with host *cone*-**3** (host–guest; 1 : 1 ratio, 5×10^{-3} M) in ($CDCl_3$–CD_3OD = 4 :1); (a) Free host *cone*-**3**; (b) *cone*-**3** ⊂ 2-phenylethylammonium picrate; (c) free 2-phenylethyl- ammonium picrate. * Denotes the solvent peaks.

indicated that the C_{3v}-symmetric structure of *cone*-**3** plays a significant role in the complexation of tris(benzyloxy) derivative **3** and C_3-symmetric guest molecules such as alkylammonium ions.

The inclusion properties of *cone*-**3** with guests dopamine, serotonin and 2-phenylethylamine were also evaluated in $CDCl_3$–CD_3OD (4 : 1) solution due to the solubility problems of the guest molecules in $CDCl_3$–CD_3CN (10 : 1). Drastic changes were observed in the ^{1}H-NMR spectra of 1 : 1 mixtures of *cone*-**3** : guest, as the signals ascribed to dopamine, serotonin and 2-phenylethylamine were dramatically shifted to higher field (Fig. 5–7).

The ^{1}H-CIS {complexation-induced shifts = δ(complex) − δ(guest)} values of guests dopamine, serotonin and 2-phenylethylamine are recorded in Table 3. The magnitude of the higher magnetic field shifts for the guest signal grows fainter with increasing distance from the amino groups. On the basis of these observations, it is clear that it is the amino group that approaches the π-cavity (which comprises the aromatic rings of the host *cone*-**3**). Fig. 5–7 show the spectral changes on complexation. Assignments of Da–De, Sa–Sf, and Phα–Phβ represent the proton peaks of dopamine, serotonin and 2-phenylethylamine, respectively. The largest upfield shifts were observed for the Dd, De, Sf, Se, and Phα, Phβ protons of dopamine, serotonin and 2-phenylethylamine, respectively, and for the NH protons of each, in their complexes with *cone*-**3**. In comparison with the free host, the axial protons in the bridging methylene ArCH_2O groups, which are related to the conformation of the calixarene ring, were shifted in the complex to lower field ($\Delta\delta$ = +0.44 ppm; +0.42 ppm; +0.46 ppm), while the equatorial protons were shifted to higher field ($\Delta\delta$ = −0.41 ppm; −0.40 ppm; −0.42 ppm), respectively, in the three complexes. The methylene protons of ArOCH_2Ph were shifted to lower field (($\Delta\delta$ = +0.45 ppm; +0.44 ppm and +0.46 ppm), and the calixbenzene Ar*H* protons were also shifted to lower field ($\Delta\delta$ = +0.26; +0.25 ppm and +0.27 ppm), respectively.

Similar ^{1}H-CIS findings are reported for the *cone*-**5** complexes with the same three guest molecules in Table 4. In comparison with the free host, the axial protons in the bridging methylene ArCH_2O groups in the complexes were shifted to lower field ($\Delta\delta$ = +0.39 ppm; +0.38 ppm; +0.43 ppm), while the equatorial protons were shifted to higher field ($\Delta\delta$ = −0.26 ppm; −0.24 ppm; −0.27 ppm). The ArOCH_2Ph methylene protons shifted to lower field (($\Delta\delta$ = +0.51 ppm; +0.49 ppm and

Table 3 Chemical shift changes ($\Delta\delta$)[a,b] of dopamine, serotonin and 2-phenylethylamine complexes with host *cone*-**3** (host–guest, 1 : 1; 5×10^{-3} M) in $CDCl_3$–CD_3OD = 4 : 1 (v/v)

cone-**3**-Dopamine complex				*cone*-**3**-Serotonin complex				*cone*-**3**-2-Phenylethylammonium complex			
	Free δ	Complex δ	($\Delta\delta$)		Free δ	Complex δ	($\Delta\delta$)		Free Δ	Complex δ	($\Delta\delta$)
Db	6.771	6.445	−0.326	Sa	7.084	6.791	−0.293	Phα	3.245	0.657	−2.588
Da	6.752	5.795	−0.957	Sb	6.766	6.670	−0.096	Phβ	2.994	0.196	−2.798
Dc	6.598	5.596	−1.002	Sc	7.225	7.113	−0.112	NH	8.908	6.224	−2.684
Dd	3.121	0.539	−2.582	Sd	7.003	6.352	−0.651				
De	2.861	0.200	−2.661	Se	3.178	0.675	−2.503				
NH	6.816	5.604	−1.021	Sf	3.094	0.247	−2.847				
				NH	7.390	6.183	−1.207				

[a] Measured in $CDCl_3$–CD_3CN (4 : 1 v/v) at 27 °C by the ^{1}H-NMR titration method of the chemical shift changes. [b] (ppm): the ^{1}H-CIS {complexation-induced shifts = δ(complex) − δ(guest)} values of guests dopamine, serotonin and 2-phenylethylamine.

Table 4 Chemical shift changes ($\Delta\delta$)[a,b] of dopamine, serotonin and 2-phenylethylamine complexes with host *cone*-**5** (host–guest, 1 : 1; 5×10^{-3} M) in $CDCl_3$–CD_3OD = 4 : 1 (v/v)

cone-**5**-Dopamine complex				*cone*-**5**-Serotonin complex				*cone*-**5**-2-Phenylethylammonium complex			
	Free δ	Complex Δ	($\Delta\delta$)		Free δ	Complex δ	($\Delta\delta$)		Free δ	δ	Complex ($\Delta\delta$)
Db	6.771	6.585	−0.350	Sa	7.084	6.749	−0.337	Phα	3.245	0.602	−2.553
Da	6.752	5.450	−0.987	Sb	6.766	6.672	−0.094	Phβ	2.994	0.206	−2.788
Dc	6.598	5.604	−1.027	Sc	7.225	7.012	−0.213	NH	8.908	6.247	−2.661
Dd	3.121	0.204	−2.626	Sd	7.003	6.351	−0.652				
De	2.861	0.537	−2.719	Se	3.178	0.704	−2.479				
NH	6.816	5.601	−1.051	Sf	3.094	0.274	−2.820				
				NH	7.390	6.197	−1.193				

[a] Measured in $CDCl_3$–CD_3CN (4 : 1 v/v) at 27 °C by the ^{1}H-NMR titration method of the chemical shift changes. [b] $\Delta\delta$ (ppm): the ^{1}H-CIS {complexation-induced shifts = δ(complex) − δ(guest)} values of guest dopamine, serotonin and 2-phenylethylamine.

Table 5 Association constants[a] (K_a, M^{-1}) of hosts *cone*-**3** and *cone*-**5** with guests dopamine, serotonin and 2-phenylethylammonium ion (host–guest, 1 : 1 ratio)

	K_a		
Hosts	Dopamine	Serotonin	2-Phenylethylammonium ion
cone-**3**	6720 ± 380	5335 ± 310	7190 ± 420
cone-**5**	5735 ± 430	4350 ± 235	6452 ± 385

[a] Measured in ($CDCl_3$–CD_3OD = 4 : 1, v/v) solution at 27 °C by the ^{1}H-NMR titration method of the chemical shift change of the ArCH_2O protons; host concentration was 5×10^{-3} M.

+0.52 ppm), as did the calix-benzene Ar*H* protons ($\Delta\delta$ = +0.33 ppm; +0.29 ppm and +0.33 ppm).

These observations suggest that there are well-defined interactions between the host and guest molecules. It is likely that the host encapsulates the guest amine molecules in the calix-cavity. The dramatic up-field shifts (Table 3) can be attributed to the shielding effect of the calix-benzene rings of the host that surround the alkyl chain to form a hydrophobic wall. The hydrophobic effect on the guest amines in the cavity may be weakened in the order: 2-phenylethylamine > dopamine > serotonin, due to the presence of hydrophilic OH groups in the dopamine and serotonin. This hypothesis is supported by the stability constants, which follow the same order of 2-phenylethylamine > dopamine > serotonin. Following the 1 : 1 complexation of *cone*-**3** with dopamine and serotonin in $CDCl_3$–CD_3OD, 4 : 1, the signals of *cone*-**3** appeared separately for the complex and the free host. With increasing amounts of guest ions, the signals for *cone*-**3** decreased and finally only the complex signals were observed (Table 5). Interestingly, *cone*-**3** showed high association constants for serotonin (K_{ass} = 5335 ± 310 M^{-1}), dopamine (K_{ass} = 6720 ± 380 M^{-1}), and 2-phenylethylamine (K_{ass} = 7195 ± 420 M^{-1}). These findings may be attributable to the different complexation rates associated with entering the cavity, as well as with the slower decomplexation rate of ammonium ions. The included ammonium molecules described herein can thus form the NH···π interactions with the three benzyl groups of *cone*-**3**.[15]

By contrast, the spectral pattern of the tris(benzyloxy) derivative of *partial-cone*-**3** did not show any significant change upon addition of 5 equivalents of dopamine (host–guest in 1 : 1 ratio, 5×10^{-3} M) in $CDCl_3$–CD_3OD (4 : 1). Only the original signals for the *partial-cone*-**3** remained. These results indicated that the C_{3v}-symmetric structure of *cone* conformation plays a significant role in the complexation of the hexahomocalix[3]arene derivatives of *cone*-**3** and *cone*-**5** with C_3-symmetric guest molecules such as alkylammonium ions, dopamine, serotonin and 2-phenylethylamine (see ESI†).

Additionally, CPK molecular models and molecular modeling[16] also clearly suggested that a molecule such as *cone*-**3** and *cone*-**5** could be an attractive candidate receptor for dopamine, serotonin and phenylethylamine. Molecular modeling "docking" simulations[16] between, *e.g.*, dopamine, serotonin, phenylethylamine and host compounds *cone*-**3** and *cone*-**5** supported our hypothesis that structures generated using cone conformers of *cone*-**3** and *cone*-**5** could form attractive energy minimized host–guest complexes. The molecular modeling results also suggested that although the host molecules were conformationally flexible, van der Waals interactions between the electron-rich aromatic rings and the electron-poor organic ammonium ions have been observed (see ESI†).

Conclusions

An interesting result was obtained by introduction of benzyl groups on to the hydroxy groups of triol **1**. We have demonstrated for the first time that *O*-alkylation of the flexible macrocycle **1** with benzyl bromide gave tri-*O*-alkylated products with cone and partial-cone conformation. These conformations possess promising complexation properties and interesting stereochemistry. Alkali metal cations can play an important role in determining the conformer distribution based on the template effect.

Receptors *cone*-**3** and *cone*-**5**, each of which provides a highly pre-organized hydrophobic environment, mimic the hydrophobic pocket predicted for a human D2 receptor, and have achieved molecular recognition of 2-phenylethylamine, serotonin, and dopamine. X-Ray crystallographic and ^{1}H-NMR spectroscopic studies have provided evidence for an unambiguous binding mode of the host–guest complexation study. The new receptor system has several unique features including ready availability and structural simplicity. By virtue of these advantages, it can be readily tailored to act as a selective receptor towards biologically important amines.

Experimental

General

All mps (Yanagimoto MP-S_1) are uncorrected. ^{1}H-NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference; *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets in a Nippon Denshi JIR-AQ2OM spectrophotometer. Elemental analyses were performed by a Yanaco MT-5.

Materials. Synthesis of *cone*-7,15,23-tri-tert-butyl-25,26,27-tris[(*N*,*N*-diethylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**4**) was carried out according to the reported procedure.[1c]

Alkylation of 1 with benzyl bromide 2 in the presence of NaH to afford 3. A mixture of **1** (100 mg, 0.174 mmol) and NaH (227 mg, 5.25 mmol, 60%) in dry tetrahydrofuran (10 mL) was heated at reflux for 1 h under N_2. Then benzyl bromide (0.21 mL, 1.74 mmol) was added and the mixture heated at reflux for an additional 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess, unreacted benzyl bromide using a Kugelrohr apparatus. ^{1}H-NMR analysis of the residue was consistent with a mixture of *cone*-**3** and *partial-cone*-**3** in the ratio of 75 : 25. The residue was washed with methanol to give the crude *partial-cone*-**3** (22 mg, 16%) as a colourless solid. The filtrate was concentrated to give a yellow oil, which was chromatographed over silica gel (Wako, C-300; 100 g) with hexane–benzene (1 : 1) as eluent to give *cone*-**3** (66 mg, 45%) as a colourless solid. Recrystallization from MeOH afforded *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris(benzyloxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**3**) as colourless prisms. Mp: 163–165 °C. ν_{max} (KBr)/cm^{-1} 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094 and 1058. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.09 (27H, s, *tBu*), 4.59 (12H, s, ArCH_2O), 4.62 (6H, s, OCH_2Ph), 6.97 (6H, s, Ar-*H*) and 7.13–7.39 (15H, s, Ph-*H*). ^{13}C NMR ($CDCl_3$) δ: 31.5, 34.2, 69.1, 69.3, 125.7, 127.7, 127.8, 128.3, 131.0, 137.5, 146.2 and 152.2. FABMS: *m*/*z* 846 (M^+). Anal. calcd for $C_{57}H_{66}O_6$ (847.16): C, 80.82; H, 7.85. Found: C, 80.61; H, 7.93%. The splitting pattern in ^{1}H-NMR shows that the isolated compound is *cone*-**3**.

Benzylation of 1 with benzyl bromide in the presence of Cs_2CO_3. A mixture of **1** (100 mg, 0.174 mmol) and Cs_2CO_3 (567 mg, 1.74 mmol) in acetone (10 ml) was heated at reflux for 1 h. Benzyl bromide **2** (0.21 mL, 1.74 mmol) was then added and the mixture heated at reflux for 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (2 × 100 mL) and washed with water (2 × 50 mL), dried (Na_2SO_4) and condensed under reduced pressure. The residue was washed with methanol to give the crude *partial-cone*-**3** (127 mg, 86%) as a colourless solid. Recrystallization from MeOH–$CHCl_3$ (3 : 1) gave *partial-cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris(benzyloxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-**3**) as colourless prisms. Mp: 180–185 °C. ν_{max} (KBr)/cm^{-1} 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094 and 1058. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (18 H, s, *tBu*), 1.20 (9 H, s, *tBu*), 3.40 (2H, s, OCH_2Ph), 4.07 (2H, d, *J* = 12.7 Hz, ArCH_2O), 4.19 (4 H, s, OCH_2Ph), 4.27 (2H, d, *J* = 9.3 Hz, ArCH_2O), 4.28 (2H, d, *J* = 12.7 Hz, ArCH_2O), 4.46 (2H, d, *J* = 12.7 Hz, ArCH_2O), 4.53 (2 H, d, *J* = 12.7 Hz, ArCH_2O), 4.54 (2H, d, *J* = 9.3 Hz, ArCH_2O), 6.72–6.78 (2H, m, Ph-*H*), 7.01–7.14 (17H, m, Ar-*H* and Ph-*H*) and 7.29 (2H, s, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 31.05, 31.41, 34.00, 34.32, 63.55, 63.73, 64.80, 64.91, 68.19, 68.41, 74.17, 126.58, 126.68, 126.92, 126.96, 127.01, 127.22, 127.25, 127.50, 127.62, 128.09, 129.89, 130.30, 131.40, 137.71, 137.88, 146.17, 146.37, 153.62, 154.15. FABMS: *m*/*z* 846 (M^+). Anal. calcd for $C_{57}H_{66}O_6$ (847.13): C, 80.82; H, 7.85. Found: C, 80.53; H, 7.73%. The splitting pattern by ^{1}H-NMR shows that the isolated compound is *partial-cone*-**3**.

Synthesis of 7,15,23-tri-*tert*-butyl-25,26,27-tris[(*N*,*N*-diethyl-2-amino)ethoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]-arene (*cone*-5). To a solution of BH_3 in THF (5 mL) was added *cone*-**4** (100 mg, 0.10 mmol), and the reaction mixture was

stirred at room temperature for 1 h and then refluxed under argon for 24 h. After refluxing, it was cooled in an ice bath, and carefully quenched by the slow addition of water (30 mL). The solvent was evaporated under reduced pressure, and the residue was extracted with dichloromethane (2 × 50 mL) and water (2 × 50 mL). After dichloromethane extraction, the solvent was evaporated and dried for 12 h under vacuum pump resulting in the product as a pure white solid (80 mg, 84.2%). Recrystallization from $CHCl_3$/MeOH afforded *cone*-5 as colourless prisms. Mp: 171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (27H, s, *t*Bu), 1.25 (18H, t, J = 7.4 Hz, CH_3), 2.90 (12H, m, –NCH_2), 3.15 (6H, t, J = 7.4 Hz, –CH_2N), 4.06 (6H, t, ArOCH_2), 4.58 (12H, d, J = 3.0 Hz, ArCH_2O), 6.96 (6H, s, Ar-*H*). ^{13}C NMR ($CDCl_3$) δ: 8.62, 31.36, 34.22, 47.80, 53.56, 57.22, 68.92, 126.12, 130.34, 130.39, 130.64, 146.61, 152.15. FABMS: *m*/*z* 873.6 (M^+). Anal. calcd for $C_{54}H_{87}N_3O_6$ (874.31): C, 74.18; H, 10.03; N, 4.81. Found: C, 74.11; H, 9.81; N, 4.77%.

Determination of association constants

The measurements were performed by ^{1}H-NMR titration experiments with a varying concentration of the guest and a constant concentration (5 mM) of the host receptor. As a probe, the chemical shifts of the CH_2 protons [ArCH_2O] and [ArOCH_2Ph] signals were used. The association constant values were calculated from the integrated intensities of CH_2 protons in the complex and in free host molecules according to literature methods.[17]

^{1}H-NMR complexation experiments

To a $CDCl_3$–CD_3OD (v/v 4 : 1, 5 × 10^{-3} M) solution of *cone*-**3** or *cone*-**5** in an NMR tube was added a $CDCl_3$–CD_3OD (v/v 4 : 1, 5 × 10^{-3} M) solution of dopamine, serotonin, or 2-phenylethylamine. The spectra were recorded after the addition and the temperature of the NMR probe was kept constant at 27 °C.

Crystallographic analyses of *cone*-3 and *cone*-5

Crystal data for *cone*-**3**: $C_{57}H_{66}O_6$, M = 847.1. Monoclinic, space group *A*2/*a* (equivalent to no. 15), a = 27.9648(13), b = 9.8510(6), c = 34.6640(17) Å, β = 101.179(4)°, V = 9368.1(9) Å^3. Z = 8, Dc = 1.201 g cm^{-3}, F(000) = 3648, T = 140(1) K, μ(Mo-Kα) = 0.76 cm^{-1}, λ(Mo-Kα) = 0.71073 Å.

Crystals were large, colourless plates. From a sample under oil, one, *ca.* 0.50 × 0.32 × 0.10 mm, was mounted on a glass fibre and fixed in the cold nitrogen stream on an Oxford Diffraction Xcalibur-3 CCD diffractometer equipped with Mo-Kα radiation and graphite monochromator. Intensity data were measured by thin-slice ω- and ϕ-scans. The total number of reflections recorded, to θ_{max} = 21°, was 32 699, of which 4948 were unique (R_{int} = 0.103); 4551 were observed with $I > 2\sigma_I$.

Data were processed using the CrysAlis-CCD and -RED[18] programs. The structure was determined by the direct methods routines in the SHELXS program[19] and refined by full-matrix least-squares methods, on F^2's, in SHELXL.[19] The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealised positions and their Uiso values were set to ride on the Ueq values of the parent carbon atoms. At the conclusion of the refinement, wR_2 = 0.139 and R_1 = 0.087[19] for all 4948 reflections weighted $w = [\sigma^2(F_o^2) + (0.0383P)^2 + 16.43P]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for the 'observed' data only, R_1 = 0.077. In the final difference map, the highest peak (*ca.* 0.19 eÅ^{-3}) was close to H(44I).

Crystal data for *cone*-**5**: *Crystal data*: $C_{54}H_{87}N_3O_6$, M = 874.3. Triclinic, space group $P\bar{1}$ (no. 2), a = 11.6724(11), b = 14.7955(9), c = 16.7566(18) Å, α = 97.920(7), β = 98.124(8), γ = 105.744(7)°, V = 2709.8(4) Å^3. Z = 2, Dc = 1.071 g cm^{-3}, F(000) = 960, T = 293(1) K, μ(Mo-Kα) = 0.7 cm^{-1}, λ(Mo-Kα) = 0.71073 Å.

Crystals are clear, colourless blocks. One, *ca.* 0.67 × 0.41 × 0.24 mm, was fixed on a glass fibre and mounted on an Oxford Diffraction Xcalibur-3 CCD diffractometer equipped with Mo-Kα radiation and graphite monochromator. Intensity data were measured by thin-slice ω- and ϕ-scans. Total no. of reflections recorded, to θ_{max} = 22.5°, was 25 513 of which 7012 were unique (R_{int} = 0.029); 5286 were 'observed' with $I > 2\sigma_I$.

Data were processed using the CrysAlis-CCD and -RED[18] programs. The structure was determined by the direct methods routines in the SHELXS program[19] and refined by full-matrix least-squares methods, on F^2's, in SHELXL.[19] The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealised positions and their Uiso values were set to ride on the Ueq values of the parent carbon atoms. At the conclusion of the refinement, wR_2 = 0.157 and R_1 = 0.076[19] for all 7012 reflections weighted $w = [\sigma^2(F_o^2) + (0.0820P)^2 + 0.93P]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for the 'observed' data only, R_1 = 0.055.

In the final difference map, the highest peak (*ca.* 0.36 eÅ^{-3}) was close to C(14A).

For both structures, scattering factors for neutral atoms were taken from reference.[20] Computer programs used in this analysis have been noted above, and were run through WinGX[21] on a Dell Precision 370 PC at the University of East Anglia.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 841827 for *cone*-**3** and 841828 for *cone*-**5**, respectively.

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