Amide-based [12]-, [12.12]- and [12.12.12.12]paracyclophanes: non-planarity of amide and phenyl groups in the [12]cyclophane

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A reaction between ethylenediaminetetraacetic dianhydride and *p*-xylene-α,α′-diamine has given three amide-based cyclophanes with different ring sizes; the (1 : 1)-reaction product is 3,10-dioxo-5,8-bis(carboxymethyl)-2,5,8,11-tetraaza[12]paracyclophane, the (2 : 2)-product is 3,10,21,28-tetraoxo-5,8,23,26-tetrakis(carboxymethyl)-2,5,8,11,20,23,26,29-octaaza[12.12]paracyclophane, and the (4:4)-product is 3,10,21,28,39,46,57,64-octaoxo-5,8,23,26,41,44,59,62-octakis(carboxymethyl)-2,5,8,11,20,23,26,29,38,41,44,47,56,59,62,65-hexadecaaza[12.12.12.12]paracyclophane. These amide paracyclophanes have been characterized by NMR, infrared, absorption and electrospray mass spectroscopies. *Ab initio* calculations have shown that the amide and phenyl groups in the (1 : 1)-product, *i.e.*, amide[12]paracyclophane, are distorted from the planar structures owing to the strain of the small cyclophane ring. This unusual structure results in physical properties different from those of the other cyclophanes having larger ring sizes: for example, (1) a low acidity of the amide hydrogen and (2) a low basicity of the amino nitrogen.

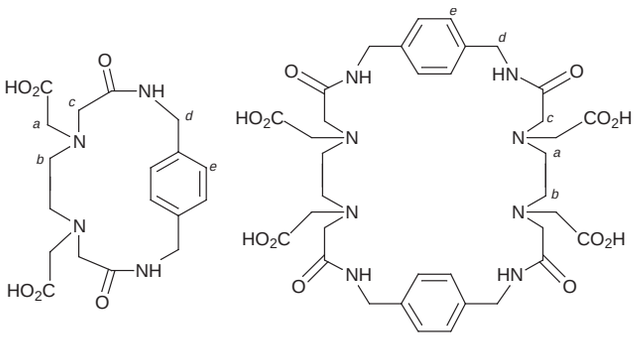
A series of chelating macrocycles having two or four amide groups in the ring systems were synthesized by reactions between ethylenediaminetetraacetic (EDTA) dianhydride and diamines.[1,2] The use of aromatic diamines, such as bis(4-aminophenyl) ether and bis(4-aminophenyl)methane, provides cyclophanes in which two EDTA and two aromatic diamine units were linked by four amide bonds.[3] The ring conformations of these cyclophanes are defined by the planarity of the amide and phenyl groups. Very little of the (1 : 1)-reaction products were formed because of the strain in the ring systems that resulted from the planarity of the amide and phenyl groups. The use of *p*-xylene-α,α′-diamine, however, was expected to give a (1 : 1)-reaction product, because the benzyl CH_2 groups reduce the strain energy in the resulting cyclophane ring system. In this work, we have synthesized (1 : 1)-reaction product (**1**), hereafter abbreviated as (1 : 1-edtaxan)H_2, which is an amide-based [12]paracyclophane, along with amide[12.12]paracyclophane (**2**), abbreviated as (2 : 2-edtaxan)H_4, although the yield of the former is very low. Geometrical optimization by *ab initio* calculations has shown that the cyclophane ring of (1 : 1-edtaxan)H_2 still suffers strain to distort its phenyl and amide groups from their planar geometries. In the [*n*]paracyclophanes and [*n.n*]paracyclophanes having short $(CH_2)_n$ bridges, the benzene rings are distorted owing to the strain of the cyclophane rings.[4–10] The bent structures of the benzene rings lead to the unusual spectral and chemical properties of these cyclophanes.[7–16] In a normal amide group, the C–NH–CO–C atoms lie in a common plane, and the amide hydrogen is weakly acidic.[17,18] These characteristics of the amide group define the structural and chemical properties of amide-based compounds such as peptides.[17,18] A distorted amide group in an amide-based compound is expected to provide unusual physical properties which are not observed in normal amide-based compounds. From these viewpoints, we have studied the new amide-based [12]cyclophane, (1 : 1-edtaxan)H_2, by NMR, infrared and absorption spectroscopies. We have also isolated and characterized the (4 : 4)-reaction product (**3**), abbreviated as (4 : 4-edtaxan)H_8, which is an amide-[12.12.12.12]paracyclophane having a very large cyclophane ring system.

Experimental

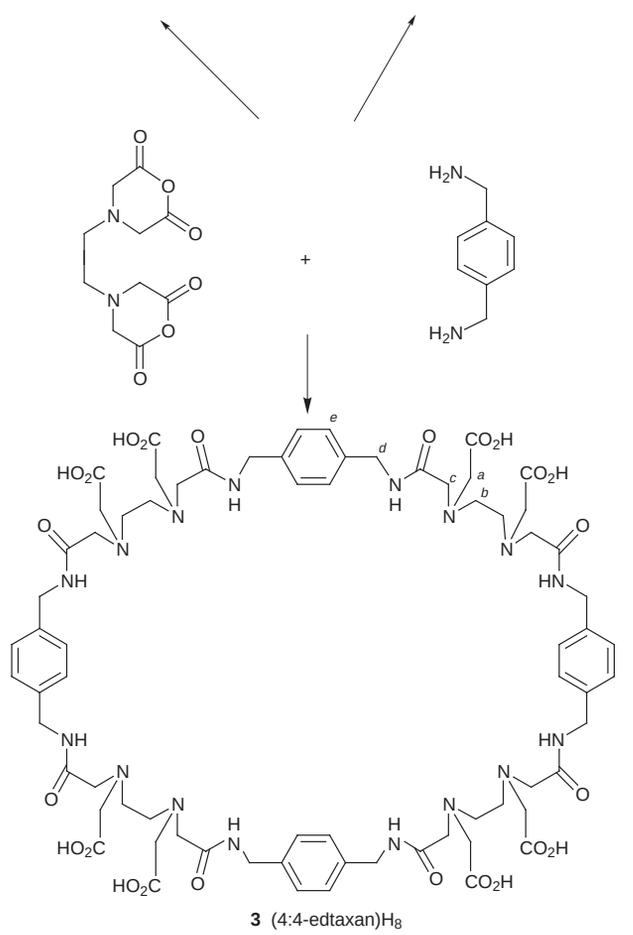
Syntheses

A dimethylformamide (DMF) solution (70 cm^3) containing 3 g (22 mmol) of *p*-xylene-α,α′-diamine (Aldrich Chemical) was slowly added to 5 g (20 mmol) of EDTA dianhydride (Aldrich Chemical) in 300 cm^3 of DMF with vigorous stirring during a period of 2 h. Any solid formed was removed by filtration and the filtrate was concentrated to a viscous liquid (*ca.* 10 cm^3). Addition of ethanol (20 cm^3) to the liquid gave a colorless solid, which was separated by filtration. The filtrate was left to stand in a refrigerator to form a colorless solid, which was recrystallized from 60% ethanol and twice from water to give (1 : 1-edtaxan)H_2. Yield, 1%. Anal. Calc for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.16; N, 14.28%. Found: C, 54.85; H, 5.99; N, 13.95% (the elemental analyses were performed at Desert Analytics, Tucson, AZ, USA). ^{1}H NMR (D_2O–Na_2CO_3, pD = 10.2, 250 MHz, referenced to DSS): δ_H 1.80 (s, 4H, assigned to H_b in **1**), 2.97 (s, 4H, H_c), 3.03 (s, 4H, H_a), 4.34 (s, 4H, H_d), 7.37 (s, 4H, H_e); in $(CD_3)_2SO$, 1.81 (s, 4H, H_b), 2.92 (s, 4H) and 3.21 (s, 4H) (H_a, H_c), 4.15 (d, *J* 6.3 Hz, 4H, H_d), 7.24 (s, 4H, H_e), 7.67 (t, *J* 6.3 Hz, 2H, amide NH). ^{13}C NMR (D_2O–NaOH, pD = 10.2, 62.9 MHz, DSS): δ_C 46.14 (C_d), 54.03 (C_b), 60.74 and 62.62 (C_a, C_c), 131.59 (C_e), 142.15 (phenyl *C*–CH_2), 176.50 (CONH), 181.87 (CO_2^-). MS (electrospray ionization): *m*/*z* (relative intensity) = 391.1 (100) $[M - H]^-$.

The solid separated by the addition of ethanol to the DMF solution described above was suspended in water (50 dm^3) and solubilized by adding a minimum amount of dilute NH_3 so that pH ≈ 7. Acidification of the resulting solution to pH = 5 with dilute HCl gave (2 : 2-edtaxan)H_4 as reported previously.[2] The product was separated by filtration (yield = 13%). The filtrate was acidified further to pH = 3.5 with dilute HCl, to yield a colorless solid, which was suspended in water (20 dm^3). To the suspension, dilute NH_3 was added until pH = 5. Any insoluble solid, if present, was removed by filtration. When the filtrate was acidified to pH = 2 with HCl, (4 : 4-edtaxan)H_8 was obtained as a colorless solid, which was recrystallized by repeated dissolution at pH = 5 and precipitation at pH = 2. The product was washed by suspension in water. Yield, 5%. Anal. Calc for



1 (1:1-edtaxan)H_2 **2** (2:2-edtaxan)H_4



3 (4:4-edtaxan)H_8

Scheme 1

$C_{72}H_{96}N_{16}O_{24}\cdot 8H_2O$: C, 50.46; H, 6.59; N, 13.08%. Found: C, 50.39; H, 6.12; N, 13.01%. ^{1}H NMR (D_2O–Na_2CO_3, pD = 10.5, 250 MHz, DSS): δ_H 2.60 (s, 16H, H_b in **3**), 3.09 (s, 16H, H_a), 3.17 (s, 16H, H_c), 4.22 (s, 16H, H_d), 7.13 (s, 16H, H_e); in $(CD_3)_2SO$, 2.76 (s, 16H, H_b), 3.31 (s, 16H) and 3.39 (s, 16H) (H_a, H_c), 4.23 (d, *J* 5.8 Hz, 16H, H_d), 7.16 (s, 16H, H_e), 8.49 (t, *J* 5.8 Hz, 8H, amide NH). ^{13}C NMR (D_2O–NaOH, pD = 11.7, 62.9 MHz, DSS): δ_C 45.08 (C_d), 55.16 (C_b), 60.96 and 61.25 (C_a, C_c), 130.41 (C_e), 139.68 (phenyl *C*–CH_2), 176.48 (CONH), 181.69 (CO_2^-). MS (ESI): *m*/*z* (relative intensity) = 1567.9 (1.4) $[M - H]^-$, 782.9 (100) $[M - 2H]^{2-}$, 521.9 (2.5) $[M - 3H]^{3-}$.

Spectroscopic measurements

The NMR spectra were obtained at a probe temperature of *ca.* 23 °C on a Bruker AM 250 spectrometer. The internal reference was sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) for D_2O solutions. The pH of each sample solution was adjusted with a minimum amount of Na_2CO_3 or DCl, and determined after the NMR measurement by using a long-stem thin pH electrode (Aldrich), which was calibrated with standard aqueous buffers (Fisher). Measured pH values were converted to pD values by $pD = pH_{measured} + 0.4$.[19] The electrospray ionization mass spectra were obtained by the use of a JEOL HX 110A spectrometer for sample solutions of an ammonia–methanol (5:95) mixture. The electronic absorption spectra were recorded on a Perkin-Elmer Lambda-2 UV-VIS spectrophotometer, and the infrared spectra on a Perkin-Elmer 1600 FT IR spectrophotometer for Nujol mulls and KBr pellets.

Table 1 Selected ^{1}H and ^{13}C NMR shifts, δ_H and δ_C, for (*n*:*n*-edtaxan)H_{2n}

		(1:1)	(2:2)	(4:4)
Ethylene[a]	H_b	1.80	2.59	2.60
	C_b	54.0	55.2	55.2
Phenyl[a]	H_e	7.37	7.08	7.13
	C_e	131.6	130.6	130.4
	para-C	142.2	139.8	139.7
Amide	NH[b]	7.67	8.45	8.49

[a] In D_2O (pD ≥ 10, referenced to DSS); for labeling see structures **1**–**3**; reference 2 for (2:2-edtaxan)H_4. [b] In dimethyl sulfoxide-d_6. The δ_H values of the other protons in the (1:1)- and (4:4)-isomers are given in the Experimental section; for the (2:2)-isomer, 2.71 (s, 8H, H_b), 3.25 (s, 8H) and 3.33 (s, 8H) (H_a, H_c), 4.20 (d, *J* 5.8 Hz, 8H, H_d), 7.12 (s, 8H, H_e), 8.45 (t, *J* 5.8 Hz, 4H, amide NH).

Results and discussion

Formation of cyclophanes

Reactions between EDTA dianhydride and *p*-xylene-α,α′-diamine gave three amide cyclophanes having different ring sizes, as shown in Scheme 1. They were readily separated because their solubilities in aqueous media were different. The formation of these cyclophanes has been confirmed by ^{1}H NMR, ^{13}C NMR and electrospray mass spectroscopies.

In the ^{1}H NMR spectrum of (1:1-edtaxan)H_2, the ethylene protons (*b* in **1**) showed a very small δ_H value in comparison with those of (2:2-edtaxan)H_4 and (4:4-edtaxan)H_8 (Table 1). The large up-field shift of the *b* proton signal in (1:1-edtaxan)H_2 indicates that these protons experience a magnetic field induced by the aromatic ring current,[20,21] giving evidence for the formation of the (1:1)-cyclophane in which the ethylene protons reside in proximity to the face of the benzene ring. The ^{1}H and ^{13}C NMR spectra of the (4:4)-condensation product in D_2O solutions showed that all EDTA and diamine moieties are equivalent, respectively, and the NMR chemical shifts are close to those of (2:2-edtaxan)H_4 reported previously.[2] These NMR results indicate that the (4:4)-reaction product is a [12.12.12.12]cyclophane represented by structure **3** rather than a [2]catenane. A condensation reaction of *p*-xylene-α,α′-diamine with isophthaloyl chloride has been reported to give a [2]catenane, in a high yield, rather than a cyclophane having a larger single ring.[22] In the reaction with EDTA dianhydride, however, a product that showed an ^{1}H NMR spectrum attributable to a catenane was not isolated.

The electrospray mass spectrum of (1:1-edtaxan)H_2 in an ammoniacal solution exhibited, in addition to the $[M - H]^-$ peak (*m*/*z* = 391.1, 100%), an extra peak at *m*/*z* = 783.1 (40%). The intervals between the isotope peaks proved that the latter species also had *z* = 1. The relative intensities of the two peaks were strongly dependent on sample concentration: for example, a solution concentrated by a factor of 10 gave an intensity of 45% for *m*/*z* = 391.1 and 100% for 783.1. These observations indicate the formation of a dimeric cluster $[2M - H]^-$ (*m*/*z* = 783.1) in which two molecules are aggregated by hydrogen bonds. The other cyclophanes did not show any peaks attributable to their aggregates.

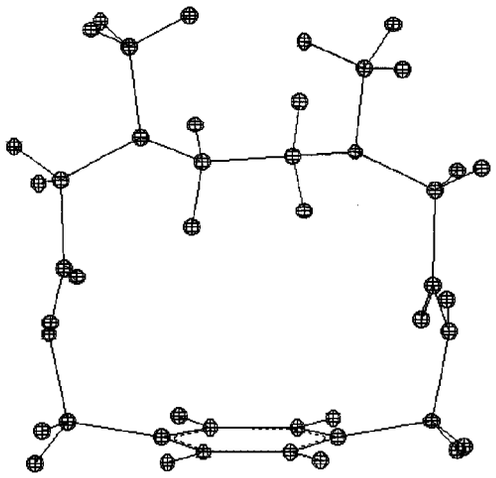


Fig. 1 Possible structure of the ring system in (1:1-edtaxan)H_2. The structure is optimized by *ab initio* calculations for a model compound, 3,10-dioxo-5,8-dimethyl-2,5,8,11-tetraaza[12]paracyclophane (**5**).

Ab initio molecular orbital calculations

Geometrical optimization was carried out for the ring system of (1:1-edtaxan)H_2 at the Hartree–Fock (RHF-SCF) level by using the 6-31G* basis set in the program package SPARTAN version 4.0 on a UNIX computer. The carboxymethyl groups were excluded in the calculations for simplicity; the model compounds were 3,10-dioxo-2,5,8,11-tetraaza[12]paracyclophane (**4**) and 3,10-dioxo-5,8-dimethyl-2,5,8,11-tetraaza[12]paracyclophane (**5**). The former was optimized in C_2 symmetry. The latter, in which its methyl groups protruded parallel to the averaged molecular plane, was optimized in a quasi C_2 symmetry, and the conformations around the phenyl and amide groups closely resembled those in **4**; when the two methyl groups were placed perpendicular to the cyclophane ring plane, the convergence was very slow and the resulting conformation was quite deformed from that of **4**, although the energies of the two optimized conformations were not significantly different. The conformation optimized for **5** in the quasi C_2 symmetry is shown in Fig. 1; it is a reasonable representation of the ring geometry in (1:1-edtaxan)$^{2-}$. The benzene ring is slightly bent in a boat form, in which the *para*-carbon atoms bridged by an aliphatic chain lie out of the averaged plane of the other ring carbon atoms with a bend angle of 3.7°. The identical bend angle was obtained in the optimized structure of a non-amide cyclophane, 2,5,8,11-tetraaza[12]paracyclophane; the angle is reasonable when compared with 5° estimated for [12]paracyclophane[7] and 9° determined for [8]paracyclophane by an X-ray structure analysis.[4] Since the bend angles in the optimized structures of tetraaza[12]paracyclophane and dioxotetraaza[12]paracyclophane are identical, the introduction of amide groups to a tetraaza[12]paracyclophane ring does not cause a further distortion of the benzene ring. Instead, the amide groups are distorted from the planar structure: an amide nitrogen is located 0.2 Å above the plane defined by the surrounding carbon and hydrogen atoms.

NMR spectra

The ^{1}H NMR chemical shifts δ_H of (1:1-edtaxan)H_2 and (4:4-edtaxan)H_8 are shown in Figs. 2 and 3, respectively, as functions of pD. Both compounds showed five singlet peaks throughout the pD range studied. The δ_H values were practically independent of sample concentration in the range 2–30 mmol dm^{-3}.

The signals of protons *a*, *b* and *c* (structure **1**) of (1:1-edtaxan)$^{2-}$ shift simultaneously to a lower field with decreasing pD in the range 6–8. The first protonation, therefore, occurs mainly on the amino nitrogen. The protonation constant K can be approximated by the pD value in the middle (or at the

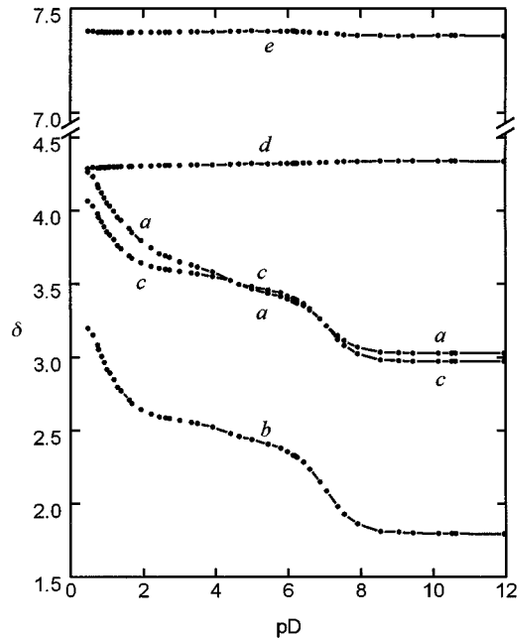


Fig. 2 ^{1}H NMR shifts δ of (1:1-edtaxan)H_2 at different pD: for labeling see structure **1**. Sample concentration = 2 mmol dm^{-3}.

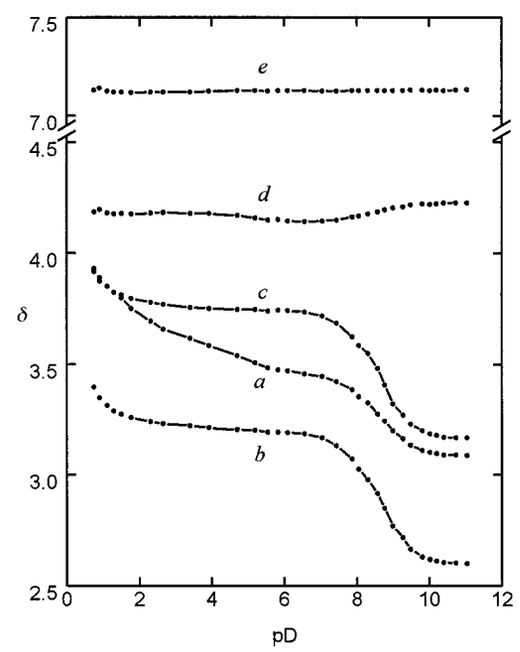


Fig. 3 ^{1}H NMR shifts δ of (4:4-edtaxan)H_8 at different pD: for labeling see structure **3**. Sample concentration = 0.5 mmol dm^{-3} except for the pD range 2.5–5.0 in which the concentration was less than 0.5 mmol dm^{-3} because of the low solubility.

maximum-slope point) of the buffer region in the δ_H *vs.* pD curve; log K = 7.0. For (4:4-edtaxan)$^{8-}$, four amino nitrogens are protonated almost simultaneously in the pD range 7–10, giving [(4:4-edtaxan)H_4]$^{4-}$. The pD of the midpoint of the buffer region is 8.7, which can be approximated as the average value of the four logarithmic protonation constants. The log K values of (1:1-edtaxan)$^{2-}$ and (4:4-edtaxan)$^{8-}$ are significantly smaller and larger, respectively, than 7.9 obtained for (2:2-edtaxan)$^{4-}$.[2] Thus, the basicity of the amino nitrogen increases with increasing cyclophane ring size. In [(2:2-edtaxan)H_2]$^{2-}$ and [(4:4-edtaxan)H_4]$^{4-}$, in which half the amino nitrogens are protonated, each proton is shared by two amino nitrogens adjacent to each other,[2] and the resulting intramolecular hydrogen bonds stabilize the protonated state. The cyclophane ring of [(4:4-edtaxan)H_4]$^{4-}$ is more flexible than [(2:2-

edtaxan)H_2]$^{2-}$, and the neighboring amino groups in the former can orient their lone-pair orbitals more favorably towards the shared proton. The stabilization energy due to the intramolecular hydrogen bonds is, therefore, larger in the (4:4)-cyclophane than in the (2:2)-cyclophane. The larger stabilization in [(4:4-edtaxan)H_4]$^{4-}$ leads to the higher basicity of the amino groups. In [(1:1-edtaxan)H]$^-$, an intramolecular hydrogen bond is not readily formed between the two amino nitrogens, because the cyclophane ring is small and rigid with lone-pair orbitals that are unfavorably oriented to share a proton (Fig. 1). This leads to a smaller stabilization of the protonated state and consequently the lower basicity of the amino nitrogen in the (1:1)-cyclophane. The next protonation occurs at pD between 2 and 6 in the three cyclophanes. In [(4:4-edtaxan)H_4]$^{4-}$, only the *a* proton signal shifts to a lower field upon protonation, indicating that the carboxylate oxygen atoms are protonated, as reported for [(2:2-edtaxan)H_2]$^{2-}$.[2] With the second protonation of [(1:1-edtaxan)H]$^-$, the signals of *b* protons as well as of *a* protons are shifted down-field, suggesting that the geometrical relation of *b* protons with respect to the benzene ring is changed upon protonation on carboxylate oxygen probably *via* formation of hydrogen bonds. The three cyclophanes did not show a well-defined buffer region in the pD range 2–6, but it is clear that their second protonation constants do not differ much from one another when compared with the first protonation constants; protonation on the pendant carboxylate oxygen atoms is unaffected by the ring size.

The ethylene groups of the EDTA moiety in (1:1-edtaxan)H_2 are located close to the face of the benzene ring, whereas *b* protons in (2:2-edtaxan)H_4 and (4:4-edtaxan)H_8 are so distant from the benzene rings that the ring current effect is negligible. The pD dependence of the ^{1}H NMR shifts indicates that all these cyclophanes are completely deprotonated at pD ≥ 10. In this pD range, protonation and aggregation effects are insignificant, and hence, the difference between the chemical shifts of *b* protons of (1:1-edtaxan)$^{2-}$ and of the other two isomers can be attributed to the ring current effect in (1:1-edtaxan)$^{2-}$. A proton NMR shift δ_{rc} caused by the ring current of a phenyl group is given by eqn. (1),[21] where *r* is the distance (in Å) of the

$$\delta_{rc} = 27.6\ (1 - 3\cos^2\theta)/r^3 \qquad (1)$$

resonant proton from the center of the phenyl ring, and θ is the angle between the normal and the vector from the ring center to the proton. On the basis of the structure optimized by the *ab initio* calculations for the amide[12]paracyclophane ring system, the δ_{rc} values of the two protons on a *b* carbon in (1:1-edtaxan)$^{2-}$ were calculated to be −0.92 and −0.32 (up-field shift). Since the *b* protons of (1:1-edtaxan)$^{2-}$ show only a single peak, the ethylene group undergoes a rapid tumbling. The simple average, −0.62, of the two calculated values is reasonable when compared with the chemical shift −0.79 observed for (1:1-edtaxan)$^{2-}$ with reference to the corresponding protons in (2:2-edtaxan)$^{4-}$ at pD > 10.

The *ab initio* calculations have shown that the amide and the phenyl groups in the amide[12]paracyclophane are distorted from the planar structures. The ^{13}C NMR shifts δ_C of the phenyl carbons in (1:1-edtaxan)$^{2-}$ are larger than the corresponding shifts in (2:2-edtaxan)$^{4-}$ and (4:4-edtaxan)$^{8-}$ (especially the difference in the *para*-carbon atoms is significant), whereas the δ_C values in the latter two isomers are practically identical (Table 1). These down-field shifts observed for (1:1-edtaxan)$^{2-}$ may be caused by the distortion of the benzene ring. Aromatic proton *e* in (1:1-edtaxan)$^{2-}$ was observed at a lower field by $\Delta\delta_H = 0.29$ than the corresponding protons in (2:2-edtaxan)$^{4-}$. If the ring current is decreased owing to the bent structure of the benzene, the *e* proton signal should be shifted to a higher field. A similar unexpected down-field shift has been reported for [5]paracyclophane.[15] The down-field shift of the aromatic proton should be caused by changes in the local electron density, because the aromatic carbons also show down-field shifts. In the tetraaza[12]paracyclophanes optimized by the *ab initio* calculations, however, every carbon atom in the benzene rings has essentially sp^2 hybridization.

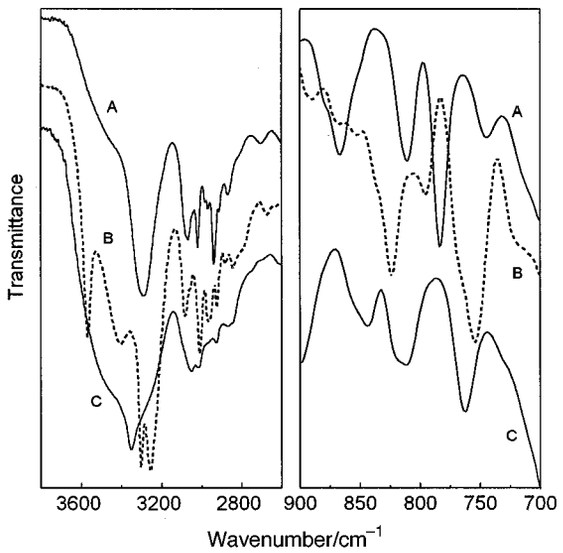


Fig. 4 IR spectra of (1:1-edtaxan)H_2 (A), (2:2-edtaxan)H_4 (B) and (4:4-edtaxan)H_8 (C) in KBr pellets. The identical spectral patterns were observed in Nujol mulls.

In an amide group, resonance between the –NH–C=O and –NH$^+$=C–O$^-$ structures results in a planar geometry around the nitrogen atom and contributes to the acidity of the NH proton. The contribution of the ionic structure is expected to decrease when an amide nitrogen is distorted from a planar bonding geometry. Bond distances in the amide group of the optimized dioxotetraaza[12]cyclophane ring are practically identical with those in the optimized structure of the acyclic amide, *N*-benzylacetamide, and atomic charges on the amide hydrogens of the two model compounds have no meaningful difference. The effect of distortion, however, has been observed in the NMR signals of amide NH protons of the three amide cyclophanes, which exhibited a well-defined triplet of an amide proton in dimethyl sulfoxide-d_6. The δ_H value of (1:1-edtaxan)H_2 was lower by 0.8 than those of (2:2-edtaxan)H_4 and (4:4-edtaxan)H_8 (Table 1). This difference cannot be explained by the ring current effect, because δ_{rc} [eqn. (1)] of the amide proton is only 0.07 for the optimized conformation of the (1:1)-cyclophane ring. The up-field shift of the amide proton in (1:1-edtaxan)H_2 is, therefore, attributed to a decrease in the ionic character of the N–H bond as a consequence of a decrease in the contribution of the ionic structure in the distorted amide group.

Infrared spectra

The IR spectra of the three amide cyclophanes were markedly different in the 2660–3800 and 700–900 cm^{-1} regions, as shown in Fig. 4; no manifest difference was observed in the 1400–1700 cm^{-1} region, in which overlapping vibrational bands of carboxylate, amide and phenyl groups are present. The peak positions observed in Nujol mulls and KBr were identical. The peaks of (4:4-edtaxan)H_8 are broad when compared with the other cyclophanes with smaller ring sizes, suggesting that the four edtaxan units of (4:4-edtaxan)H_8 are in different environments in the solid state. The amide N–H stretching band of (1:1-edtaxan)H_2 is observed at 3290 cm^{-1} whereas (2:2-edtaxan)H_4 shows two bands (3302 and 3252 cm^{-1}) assignable to the N–H stretching frequencies in the amides. This indicates that the effect of the distortion of the amide groups is smaller than the solid state effects including intermolecular electrostatic

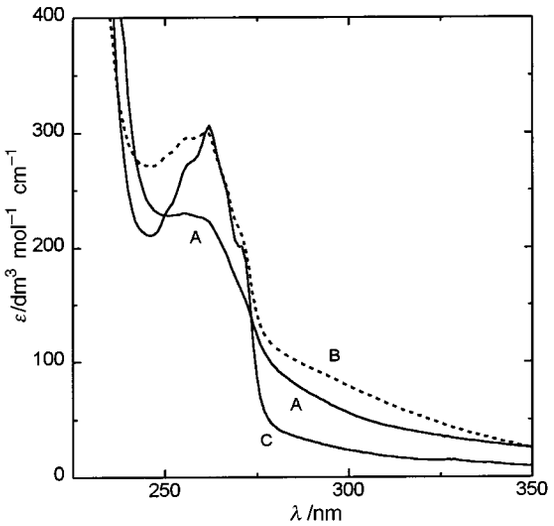


Fig. 5 UV spectra of (1:1-edtaxan)H_2 (A), (2:2-edtaxan)H_4 (B) and (4:4-edtaxan)H_8 (C) at pH = 5.0–5.6. The molar absorptivities, ε/mol^{-1} dm^3 cm^{-1}, of the three compounds are given for each benzene unit for purposes of comparison.

interaction and hydrogen bond formation. The aromatic ν_{C-H} bands of (1:1-edtaxan)H_2 appear at 10–20 cm^{-1} smaller wavenumbers than those of (2:2-edtaxan)H_4, and the aromatic δ_{C-H} (out-of-plane), 811 cm^{-1}, of the (1:1)-cyclophane is also smaller than 824 cm^{-1} of the (2:2)-cyclophane. These differences may be attributed to the bent benzene ring in the (1:1)-cyclophane, although the solid state effects, to which the C–H bands are less susceptible, cannot be entirely ruled out. This is consistent with the finding that δ_{C-H} (out-of-plane) is 806.6 cm^{-1} for largely distorted benzene in [2.2]paracyclophane and 828.7 cm^{-1} for undistorted *p*-diethylbenzene.[23]

Electronic absorption spectra

The solution spectra of the amide cyclophanes showed two π–π* transition bands in the 220 and 260 nm regions. The former band of every cyclophane was observed as an ill-defined shoulder on a strong absorption envelope at the shorter wavelength side. The latter band is shown in Fig. 5 for the three cyclophanes. The absorption maximum observed for (1:1-edtaxan)H_2 at 255 nm was not changed with pH, whereas the molar absorptivity increased with increasing pH: ε_{255}/mol^{-1} dm^3 cm^{-1} = 190 at pH = 1.9; ε_{255} = 230, pH = 5.0; $\varepsilon_{255} \approx 250$ (shoulder), pH = 9.0. The 260 nm band of (4:4-edtaxan)H_8 was weakly pH-dependent: λ_{max} = 262 nm (ε = 1200) at pH = 2.0; 262 nm (1230) at pH = 5.6; 256 nm (1080) at pH = 8.2. The absorption bands of [*n*]paracyclophanes shift to a longer wavelength with decreasing *n*.[7,9,16] This red shift is related to the distortion of the benzene rings. The absorption maximum of (1:1-edtaxan)H_2 is practically identical with the corresponding maxima of (4:4-edtaxan)H_8 and (2:2-edtaxan)H_4. The electronic energy levels in the (1:1)-cyclophane are substantially unchanged by the small bend angle. The molar absorptivity of (1:1-edtaxan)H_2 is, however, clearly smaller than the molar absorptivities for each benzene unit in (2:2-edtaxan)H_4 and (4:4-edtaxan)H_8, and the vibrational structure collapses and differs from the larger ring cyclophanes (Fig. 5). These spectral differences may be related to the strain in the cyclophane rings.

Conclusions

The reaction between EDTA dianhydride and *p*-xylene-α,α′-diamine gave three amide-based cyclophanes having different ring sizes. The ring size effect results in different spectral and chemical properties. Of the most significance is the strain of the cyclophane ring in the amide[12]paracyclophane, in which the amide and phenyl groups are distorted from the planar conformations. The effect of the distortion is observed in the NMR and IR spectra: for example, the amide group of the amide-[12]paracyclophane leads to the large up-field shift of the amide proton signal, as a result of the decrease in the ionic character of the N–H bond; the IR spectra in the aromatic out-of-plane C–H bending region are sensitive to cyclophane ring size.

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