Binding Properties of Amide and Amide–Ester *N*-Functionalised Polyaza Macrocycles

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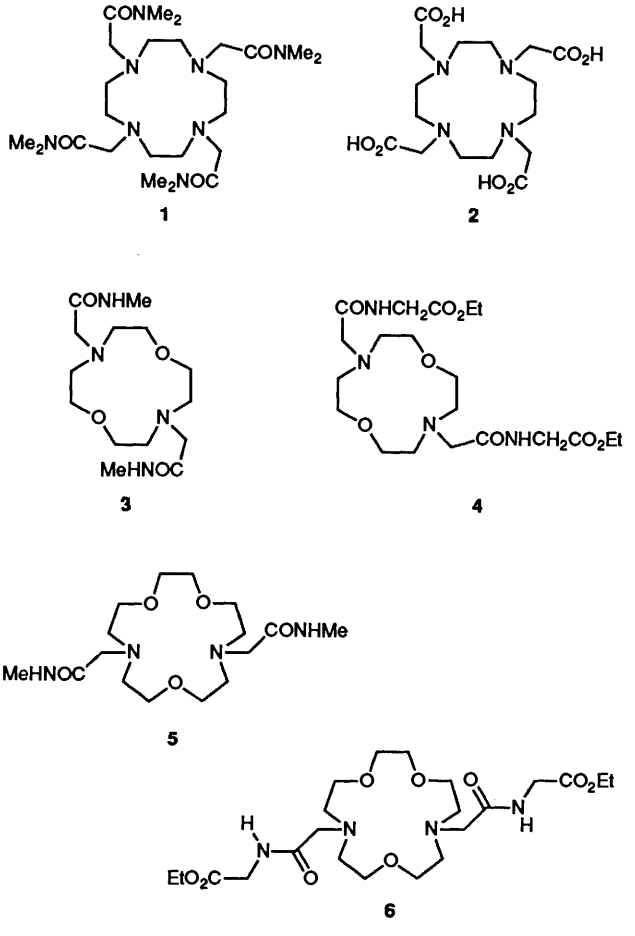
A series of amide and amide–ester *N*-functionalised coronands has been prepared based on [12]-N_2O_2, [15]-N_2O_3 and [18]-N_2O_4 polyazaoxa macrocycles. Complexation of certain alkali and alkaline-earth metal cations has been monitored by ^{13}C NMR and IR spectroscopy, enthalpies of complexation measured in methanolic solution by calorimetry and stability constants measured in aqueous solution by potentiometric methods. Strong complexation of Ca^{2+} in aqueous solution was observed with high selectivities (*ca.* 10^2 to $10^{3.5}$) over Na^+ and K^+.

The complexation of univalent and divalent ions by synthetic ionophores remains a topic of considerable current interest.[1–9] Particular attention has been paid to polyaza-polyoxa macrocycles with an emphasis on the search for discrimination in favour of binding a particular group Ia or IIa metal cation. In this respect, the introduction of pendant amide substituents at nitrogen centres has been used to enhance discrimination in favour of the binding of cations with higher charge density (*e.g.* Li^+/Na^+ and Ca^{2+}/M^+). Such effects have been used, for example, to optimise Li^+/Na^+ selectivity *via* amide-*C*-substituted 14-crown-4-derivatives,[1,2] or in enhancing the transport of Na^+ and K^+ in *N*-substituted [18]-N_2O_4 coronands.[2] Some recent work with 'peptide' derivatives of 4,13-diaza-18-crown-6 suggested that exceedingly stable complexes of calcium (log K_s, *ca.* 10^7) were obtained in water which showed pronounced selectivity over sodium (ratio of 1:1 stability constants of $> 10^4$ and up to $10^{5.5}$).[3] Given that the tetraamide derivative of 12-N_4 **1**, exhibits a 1:1 complexation constant of $10^{6.82}$ in aqueous solution[1] and that it bears a striking structural homology to DOTA, **2**, [log K_s = 17.2 (H_2O, 298 K)] with which calcium forms its most stable complex,[11] the high reported values with the peptide-substituted diaza-crown ether ligands (with 2-amide and 2-ester donor groups) are worthy of further investigation. Accordingly, the secondary diamide derivatives of the [12]-N_2O_2, [15]-N_2O_3 and [18]-N_2O_4 coronands **3**, **5** and **7** have been prepared and their binding ability compared with the simple derivatives **4**, **6** and **8** bearing a potentially ligating CH_2CO_2Et group in place of the *N*-methyl substituent.



Results and Discussion

Ligand Syntheses.—Alkylation of the parent diamines with *N*-methyl-2-bromoethanamide under basic conditions (K_2CO_3, NaI, CH_3CN) afforded the desired diamides **3**, **5** and **7** in yields of 88, 67 and 71% respectively. The related compounds **4**, **6** and **8** were prepared in a similar manner using ethyl (*N*-2-bromoethanoyl)glycinate in yields of 59, 69 and 68%, respectively.

^{13}C NMR and IR Studies of Complexation.—Admixture of increasing amounts of solid anhydrous calcium chloride to **7** in CD_3OD led to changes in the ^{13}C NMR chemical shift of all of the ligand resonances. Discrete lines for free and complexed ligands were observed for all carbons except the carbonyl carbon at stoichiometries between 0.1:1 and 1.0:1 (salt:ligand) consistent with slow kinetics of cation exchange (on the NMR timescale) and typical of a complex with a stability constant log $K_s \geqslant 5$. The resonance of the carbonyl broadened between stoichiometries of 0.1 to 0.5 (ligand:Ca^{2+}) but sharpened thereafter and was sharp beyond 1:1 stoichiometry. This behaviour is consistent with more rapid intermolecular exchange between free and bound amide prior to formation of the 1:1 complex in which the amide carbonyl is bound. Resonances due to free ligand had disappeared completely following addition of one equivalent of $CaCl_2$ indicating that a 1:1 (or *n*:*n*) complex had been formed. A similar 1:1 stoichiometry of complexation with calcium was observed with ligands **3**–**6** and **8** (Table 1). The magnitude of the coordination shift of the amide carbonyl resonance varied from one ligand to another (0.15 to 0.76 ppm) probably reflecting the different degree of conformational change of the ring and side-arm that occurs on complexation, rather than any trend in the strength of binding of the carbonyl

Table 1 Representative ^{13}C NMR coordination shifts ($\Delta\delta$) following 1:1 complexation with $CaCl_2$ or NaOAc (293 K, CD_3OD)

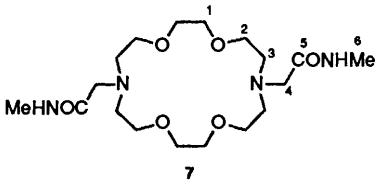
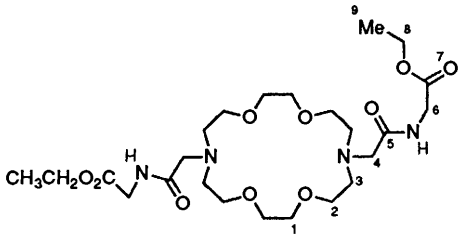
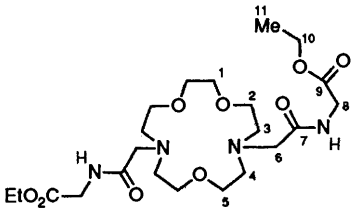
Compound	Carbon atom	$\Delta\delta_{(Ca)}$/ppm	$\Delta\delta_{(Na)}$/ppm
 **7**	1	0.82	1.57
	2	1.13	1.62
	3	0.82	1.27
	4	1.95	0.28
	5	0.15	1.20
	6	0.10	1.11
 **8**	1	0.77	—
	2	0.96	—
	3	0.35	—
	4	3.38	—
	5	0.55	—
	6	0.08	—
	7	0.35	—
	8	0.53	—
	9	0.06	—
 **6**	1	0.29	0.79
	2	0.89	1.54
	3	1.65	0.91
	4	3.63	1.40
	5	0.58	1.35
	6	0.08	0.23
	7	0.76	0.16
	8	0.00	0.02
	9	0.34	1.32
	10	0.26	0.09
	11	0.03	0.03

Table 2 Dissociation constants for protonation of ligands **3**–**9** (298 K, I = 0.1 mol dm^{-3} NMe_4NO_3, ±0.03)

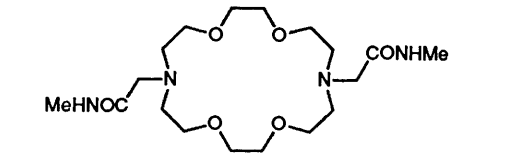
Ligand	pK_{a1}	pK_{a2}
3	6.73	4.84
4	6.98	4.50
5	6.48	5.43
6	6.24	5.23
7	6.49	4.82
8	6.42	4.79
9[a]	6.68	5.40
4,13-Diaza-18-crown-6[b]	8.94	7.81
Me_2-4,13-18-crown-6[c]	9.58	7.61

[a] Data from reference 6. [b] From reference 8. [c] From reference 9.

oxygen to calcium. The small shift of the ester carbonyl carbon (0.34, 0.35 ppm in **6** and **8**) is suggestive of but not proof of ester carbonyl ligation. Such a conclusion is echoed in the complexation behaviour with sodium ions. Addition of sodium acetate (in CD_2OD) or NaCl (in 90:10 CD_3OD:D_2O) to solutions of the ligands revealed 1:1 stoichiometries of complexation, although generally with larger measured coordination shifts (Table 1). Time-averaged signals were observed for free and complexed ligands in formation of the 1:1 complex, characteristic of a weaker 1:1 complex (log K_s < 4). Confirmation of amide participation in cation binding was provided by IR spectroscopy, comparing the spectra of thin films of the ligand and of the complex. With ligand **7**, complexation by Ca^{2+} was accompanied by a reduction in the carbonyl stretching frequency of 13 cm^{-1}, while with the ester derivative **8**, the amide stretch dropped by 22 cm^{-1} and the ester carbonyl by 10 cm^{-1} (relatively sharp bands). This clearly suggests simultaneous coordination of both types of carbonyl oxygen in **8**. In the [15]-ring series, amide participation was seen with **5** and **6** (13 and 10 cm^{-1} shifts to lower frequency, respectively, although the amide band was very broad with **6**) and with the ester **6**, the observed reduction was only 3 cm^{-1} indicative of very weak or no ligation.

Aqueous Potentiometric Measurements of pK_a *and* log K.—Successive acid dissociation constants for ligands **3** to **8** were determined by pH-metric titration followed by iterative data analysis using SCOGS-2 and SUPERQUAD (Table 2).[1] Similar values were recorded for all of the ligands and the values measured previously for the primary amide derivative **9** show reasonable correspondence.[6] The diminution of the pK_a values compared to both diaza-18-crown-6 and its *N*-methylated derivative (Table 2) may be explained by both the modest electron-withdrawing effect of the β-carbonyl group reducing *N*-basicity and also a steric inhibition to solvation of the protonated species LH^+ and LH_2^{2+}. A crystal structure analysis of a [12]-N_2O_2 derivative bearing two $CH_2CH_2CONMe_2$ substituents on nitrogen [10] and of the methyl ester analogue of **8**,[5] has shown that the *N*-lone pairs are directed into the cavity of the ring so that although *N*-inversion must occur prior to protonation this is probably not an important factor in perturbing nitrogen basicity.

Metal complexation constants were determined using potentiometric titration methods followed by iterative data analysis. Values are reported for the 1:1 complexes with sodium, potassium and calcium (Table 3). The stability constants for complexation of Na^+ and K^+ were uniformly low (log K = 2.24–2.70) and fairly constant for all of the examples studied. No selectivity for sodium over potassium was found. Similar values have been reported by other workers [3] using ion-selective electrode methods of analysis [*e.g.* for the methyl ester analogue of **8**, log K_{LNa} = 2.2 (H_2O, 298 K)].



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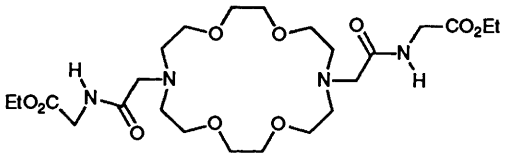

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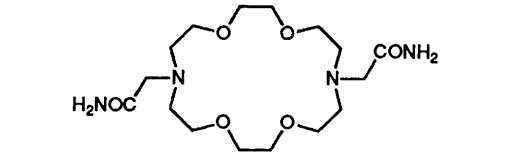

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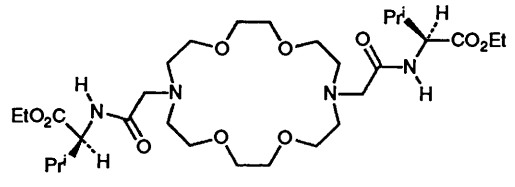

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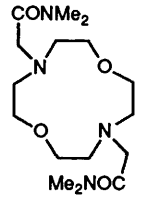

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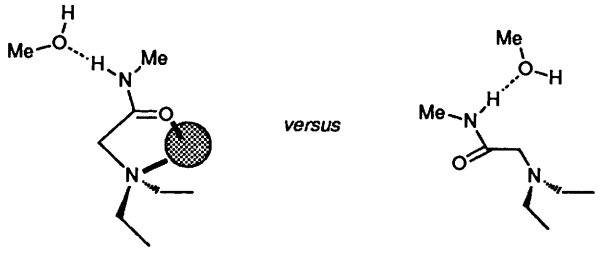
Table 3 Stability constants for complexation of **3–9** with cations (298 K, I = 0.1 mol dm^{-3} NMe_4NO_3, ±0.05)

Ligand	Na^+	K^+	Ca^{2+}
3	2.65	2.70	4.74
4	2.48	2.50	4.52
5	2.55	2.24	4.93
6	2.67	2.51	4.46
7	2.48	2.36	4.99
8	2.36	2.45	5.97
9[a]	<2	<2	5.65

[a] Data from reference 6 (0.5 mol dm^{-3}).

The values found for the 1:1 calcium complexes were higher and ranged from log K = 4.52 for the [12]-ring amide–ester **4**, to a maximum value of 5.97 for the [18]-N_2O_4 amide–ester derivative **8** (in which simultaneous amide and ester ligation was suggested by IR). The maximum observed selectivity (Ca^{2+}/Na^+) is therefore $10^{3.6}$[1] with **8**, but more typically was of the order of $10^{2.5}$. These values of the calcium complexation constants are significantly lower than those observed previously.[3] This is most likely caused by the inaccuracy inherent in the previous determination of calcium complexation caused by attempting to evaluate binding constants using a calcium-ion selective electrode operating beyond its working range.[3,*] Nonetheless, the ester carbonyl in the case of **8** does appear to cause a marked increase in complex stability and IR studies of complexation are suggestive of some ester carbonyl ligation.

Calorimetric Experiments.—Complexation of ligands **3–8** by a range of group Ia and IIa metal cations in methanol solution was studied by measuring the enthalpy of complexation using standard microcalorimetric methods. Exothermic complexation was observed, except with lithium (Table 4) where complexation was endothermic. Similar endotherms were observed in the complexation of the ammonium ion by ligands **3** and **4**. The lithium ion is highly solvated in methanol (and in water) and cation desolvation is energetically expensive, although contributing very favourably (usually) to the $T\Delta S$ term in the overall free energy change. The enthalpy of complexation of the calcium ion falls steadily as the ring increases in size from [12] to [18]. This presumably reflects the relatively greater conformational rigidity of a [12]-N_2O_2 ring (compared to [18]-N_2O_4) which undergoes a relatively small ring conformational change upon complexation. Similar effects have been observed with other [12]-N_2O_2 derivatives[1] and with various [12]-N_4 derivatives.[1,7,10] An interesting comparison may be made between the enthalpies of Ca^{2+} complexation observed with **3** (a secondary amide) and **11** (a tertiary amide) for which ΔH = −46.6 kJ mol^{-1} (CH_3OH, 298 K). The enhanced enthalpy observed with **11** may be attributable to the lesser ligand solvation of **11** compared to **3**. In **3** strong hydrogen-bonding between methanol and the amide NH may occur, and desolvation (prior to Ca^{2+} complexation) is energetically expensive. Indeed if the difference in the enthalpy of complexation of **3** and **11** with the various cations is compared, a fairly constant value is obtained (averaging −18.8 kJ mol^{-1}). This value will approximate to the differential enthalpy of solvation of the free ligand in methanol alone compared to the complex. This term will primarily be associated with the differential degree of hydrogen-bonding between the N–H of the secondary amide and the oxygen of the solvent in the free and complexed state (Scheme 1). If it is further assumed that the difference in σ-binding ability of the carbonyl oxygen in CONHMe *vs.* CONMe is minimal, then this value (18.8 kJ mol^{-1} for two amide NH groups) allows an estimate of the enthalpy of hydrogen bonding between methanol and a secondary amide NH (−9.4 kJ mol^{-1}).[13] This value probably represents a lower limit since the NH group in the complex will undoubtedly be hydrogen bonded to some extent to the methanol solvent (*n.b.* the tertiary amide cannot participate in



Scheme 1 Possible solvation models for ligand and complex in MeOH

such interactions, only in CO - - - HOMe hydrogen bonding which probably occurs to a similar extent in both ligand systems). In summary, these data highlight the importance of the energetics of both cation and ligand desolvation in

* The reported values[3] of ΔH = −35 kcal mol^{-1} (H_2O, 298 K) for calcium complexation with ligand **10** also look rather high: ligand **2** [DOTA, log K_s = 17.2 (H_2O, 298 K)] gives ΔH = −11.7 kcal mol^{-1},[11] (see also Table 4). More recent calorimetric studies suggest that a value nearer to 10 kcal mol^{-1} is observed for the enthalpy of complexation of Ca with ligand **10** (G. W. Gokel, personal communication).

Table 4 Enthalpies of complexation ($-\Delta H$/kJ mol^{-1}, 298 K, CH_3OH) for reaction of **3–8** with cations

Ligand	Li^+	Na^+	K^+	Rb^+	Cs^+	Ag^+	Ca^{2+}	Sr^{2+}	Ba^{2+}
11[b]	12.7	26.0	25.7	22.7	—	59.1	46.6	35.8	33.0
3	—	9.8	2.0	0.6	0.8	43.3	29.6	15.3	16.6
4	—	14.5	5.2	3.2	2.8	45.6	34.9	24.8	24.4
5	−1.9	12.4	23.4	23.3	12.7	40.9	25.0	21.8	30.2
6	−3.3	12.2	18.2	12.5	−1.3	48.3	19.0	22.5	23.7
7	−3.0	11.1	16.2	10.4	0.6	50.5	15.7	17.4	19.5
8	−1.2	5.0[a]	13.5	13.5	3.7	31.9	18.6	20.1	23.9

[a] A value of 5.8 is reported for the related methyl ester in reference **5** [log K = 3.35 (298 K, MeOH) for Na^+ complex and 3.32 for the K^+ complex]. [b] Data from reference 1.

contributing to the overall free energy of cation complexation. Further work is in progress to clarify the significance of *N*-alkyl substitution in cation complexation.

Experimental

Proton and carbon NMR spectra were recorded on a Bruker AC 250 (250.13 MHz and 62.1 MHz) spectrometer. Chemical shifts are quoted to higher frequency of $SiMe_4$ as internal standard and are given in ppm, with coupling constants J in Hz. IR spectra were recorded on a Perkin-Elmer 580A infrared spectrophotometer, and mass spectra were recorded either in the EI, CI, DCI, or FAB mode using a VG 7070E spectrometer. TLC was effected using Merck 60 7354 or 9385 for flash chromatography. HPLC analyses were carried out with a Varian 5500 instrument using both ion-exchange (TSK DEAE) or reverse-phase (Hypersil 5005) columns for analytical or semi-preparative work typically using aqueous acetate–acetonitrile gradient elution. Compounds that did not give correct combustion microanalyses were examined for the purity by TLC and/or HPLC and were ≥96% homogeneous.

^{13}C *NMR Experiments.*—Titration curves were obtained in CD_3OD or 90:10 CD_3OD–D_2O solution by sequential addition of solid salts NaOAc (Sigma) or $CaCl_2$ (Aldrich) to a solution of the ligand. After each addition of salt, the ^{13}C NMR chemical shift (relative to TMS) was measured at 293 K using a Bruker AC 250 instrument operating at 62.1 MHz for the carbon nucleus.

pH-Metric Titration Experiments.—The apparatus and instrumentation used was as described earlier.[1] The measurement of the acid dissociation constants and of metal complexation constants used the same methods reported previously[1] with data analysis by SCOGS-2, then SUPERQUAD.

Synthesis.—The preparation of *N*-methyl-2-bromoethanamide and of ethyl *N*-(2-bromoethanoyl)glycinate were carried out according to published methods.[5]

Ethyl N-(2-*bromoethanoyl*)*glycinate.* To a solution of glycine ethyl ester hydrochloride (10 g, 0.07 mol) in water (20 cm^3) was added aqueous sodium carbonate until the pH was 10.0. The free amine was extracted using dichloromethane (5 × 40 cm^3), the combined extracts were dried ($MgSO_4$), and the solvent reduced to a volume of *ca.* 80 cm^3. Following sequential addition of sodium carbonate (8 g, 75 mmol) and a solution of bromoacetyl bromide (16 g, 79 mmol) in dichloromethane (30 cm^3), the mixture was stirred for 1 h. After being filtered, washed with water (2 × 50 cm^3) and dried ($MgSO_4$), solvent was removed under reduced pressure to yield a residue that was recrystallised from propan-1-ol giving a colourless solid, 8.5 g (54%); m.p. 68–69 °C; $\delta_H(CDCl_3)$ 1.30 (3 H, t, CH_3), 3.93 (2 H, s, CH_2Br), 4.07 (2 H, d, J = 5.2), 4.25 (2 H, q, CH_2O) and 7.10 (1 H, br s, NHCO); m/z (CI) 224 (M^+ + 1), 226 (M^+ + 1) and 146; $\delta_C(CDCl_3)$ 13.9 (CH_3), 28.21 (CH_2Br), 41.60 (CH_2N), 61.56 (CH_2O), 166.36 (CONH) and 169.22 (Found: C, 31.8; H, 4.50; N, 6.10. $C_6H_{10}BrNO_3$ requires: C, 32.0; H, 4.44; N, 6.22%). The ligands **3–8** were prepared by very similar routes and representative procedures are given below.

7,16-*Bis*(*ethoxycarbonylmethylcarbamoylmethyl*)-1,4,10,13-*tetraoxa*-7,16-*diazacyclooctadecane* (**8**). To a solution of 4,7,10,13-tetraoxa-1,10-diazacyclooctadecane (0.42 g, 1.60 mmol) in dry acetonitrile (25 cm^3) was added potassium carbonate (0.50 g, 3.62 mmol), sodium iodide (0.5 g, 3.33 mmol) and ethyl *N*-(2-bromoethanoyl)glycinate (0.76 g, 3.41 mmol). The mixture was then heated to reflux for 72 h when it was filtered, the residue washed with dichloromethane (2 × 15 cm^3), and the solvent removed to yield a pale yellow residue. Dichloromethane (20 cm^3) was added and the mixture passed through a small bed of alumina under suction, washing with methanol (2 × 10 cm^3). The solvent was then removed under reduced pressure to yield a residue which was purified by chromatography on neutral alumina, eluting with dichloromethane–methanol (7%) (R_f = 0.55) to give a white crystalline solid, 600 mg (68%) m.p. 108–111 °C; $\delta_H(CDCl_3)$ 1.26 (6 H, t, CH_3C), 2.81 (4 H, m, CH_2N), 3.17 (4 H, s, CH_2CO), 3.47 (16 H, m, CH_2O ring), 4.08 (4 H, d, CH_2CO), 4.16 (4 H, q, CH_2CO arm) and 8.22 (2 H, br s, NH); $\delta_C(CDCl_3)$ 14.2 (CH_3C), 41.4 (CH_2NH), 56.5, 57.8 (CH_2N), 60.8, 68.8, 70.4 (CH_2O), 170.0 (amide CO) and 172.6 (ester C=O); ν_{max}(Nujol)/cm^{-1} 3600–3100 (NH stretch), 1749 (ester CO), 1670 (C=O) and 1540 (NH, bend); m/z (CI, chloroform) 549 (M^+ + 1, 29%), 548 (M^+, 100%), 406 [M^+ − (CONHCH$_2$COOEt + 2)], 146 (13%) and 133 (32%) (Found: C, 52.8; H, 8.2; N, 9.90. $C_{24}H_{44}N_4O_{10}$ requires C, 52.5; H, 8.18; N, 10.2%).

7,16-*Bis*(*methylcarbamoylmethyl*)-1,4,10,13-*tetraoxa*-7,16-*diazacyclooctadecane* (**7**). To a solution of 4,7,13,16-tetraoxa-1,10-diazacyclooctadecane (0.65 g, 2.48 mmol) in dry acetonitrile (25 cm^3) was added potassium carbonate (0.76 g, 5.51 mmol), sodium iodide (0.78 g, 5.20 mmol) and *N*-methyl-2-bromoethanamide (0.79 g, 5.23 mmol). The mixture was then heated to reflux for 72 h. The mixture was filtered, the residue washed with dichloromethane (2 × 15 cm^3), and the solvent removed to yield a residue. Dichloromethane (20 cm^3) was added to the residue and the mixture passed through a small bed of alumina under suction, washing with methanol (2 × 10 cm^3). The solvent was then removed under reduced pressure to yield a residue which was purified by chromatography on neutral alumina, eluting with dichloromethane–methanol (7%) (R_f = 0.52) to give a yellow crystalline solid, 710 mg (71%). M.p. 118–122 °C; $\delta_H(CDCl_3)$ 2.76–2.85 (14 H, m, CH_2N + CH_3N), 3.15 (4 H, s, CH_2CO), 3.48–3.65 (16 H, m, CH_2CO) and 7.95 (2 H, broad s, NH); $\delta_C(CDCl_3)$ 25.7 (CH_3N), 56.2, 58.3 (CH_2N), 68.9 and 70.5 (CH_2O) and 172.1 (C=O); ν_{max}(KBr disc)/cm^{-1} 3340–3040 (NH stretch), 1670 (C=O) and 1540 (NH bend); m/z (CI, chloroform) 406 [M^+ −(CH$_2$CONHMe + 2), 23%] and 74 (31%) (Found: C, 53.2; H, 9.2; N, 13.5. $C_{18}N_{36}N_4O_6$ requires: C, 53.4; H, 9.0; N, 13.8%).

7,13-*Bis*(*ethoxycarbonylmethylcarbamoylmethyl*)-1,4,10-*trioxa*-7,13-*diazacyclopentadecane* (**6**). R_f = 0.64 [CH_2Cl_2–MeOH (7%)]; m.p. 85–86 °C; $\delta_C(CDCl_3)$ 14.2 (Me), 41.0 (CH_2NH), 56.2, 56.4, 59.0 (CH_2N), 60.8, 68.3, 69.7 (OCH_2), and 170.0 and 172.6 (C=O); $\delta_H(CDCl_3)$ 1.27 (6 H, t, CH_3), 2.77 (8 H, m, CH_2N), 3.20 (4 H, s, NCH_2CON), 3.47–3.55 (12 H, m, CH_2O), 4.04 (4 H, d, NCH_2CO), and 8.32 (2 H, t, NHCO); ν_{max}(Nujol)/cm^{-1} 3350–3050 (NH stretch), 1746 (ester CO), 1670 (C=O) and 1540 (NH bend); *m*/*z* (CI, $CHCl_3$) 505 (M^+ + 1, 27%), 504 (M^+, 100%), 362 (M^+ − $CONHCH_2COOEt$ + 2, 38%), 146 (12%) and 133 (32%) (Found: C, 53.1; H, 8.05; N, 10.75. $C_{22}H_{40}N_4O_9$ requires: C, 52.4; H, 8.0; N, 11.1%).

7,13-*Bis*(*methylcarbamoylmethyl*)-1,4,10-*trioxa*-7,13-*diazacyclopentadecane* (**5**). R_f = 0.54 [CH_2Cl_2–MeOH (7%)]; oil, $\delta_H(CDCl_3)$ 2.73 (8 H, t, CH_2N), 2.77 (6 H, d, CH_3N), 3.10 (4 H, s, CH_2CO), 3.77–3.93 (8 H, m, CH_2O) and 8.03 (2 H, br s, NH); $\delta_C(CDCl_3)$ 26.4 (CH_3N), 57.2, 57.1 and 60.5 (CH_2N), 69.3, 70.1 (CH_2O) and 173.0 (C=O); ν_{max}(Nujol)/cm^{-1} 3600–3100 (NH stretch), 1670 (C=O) and 1545 (NH bend); *m*/*z* (CI, chloroform) 361 (M^+ + 1, 100%) and 290 (M^+ − $CCH_2CONHMe$ + 1, 16%) (Found: 360.2379. $C_{16}H_{32}N_4O_5$ requires: 360.2373).

4,10-*Bis*(*ethoxycarbonylmethylcarbamoylmethyl*)-1,7-*dioxa*-4,10-*diazacyclododecane* (**4**). R_f = 0.61 [CH_2Cl_2–MeOH (7%)]; m.p. 173–175 °C; $\delta_H(CDCl_3)$ 1.27 (t, 6 H, CH_3), 2.75 (t, 8 H, CH_2N), 3.24 (s, 4 H, CH_2CO), 3.64 (t, 8 H, CH_2O), 4.00 (d, 4 H, CH_2NH), 4.18 (q, 4 H, OCH_2) and 8.54 (t, 2 H, NH); $\delta_C(CDCl_3)$ 14.65 (CH_3), 41.42 (CH_2NH), 56.48 (CH_2N), 59.69 (CH_2CO), 61.63 (OCH_2), 69.40 (ring CH_2O), 170.29 (amide CO) and 172.63; *m*/*z* (DCI) 461 (M^+ + 1, 100%), 460 (M^+, 99%), 318 (M^+ − 143, 26%); ν_{max}(Nujol)/cm^{-1} 3310 (NH), 1750 (ester (CO), 1660 (amide CO) and 1530 (NH bend) (Found: C, 51.9; H, 7.95; N, 12.0. $C_{20}H_{36}N_4O_8$ requires: C, 52.2; H, 7.83; N, 12.2%).

4,10-*Bis*(*methylcarbamoylmethyl*)-1,7-*dioxa*-4,10-*diazacyclododecane* (**3**). R_f = 0.55 [CH_2Cl_2–MeOH (7%)]; m.p. = 146–147 °C; $\delta_H(CDCl_3)$ 2.69–2.76 (14 H, m, CH_2N + CH_3N), 3.19 (4 H, s, CH_2CO), 3.55 (8 H, t, CH_2O) and 8.10 (2 H, br s, NH); $\delta_C(CDCl_3)$ 25.50 (CH_3N), 54.38 (CH_2N), 58.49 (CH_2N), 67.31 (CH_2O) and 170.2 (CONH); *m*/*z* (DCI) 319 (M^+ + 1, 100%), 318 (M^+, 96%), 258 (M^+ − CONHMe, 90%); ν_{max}(Nujol)/cm^{-1} 3320 (N–H), 1670 (CO) and 1540 (NH bend) (Found: C, 53.5; H, 9.00; N, 17.4. $C_{14}H_{28}N_4O_4$ requires: C, 53.1; H, 8.92; N, 17.7%).

Acknowledgements

We thank the SERC for support.

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Paper 2/01931K
Received 13*th April* 1992
Accepted 11*th May* 1992