Synthesis, Conformation and Equilibrium Study of New Piperazine and Azamacrocyclic Ligands with *N*-(Tetrahydro-2-oxofuran-3-yl) and *N*-[(Carboxy)(2-hydroxyethyl)methyl] Pendant Arms

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New piperazine (**1**), homopiperazine (**2**), 1-tosyl-1,4,7-triazacyclononane (**3**), 1,4,7-triazacyclononane (**4**), and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**5**) derivatives **1a**–**5a** with 2-oxotetrahydrofuran-3-yl pendant arms have been synthesized from the parent cyclic polyamines **1**–**5** and 2-bromobutyrolactone in acetonitrile. Their conformational properties have been studied by molecular mechanics and NMR spectroscopy, and new sets of Karplus parameters for calculation of the vicinal coupling constants of the butyrolactone moieties have been determined. Compounds **1a**–**5a** were hydrolysed to (carboxy)(2-hydroxyethyl)methyl derivatives **1b**–**5b** by treatment with aqueous sodium hydroxide. The protonation and complexation properties of **4b** (HOETNOTA) were studied by pH potentiometry, photometry, and ^{1}H NMR titrations, and the results were compared with the corresponding values for NOTA. It was found that, although complexation of **4b** with smaller metal ions was approximately two orders of magnitude weaker, its stability constants with the lanthanides remained unchanged.

Introduction

γ-Butyrolactone shows advantageous biological activity in humans as a sedative and painkiller, with fairly low toxicity.[1] Synthetic and semisynthetic derivatives can be found in pharmaceuticals[2] or as aroma components in the food industry (jasmolactone).[3] Basic hydrolysis of the γ-butyrolactone ring results in γ-hydroxybutyric acid salts, the most widely known representative of which is γ-hydroxybutyrate or GHB, a mild sedative and painkiller.[4] Hydrolysis of the lactone ring can be promoted by several types of endogenous enzymes to deliver derivatives containing hydroxybutyric acid moieties in vivo.[5,6]

Piperazines and homopiperazines are widely used in the pharmaceutical industry as key building blocks in many drugs that target several types of health problems, from hypertension through mood disorders to systemic mycosis.[2,7] New complexing agents containing crown ether and piperazine subunits have been developed and their equilibrium and complexing properties thoroughly studied.[8] Recent studies of piperazine and homopiperazine derivatives revealed that the compounds, besides displaying the expected bridge-like coordination mode with the chair conformation in the piperazine ring, also form "macrocycle-like" complexes with transition metal ions in which the piperazine ring adopts a boat conformation and both nitrogen atoms are coordinated to the same metal ion.[9,10] Both their potential pharmacological activity and their interesting complexing properties made the newly synthesized derivatives **1a**−**2b** selected targets for further coordination chemistry examination.

So far a significant number of new polyaza- and polyoxa-polyazamacrocyclic derivatives has been synthesized and studied. One of the main driving forces behind the interest in them was to find more effective magnetic resonance imaging (MRI) contrast agents for medical diagnosis.[11−15] Now, however, other applications have also emerged; these include the fabrication of highly metal ion selective electrodes,[16] the removal of toxic and radioactive metal ions from the human body,[17] determination of intracellular metal ion concentrations,[18] potential applications of luminescent macrocyclic complexes in bioanalytics,[19−22] and others.

Results and Discussion

Our interest in the preparation, characterization and biomedical applications of new complexing agents led us to the synthesis of enzymatically hydrolysable derivatives of macrocyclic polyaminopolycarboxylates and their analogues capable of being loaded into living cells for diagnostic purposes.[23] In this paper we report the synthesis of the first representatives of these − namely a series of new piperazine, homopiperazine and macrocyclic derivatives

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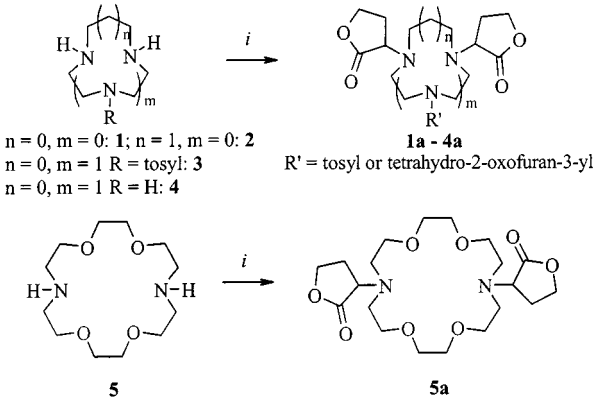
containing butyrolactone (tetrahydro-2-oxofuran-3-yl; **1a−5a**) rings − and their hydrolysis to afford derivatives with (2-hydroxyethyl)acetate [(carboxy)(2-hydroxyethyl)methyl; **1b−5b**] pendant arms and their conformational features, protonation constants, metal ion selectivity and binding properties.

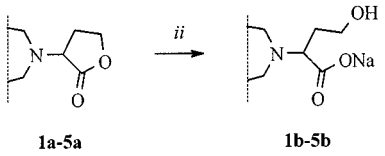
Synthesis

Piperazines and macrocycles containing tetrahydro-2-oxofuran-3-yl (butyrolactone) rings (**1a−5a**) served as intermediates in the synthesis of derivatives with (2-hydroxyethyl)acetyl pendant arms. Compounds **1a−5a** were synthesized from the parent cyclic polyamines [piperazine (**1**), homopiperazine (**2**), 1-tosyl-1,4,7-triazacyclononane (**3**), 1,4,7-triazacyclononane (**4**), and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**5**)] and 2-bromo-γ-butyrolactone in anhydrous media in the presence of ethyldiisopropylamine as a non-nucleophilic base (Scheme 1). The high toxicity of benzene, used[24] in previous syntheses of secondary monoamines containing butyrolactone rings, prompted us to examine the application of other, less toxic, dipolar aprotic solvents. Acetonitrile was found to be an appropriate solvent for this reaction, although dimethyl formamide (DMF) was also tested. In this latter case, however, the high boiling point of DMF was a disadvantage during its removal and the yields were quite low, due to the increased production rate of so far unidentified side reactions, and the products required further purification by extraction and column chromatography.



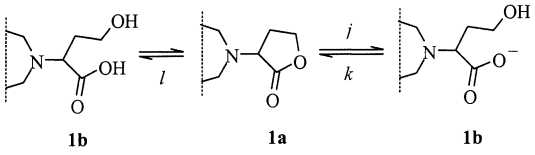
Scheme 1. Synthesis of cyclic polyamine derivatives **1a−5a** with *N*-(tetrahydro2-oxofuran-3-yl pendant arms: *i*: γ-bromobutyrolactone, DIPEA, CH_3CN, room temperature, 1−3 d

The lactone rings were then hydrolysed in nearly quantitative yields to the corresponding sodium salts **1b−5b**, with stoichiometric amounts of aqueous sodium hydroxide (Scheme 2). In these macrocycles, with (carboxy)(2-hydroxyethyl)methyl pendant arms, the presence of at least two alcoholic hydroxy groups increased the water solubility of the complexes, while the presence of the additional hydroxy donor sites, which were, as expected, capable of deprotonation even in aqueous solutions,[25,26] opened further possibilities for coordination and complex stabilization.



Scheme 2. Schematic representation of the hydrolysis of **1a−5a** to **1b−5b**: *ii*: $NaOH/H_2O$, 25 °C 1−3 h, or reflux for 1 d

To find appropriate conditions for pH-potentiometric studies of the protonation and complex formation properties of macrocycles with (carboxy)(2-hydroxyethyl)methyl pendant arms, we examined the rate of relactonisation by ^1H NMR spectroscopy; both lactone and open-chain derivatives of piperazine (**1a** and **1b**, respectively; Scheme 3) were used as models. It was found that no detectable ring-closure occurred at pH = 2 or above on the normal timescales and pH ranges of standard potentiometric titrations. In very acidic solutions [i.e., in DCl/D_2O (1:10)], however, approximately 40% lactonisation of the (hydroxyethyl)acetate arms of **1b** took place in 1 h, as estimated from the intensity ratios of the corresponding peaks in the ^1H NMR spectrum of the equilibrium mixture. Experiments with pure lactone **1a** under identical conditions resulted in the same equilibrium mixture.



Scheme 3. Lactone/hydroxy acid equilibrium in aqueous solutions of **1a** and **1b**: *j*: strong base; *k*: acidic solution, pH < 2; *l*: very acidic solution, pH ≈ 0

Conformational and NMR Studies

In solution, provided that the substituents can rotate freely and the molecule is flexible enough, a virtual C_{2v} or C_{3v} symmetry is in general characteristic of symmetrically per-*N*-substituted derivatives of polyamines **1**, **4**, and **5**. Because of rapid intramolecular movements, nitrogen inversion, and symmetry considerations, highly symmetric ^1H NMR resonances were expected for the central macrocyclic or piperazine methylene protons. However, compounds **1a−5a** showed fairly complicated and strongly coupled multiplets, indicating that the molecular symmetry was for some reason quite low. In order to determine the structures of the lactone rings and to examine the possibility of rotation within the molecules, several NMR techniques were used and molecular mechanics calculations were performed. The ^1H NMR spectra of **1a−5a** were so complicated that individual $^3J_{H,H}$ coupling constants had to be determined by interactive computer simulation of the entire strongly coupled five-spin system. The values of the experimental coupling constants, along with the calculated coupling con-

Table 1. Experimental and calculated scalar coupling constants [Hz] in the equatorial and axial conformers of the lactone ring of molecules **1a−5a**; MM+ calculated torsion angles are included in parentheses

Equatorial conformer[a]		$^3J_{12}$	$^3J_{13}$	$^3J_{24}$	$^3J_{25}$	$^3J_{34}$	$^3J_{35}$	$^2J_{23}$	$^2J_{45}$
1a	exp.	8.6	10.8	6.4	1.6	10.4	9.6	12.9	9.2
	calcd.	6.0	10.2	7.5	1.6	9.8	8.6	–	–
	φ	(36.53)	(159.64)	(30.98)	(94)	(151.25)	(26.27)	–	–
2a	exp.	8.4	10.9	6.5	1.4	10.5	8.9	12.9	9.2
	calcd.	6.5	10.1	7.8	1.6	9.8	8.8	–	–
	φ	(34.62)	(157.21)	(29.59)	(95.31)	(150.07)	(25.18)	–	–
3a	exp.	8.4	11.4	6	1.8	10.5	8.9	12.7	9.2
	calcd.	6.7	10.1	7.9	1.6	9.8	8.9	–	–
	φ	(34)	(156.34)	(29.32)	(95.62)	(149.87)	(24.94)	–	–
4a	exp.	8.4	11.4	6	1.8	10.5	8.9	12.9	9.2
	calcd.	6.1	10.2	7.5	1.6	9.8	8.7	–	–
	φ	(36.12)	(159.09)	(30.65)	(94.36)	(150.94)	(25.93)	–	–
5a	exp.	8.9	11.1	6.5	1.4	10.3	9.6	13.0	9.0
	calcd.	7.3	9.9	8.2	1.7	9.7	9.4	–	–
	φ	(31.69)	(153.08)	(28.07)	(96.94)	(147.51)	(22.51)	–	–
Axial conformer[a]		$^3J_{12}$	$^3J_{13}$	$^3J_{24}$	$^3J_{25}$	$^3J_{34}$	$^3J_{35}$	$^2J_{23}$	$^2J_{45}$
1a	exp.	10.8	8.6	9.6	10.4	1.6	6.4	12.9	9.2
	calcd.	10.6	8.5	9.6	10.1	1.7	8.3	–	–
	φ	(15.36)	(105.6)	(21.27)	(146.4)	(97.21)	(27.45)	–	–
2a	exp.	10.9	8.4	8.9	10.5	1.4	6.5	12.9	9.2
	calcd.	11.0	8.6	9.9	10.0	1.8	8.7	–	–
	φ	(12.61)	(108.21)	(19.97)	(144.58)	(99.03)	(25.57)	–	–
3a	exp.	11.4	8.4	8.9	10.5	1.8	6	12.7	9.2
	calcd.	10.4	8.5	9.7	10.0	1.7	8.6	–	–
	φ	(16.9)	(103.11)	(20.58)	(145.24)	(98.33)	(26.33)	–	–
4a	exp.	11.4	8.4	8.9	10.5	1.8	6	12.9	9.2
	calcd.	10.4	8.5	9.8	10.0	1.7	8.6	–	–
	φ	(16.85)	(103.07)	(20.2)	(144.83)	(98.67)	(25.97)	–	–
5a	exp.	11.1	8.9	9.6	10.3	1.4	6.5	13.0	9.0
	calcd.	11.1	8.6	10.6	9.7	2.1	9.7	–	–
	φ	(11.49)	(108.26)	(15.08)	(139.57)	(103.75)	(20.75)	–	–

[a] Reported ranges of the coupling constants determined for a variety of butyrolactone and homoserine derivatives are as follows: $^3J_{12}$ = 7.16−9.1, $^3J_{13}$ = 8.13−12.8, $^3J_{24}$ = 5.53−7.67, $^3J_{25}$ = 0−3.64, $^3J_{34}$ = 8.35−11.75, $^3J_{35}$ = 7.5−9.08, $^2J_{23}$ = 12.4−13.4, $^2J_{45}$ = 8.8−9.16, refs.[27−32]

stants and the torsion angles for the lactone rings, in **1a−5a** are listed in Table 1.

Neither DQF-COSY nor TOCSY spectra (Figure 1) of **5a** revealed long-range or through-space coupling between the protons of the cyclic polyamines and the lactone rings. However, ROESY spectra indicated a close proximity of the macrocyclic and the lactone hydrogen atoms; in the absence of a reliable internal standard no accurate measurement of interatomic distances were carried out (Figure 2). Although no long-range coupling was observed for **5a**, there were minor time-dependent changes between the spectra of freshly synthesized and stored samples, which could be the result either of slow conformational change or intramolecular interaction with non-lactone spins and further study of this might be merited in the future.

The lowest-energy structures of **1a−5a** were determined by molecular mechanics calculations with MM+ and Amber94 force fields. As had been expected, these molecules exist in a number of low-energy, energetically very similar structures. Interestingly, in their lowest-energy conformers one (or two, in **4a**) of the lactone rings adopts a quasi-equatorial conformation and one a quasi-axial conformation (Figure 3), in spite of the fact that the ring energy of the axial lactone conformer is approximately 1.0 kcal/mol higher.

We determined the height of the rotational energy barriers for both lactone conformers in each molecule. It was found that the axial conformer has one global maximum, and the equatorial conformer two, calculated for **1a** as 12−14 kcal/mol value (Figure 4a). The height of the energy barrier increases with the size of the central polyamine and is high enough to prevent free rotation of the lactone rings at room temperature. This is probably one of the most important factors, perhaps the most important factor, resulting in the magnetic non-equivalence of the piperazine ring methylene protons and hence lower molecular symmetry, complicated NMR spectra and the appearance of geminal and axial-equatorial couplings.

As both the C^3 and the C^4 atoms were reported in the literature to be in the out-of-plane orientation,[27,30,33] mo-

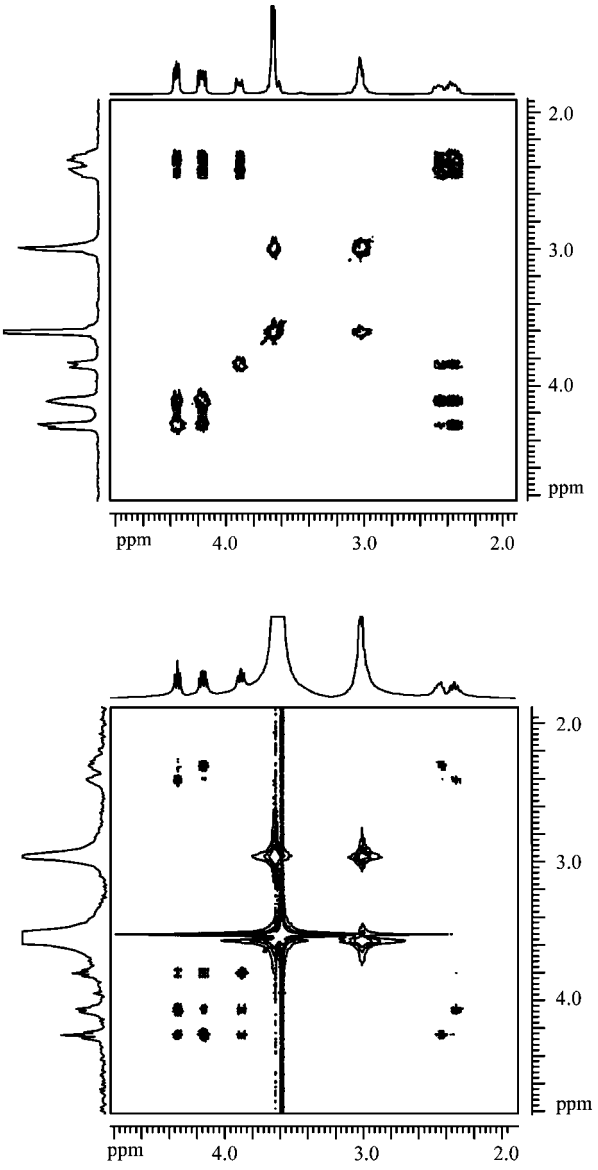


Figure 1. DQF-COSY and TOCSY spectra of **5b** show no coupling between the hydrogen atoms of the lactone rings and the central macrocycle ring

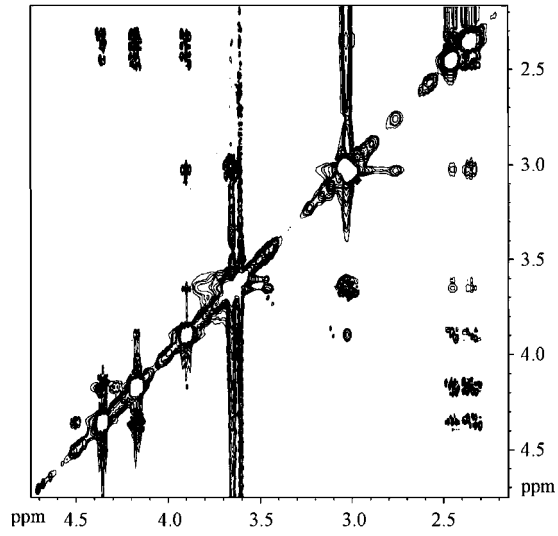


Figure 2. ROESY spectrum of **5b** indicates that macrocyclic and lactone ring protons are in close proximity in $CDCl_3$ solution

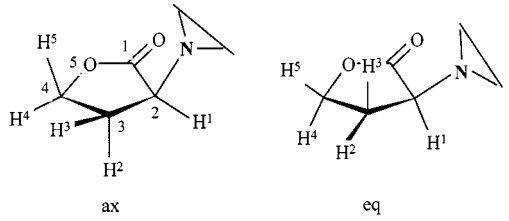


Figure 3. Numbering of the lactone ring and representations of the ring conformations associated with quasi-axial-N (ax) and quasi-equatorial-N (eq) positions of the connecting cyclic nitrogen atom

lecular mechanics calculations were performed to find the most stable conformations and the actual position of the plane of the lactone rings in **1a−5a**. It was found that the lactone ring could adopt two stable conformations of envelope type, in which the connecting nitrogen atom could be in either a quasi-equatorial or a quasi-axial position (Figure 3). Use of the MM+ force field resulted in structures in which the C^3 methylene group was flipped either over or below the $C^4-O^5-C^1-C^2$ plane. The values of the $C^4-O^5-C^1-C^2$ torsion angles in all derivatives and conformers were in the $\pm 5°$ range. In the equatorial conformer, both the nitrogen and the C^3 atoms were on the same side of the plane, while in the axial conformer they were positioned on opposite sides of the plane. When the value of the $O^5-C^1-C^2-N$ torsion angle was below approximately 120°, the conformer could be considered as quasi-axial and above 130° as quasi-equatorial. If the calculations were performed for a box containing 70 water molecules, the result was virtually the same as in vacuum. The Amber94 force field gave a different structure for the quasi-axial conformer, in which the plane of the lactone ring consisted of atoms $O^5-C^1-C^2-C^3$ and atom C^4 was found to be in the out-of-plane position. In both conformers, the connecting nitrogen atom and either C^3 or C^4 were on the same side of the lactone plane. In addition, it was possible in two of the five cases examined to observe a special twisted axial conformation of the lactone ring, in which the values of the $O^5-C^1-C^2-C^3$ and $C^4-O^5-C^1-C^2$ torsion angles were equal and the $O^5-C^1-C^2-N$ torsion angle was below 110° (Table 2).

The question emerged of whether the equatorial and axial conformers could be converted into one another at room temperature. Homoserine lactone was used as a model compound to determine the energy barrier of the conformational change. We calculated the ring energies of several conformers with restrained $O^5-C^1-C^2-N$ torsion angles, and the results are plotted in Figure 4b. The energy barrier was found to be 1.4 kcal/mol, which is fairly low, and so the axial-equatorial transition can take place readily. We assume that there is no significant difference in the transition of the lactone conformers in **1a−5a**; thus, although

free rotation is not possible, the lactone rings are probably oscillating back and forth between the two sides of the highest rotational energy barrier. This oscillation may result in the non-equivalence of the neighbouring macrocyclic methylene groups but does not give rise to complete rigidity of the structure. This is shown well by the quasi-triplet and singlet structures of the $O-CH_2$ protons in **5a**, which would be observed only if the flexibility of this part of the ring were high enough on the NMR timescale.

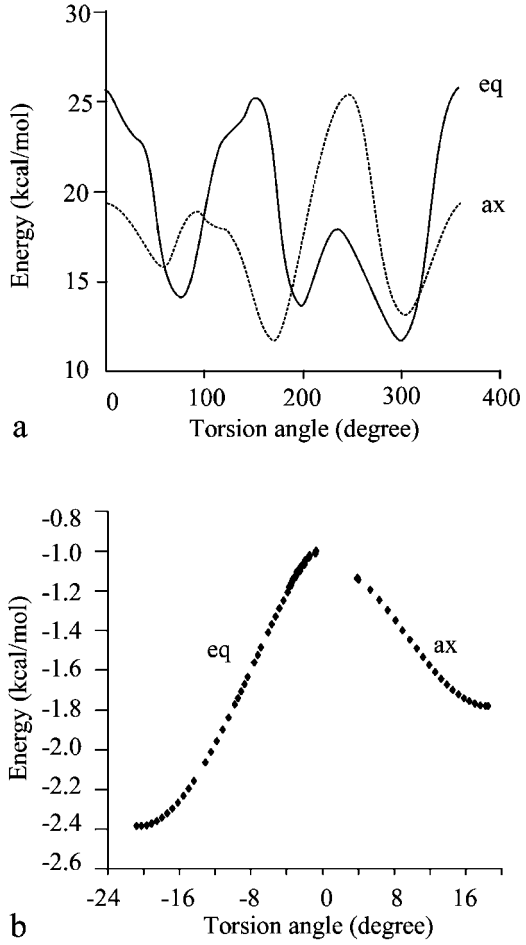


Figure 4. a) Rotational energy of the lactone rings versus $H^{\gamma}-C^{2}-N-C_{ring}$ torsion angle in the lowest energy conformation of **1a**; b) conformational energy versus $O^{5}-C^{1}-C^{2}-C^{3}$ torsion angle calculated for the equatorial-axial transition in homoserine lactone as a model system using the MM+ force field

When the role of hindered rotation in the NMR spectra is considered, it is important to take the effect of at least two chiral centres in lactone derivatives **1a−5a** into account. If the non-equivalence of the azacycle methylene groups were merely a consequences of the presence of the chiral centres, similar behaviour would probably have been observed for **1b−5b** derivatives. The ^{1}H NMR spectra of **2b−5b** in general show pH-sensitive, variable multiplet systems; however, **1b** possesses a broad singlet for piperazine methylene groups, very probably because of rapid rotation of the pendant arms on the NMR timescale. This observation suggests the conclusion that the chiral centres of the lactone rings in **1a−5a** may give rise to non-equivalence of the azacyclic nitrogen atoms, but they do not necessarily have to. Hindered rotation of the lactone rings in **1a−5a** itself may itself, however, also result in the non-equivalence mentioned above.

Coupling Constants

Several papers and formulae on the values of scalar $^{3}J_{H,H}$ coupling constants and the structure of lactone rings have been published.[28,30,32,34,35] Although recent seven- and eight-parameter calculation methods can predict coupling constants with fairly high accuracy for a wide range of compounds,[36] the modified Karplus[37,38] Equation (1) is still used in the determination of molecular conformations.[39,40] Since conformational data from molecular mechanics calculations and values of the experimental scalar coupling constants were available, we set out to find the parameters of the Karplus equation characteristic for this class of compounds for future conformational studies.

$$J = A\cdot\cos^2\varphi + B\cdot\cos\varphi + C \quad (1)$$

As Equation (1) cannot take account of substituent effects and the asymmetry of the $^{3}J/\varphi$ function around 90°,

Table 2. Molecular mechanics calculations of $C^{4}-O^{5}-C^{1}-C^{2}$ (φ_1), $O^{5}-C^{1}-C^{2}-C^{3}$ (φ_2) and $O^{5}-C^{1}-C^{2}-N$ (φ_3) torsion angles using MM+ and Amber94 force fields and conformations of the lactone rings in molecules **1a−5a** (eq = quasi-equatorial, ax = quasi-axial)

Compound	MM+			Conformation	Amber94			Conformation
	φ_1	φ_2	φ_3		φ_1	φ_2	φ_3	
1a	1.36	18.11	143.31	eq	5.44	12.44	133.30	eq
	0.88	13.27	113.17	ax	10.91	10.59	106.85	twisted ax
2a	1.36	17.26	143.85	eq	5.81	12.01	132.73	eq
	0.62	12.10	114.45	ax	12.75	5.75	114.79	ax
3a	1.32	17.10	143.23	eq	5.18	13.68	134.81	eq
	1.67	13.62	110.95	ax	13.90	2.15	118.73	ax
4a	1.15	17.52	146.28	eq	5.24	13.86	135.26	eq
	4.71	23.67	144.61	eq	5.51	13.74	135.50	eq
	2.18	13.91	110.70	ax	14.06	0.60	123.14	ax
5a	0.60	15.64	138.97	eq	5.02	13.72	135.56	eq
	1.61	10.56	113.09	ax	10.50	11.01	109.21	twisted ax

two sets of parameters are generally determined, one for the small and near diagonal and the other for wide angles. Surprisingly, fitting of our data by the least-squares method resulted in three sets of parameters; coupling constants for near diagonal angles could not be calculated at acceptable accuracy either with small or with wide angle parameters. Parameter values were found as follows: $\varphi < 80°$: $A = 13.64$, $B = 4.66$, $C = -6.57$; $\varphi = 80°-100°$: $A = 9.5$, $B = -0.15$, $C = 1.51$; $\varphi > 100°$: $A = 4.69$, $B = 2.45$, $C = 8.86$.

The calculated (MM+) and experimental coupling constants, as well as the calculated torsion angles, are listed in Table 1. The fit of the calculated and the experimental values near to and above 90° is good, especially if we take the ±0.3 Hz error level of the experimental coupling constants into account, but significant differences can be observed for smaller torsion angles. This deviation is probably the consequence of the continuous movement of the lactone rings, resulting in a time-averaged value of the torsion angles. We have attempted to use the extended Karplus equation including sine terms[41,42] but no significant improvement in the accuracy was observed and the number of available data was too low for reliable calculations.

Protonation and Complex Formation

Protonation constants were determined by a pH-potentiometric titration cycle, which was performed from basic to acidic medium and then, with the same solution, back from acidic to basic. As these runs gave identical results backwards and forwards, it meant that no lactonization had taken place at 25 °C and that the protonation constants and metal ion stability constants of ligands containing (2-hydroxyethyl)acetate pendant arms can hence be determined by pH-potentiometric techniques (Figure 5); this conclusion was also supported by NMR examinations as mentioned above. All potentiometric measurements were carried out with the same standardized stock solution of **4b** and each sample was acidified with a known amount of standardized hydrochloric acid solution immediately before the beginning of the titration. Protonation and metal ion complex stability constants were calculated by the PSEQUAD computer program.[43]

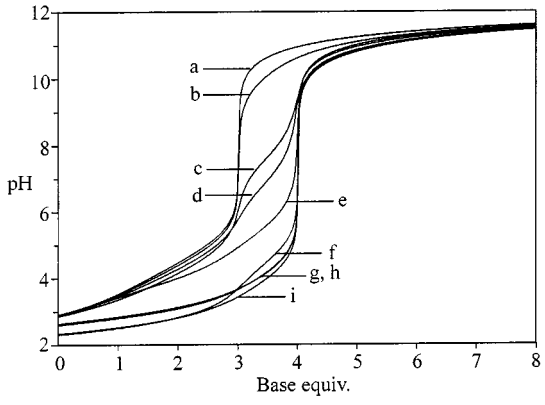


Figure 5. pH-potentiometric titration curves of the free ligand **4b** and its metal ion complexes as functions of added base equivalents: a: free ligand; b: Sr^{2+}; c: Ca^{2+}; d: Mg^{2+}; e: Mn^{2+}; f: Cu^{2+}; g: Cd^{2+}; h: Pb^{2+}; i: Zn^{2+}

As shown in Table 3, pH potentiometry and NMR titrations produced virtually the same results; because of the nature of the techniques and the number of available data points, however, the error level of the latter was higher. On comparison of the protonation constants of **4b** (HOET-NOTA) with the values for NOTA (NOTA = 1,4,7-triazacyclononane-1,4,7-triacetic acid), it can be seen that the first protonation constant remained virtually unchanged on substitution of the acetate pendant arms with (2-hydroxyethyl)acetate arms, and this step obviously represented the protonation of the triazacyclononane ring. If we take into account that the ionic strength of the sample during NMR titration was low and not kept constant, these results are in excellent agreement with potentiometric data. The second protonation constant is somewhat lower and, as a consequence, the plateau of the NMR titration curve around physiological pH values became wider than that observed with NOTA. The third protonation step may correspond to the two ring nitrogen atoms or to the carboxylate groups. During the fourth step, a rearrangement of the triazacyclononane ring conformation and a virtual shift of the proton density from the nitrogen atoms towards the carboxylate groups occurs; this is indicated by the local minimum of the CH_c chemical shift at pD ≈ 2.0−2.3 (Figure 6).

The coordination tendencies of NOTA and of **4b** (HOET-NOTA) (Figure 7) show very similar trends, as would be expected if the nature and electrical charges of the donor sites were taken into account. However, **4b** (HOET-NOTA) binds metal ions in M−L and M−HL complexes

Table 3. Protonation constants of the free ligand **4b** (HOET-NOTA) determined by pH potentiometry and ^{1}H NMR techniques, in comparison with the corresponding values for NOTA (n.a. = not available)

	4b (HOET-NOTA)[a]	4b (HOET-NOTA)[b]	NOTA[c]	NOTA[d]	NOTA[e]
$\log K_1$	11.64 (0.020)	10.71 (0.1)	11.73	10.77	11.3 (0.1)
$\log K_2$	4.92 (0.025)	4.87 (0.1)	5.74	6.03	5.59 (0.02)
$\log K_3$	3.96 (0.024)	4.03 (0.1)	3.16	3.16	2.88 (0.02)
$\log K_4$	2.66 (0.022)	2.68 (0.1)	n.a.	1.96	n.a.
$\log K_5$	n.a.	1.15 (0.1)	n.a.	n.a.	n.a.

[a] This work, determined by pH potentiometry, 0.1 M KNO_3, 25 °C, protonation constants are defined as follows (HOET-NOTA^{3-} = L^{3-}): $K_i = [LH_i^{i-3}]/[LH_{i-1}^{i-4}][H_3O^+]$. [b] This work, determined by ^{1}H NMR titration, ionic strength was not kept constant, in the presence of sodium ions. [c] Ref.[45], 1.0 M $NaClO_4$, 25 °C. [d] Ref.[45], 0.1 M $NaNO_3$, 25 °C. [e] Ref.[46], 0.1 M $NaClO_4$, 25 °C.

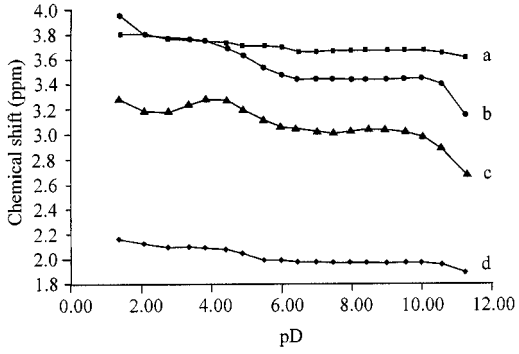


Figure 6. ^{1}H NMR titration curve of **4b** (HOET-NOTA): a: CH_2OH: b: CH: c: NCH_2C: d: CHCH_2C

approximately two orders of magnitude more weakly than NOTA does, probably because of the mutual steric hindrance of the 2-hydroxyethyl side arms (Table 4). Since each (2-hydroxyethyl)acetate function contains a chiral centre, special steric arrangement of the pendant arms would be required for optimal coordination. Among the hard alkaline earth metal ions, the most stable complex is formed with the smallest (magnesium) ion; the stabilities of the ML complexes in this series decrease nonlinearly with increasing size of the metal ion.

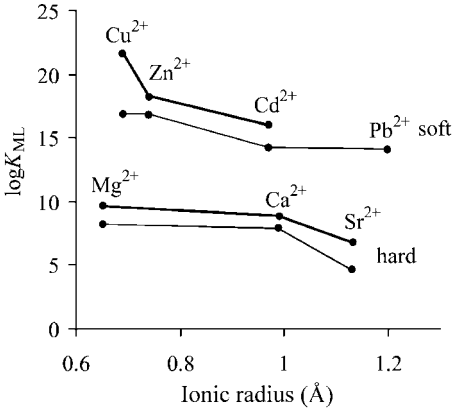


Figure 7. Plot of logK_{ML} stability constants of complexes with divalent metal ions for **4b** (HOET-NOTA) and NOTA versus ionic radius of the metal ions; thick line: NOTA; thin line: **4b**

Soft metal ions such as copper(II), zinc(II), cadmium(II), and lead(II) prefer nitrogen donors; thus, they coordinate primarily to the ring nitrogen atoms and only secondly to the pendant oxygen donor arms. Since mono- and diprotonated species contain ligands protonated at the ring nitrogen atoms, strong binding to the ring nitrogen atoms results in a lack of mono- and diprotonated complexes. On the other side, oxygenophilic alkaline earth metal ions can form even diprotonated complexes, which are still stable enough to be detected. Here, pendant arms with oxygen donor atoms take a relatively greater share from the complex stability constants.

Alcoholic hydroxy groups are very weak donors in their neutral forms, but can coordinate to the metal ions when they are deprotonated. This deprotonation may be promoted by the presence of both a metal ion and an advantageous coordination environment. In the case of **4b** complexes, the logK_{MLO-H} protonation constants found for the alkoxide group of the [MLO]$^-$ species are very high, which means that these complexes are very weak. Since no size dependence of this constant on the metal ion side can be observed, this process seems to be independent of the size selectivity of the macrocycle. In the cases of strontium, copper and zinc ions, no hydroxy coordination was observed. Cerium(III) and gadolinium(III) ions showed the same logK_{ML} stability constants with both HOET-NOTA and NOTA, indicating that the effect of the 2-hydroxyethyl moieties was negligible here, probably because of the larger metal ion size and the variable coordination number.

All of these observations show that, although complexing agents containing (2-hydroxyethyl)acetate pendant arms may be less effective for smaller macrocycles and smaller metal ions, larger macrocyclic derivatives show the same coordination properties with f-group metal ions as the corresponding (carboxy)methyl derivatives do. In addition, if we extrapolate these properties to those of DOTA (1,4,7,10-

Table 4. Stability constants of **4b** (HOET-NOTA) complexes with selected di- and trivalent metal ions (n.o. = not observed, n.a. = not available); standard deviations are in parentheses

Metal ion	**4b** (HOET-NOTA)[a] log$K_{(M\cdot L)}$	log$K_{(M\cdot HL)}$	log$K_{(M\cdot H2L)}$	log$K_{(MLO\cdot H)}$	NOTA log$K_{(M\cdot L)}$[b]	log$K_{(M-HL)}$[b]
Mg^{2+}	8.22 (0.03)	3.12 (0.02)	2.45 (0.04)	11.81 (0.03)	9.69 (0.03)	4.6 (0.2)
Ca^{2+}	7.84 (0.11)	3.66 (0.09)	2.99 (0.12)	11.07 (0.12)	8.92 (0.01)	5.06 (0.03)
Sr^{2+}	4.60 (0.07)	2.58 (0.12)	2.23 (0.22)	n.o.	6.83 (0.01)	6.1 (0.1)
Mn^{2+}	10.14 (0.08)	3.87 (0.06)	n.o.	11.33 (0.10)	5.10 (0.01)	n.a.
Cu^{2+}	16.84 (0.14)	9.70 (0.09)	n.o.	n.o.	21.63 (0.03)	n.a.
Zn^{2+}	16.85 (0.04)	9.11 (0.02)	n.o.	n.o.	18.3[c]	n.a.
Cd^{2+}	14.29 (0.13)[d]	7.08 (0.05)	n.o.	11.25 (0.16)	16.0[c]	n.a.
Pb^{2+}	14.13 (0.08)[d]	6.88 (0.04)	n.o.	11.03 (0.10)	n.a.	n.a.
Ce^{3+}	13.0 (0.08)[e]	n.a.	n.a.	n.a.	13.2[f]	n.a.
Gd^{3+}	13.6 (0.05)[e]	n.a.	n.a.	n.a.	13.6[f]	n.a.

[a] This work, determined by pH potentiometry, 0.1 M KNO_3, 25 °C; stability constants are defined as follows (HOET-NOTA = L): $K_{(ML)}$ = [ML]/[M][L], $K_{(M-HL)}$ = [MHL]/[M][HL], $K_{(M-H2L)}$ = [MH_2L]/[M][H_2L], $K_{(MLO-H)}$ = [MLOH]/[MLO][H_3O^+]. [b] Ref.[45], 1.0 M $NaClO_4$, 25 °C. [c] Ref.[47], 0.1 M KCl, 25 °C. [d] This work, 0.1 M KNO_3, 25 °C. [e] This work, determined by spectrophotometry, 25 °C. [f] Ref.[48], 0.1 M NaCl, 25 °C.

tetraazacyclododecane-1,4,7,10-tetraacetic acid), which is widely used in MRI in its gadolinium complex form, quite similar stability constants and kinetic behaviour are to be expected but solubilities, interaction with proteins in the blood plasma, clearance from the body and tissue selectivities would be expected to be different. Substitution of acetate pendant arms with (2-hydroxyethyl)acetate pendant arms in complexing agents thus opens possibilities for fine-tuning of properties to fit better for specific applications.

Experimental Section

General: All solvents were of reagent grade and used without further purification except for acetonitrile, which was dried and distilled from calcium hydride. Ethyldiisopropylamine was purchased from Aldrich and distilled from solid KOH pellets and then from zinc powder. 2-Bromo-γ-butyrolactone was purchased from Aldrich and used without further purification. Silica gel 60 for column chromatographic separations were purchased from Fluka. Elemental analysis were carried out with a Carlo Erba Elemental Analyzer Mode 1106 instrument. 1D and 2D NMR spectra were recorded with Bruker AM 360 and DRX 500 spectrometers, respectively, and processed and modelled using a PC with the computer programs MestRe-C 2.3 and MestReCnD 1.1.1. Samples of **1a−5a** and **1b−5b** were dissolved in $CDCl_3$ and D_2O, respectively. Chemical shift references were tetramethylsilane as $\delta = 0$ for $CDCl_3$ and HDO as $\delta = 4.79$ for D_2O in ^1H NMR measurements, and $CDCl_3$ as $\delta = 77.0$ for $CDCl_3$ and CH_3CN as $\delta = 0.3$ for D_2O in ^{13}C NMR measurements. Molecular mechanics calculations were performed with the computer program HyperChem, using the MM+ and Amber94 force fields. The pH-potentiometric titrations were carried out with a Radiometer ABU 80 automatic burette, a Radiometer pH meter, an Orion glass electrode and a silver/silver chloride reference electrode. The ionic strength during all titrations was kept constant (0.10 M KNO_3, $t = 25$ °C, $A = 0.060$, $pK_w = 13.81$). For titrations, carbonate-free, standardized 0.2002 M KOH solution was used and the ligand concentration was kept in the range of $1.8\cdot10^{-3}$ to $2.2\cdot10^{-3}$ M. The pH range for titration of the complexes was 1.9−11.5, except for cerium, with which a precipitate formed at pH > 8, due to very slow complex formation and rapid hydrolysis of the metal ions. Individual samples were thus taken for cerium and gadolinium ions and the stability constants were determined by photometry. Molar absorptivities were calculated from the intensities of the absorption maxima recorded at eight different wavelengths in the 267−296 nm spectral range for the $2\cdot10^{-4}-7\cdot10^{-4}$ M [Ce^{3+}] and $2.2\cdot10^{-4}-7.3\cdot10^{-4}$ M [HOET-NOTA] concentration ranges. Individual samples were prepared by very slow addition of calculated amount of a standardized $CeCl_3$ solution to a known amount of standardized Na_3HOET-NOTA solution with vigorous stirring and the solution was left to stand at 25 °C until a constant pH reading was reached. Individual absorption values were then plotted against metal ion concentration for each wavelength and, after linear regression analysis of the data points, the value of the slope gave the molar absorptivities of the [Ce-HOET-NOTA] complex. The molar absorptivities of Ce_{aq}^{3+} ion were determined by the same method for the 280−320 nm region, with $1.5\cdot10^{-2}-2\cdot10^{-4}$ M $CeCl_3$ solutions. The stability constant of the gadolinium complex was determined by a competition reaction with CeHOET-NOTA in the pH range of 4−5. Five different pH values were set in this region and UV absorptions of the equilibrated mixtures at ten different wavelengths were recorded after 4 d of conditioning at room temperature. Data were analysed by the PSEQUAD computer program.[43] Equation (2) was used to fit $\log K_i$ values of a system with n independent protonation steps to the experimental chemical shifts (δ) and pH values (pH), which were in turn calculated from the experimental pD values by Equation (3).[44] Chemical shifts characteristic of species of high and low protonation states (δ_{HiA}) can be derived or estimated from the low and high pH region of the titration curves, respectively; other values can be also fitted by using Equation (2). The number of valuable data points should be at least $2n + 2$ or higher.

$$\delta = \frac{\delta_A + \sum_{i=1}^{n} \delta_{HiA} \cdot 10^{\left(\sum_{j=1}^{i} \log K_j - i \cdot pH\right)}}{1 + \sum_{i=1}^{n} 10^{\left(\sum_{j=1}^{i} \log K_j - i \cdot pH\right)}} \quad (2)$$

$$pD = pH + 0.4 \quad (3)$$

General Procedure for the Preparation of Tetrahydro-2-oxofuran-3-yl Derivatives 1a−5a: Coupling of the butyrolactone ring to the secondary polyamines **1−5** containing amino groups was achieved by a method similar to that published by Lehnmann for cyclic monoamines.[24] The starting cyclic polyamine **1−5** was treated with a stoichiometric amount of bromobutyrolactone in dry acetonitrile in the presence of an excess of ethyldiisopropylamine as a non-nucleophylic base at room temperature for several days. The reaction mixture was then concentrated to dryness in a rotary evaporator and the remaining material was redissolved in chloroform. This solution was rapidly extracted with ice-cold 0.1 M sodium carbonate solution. The chloroform phase was removed and the remaining aqueous phase was extracted with two additional portions of chloroform. The organic phases were combined, dried with anhydrous sodium sulfate for several hours and then filtered, and the filtrate was further dried with anhydrous magnesium sulfate overnight. The drying agent was filtered off and the filtrate was concentrated under reduced pressure to yield a very viscous, yellow or orange-brown oil, which was redissolved in the minimum possible volume of dichloromethane and the solution was left to stand overnight, after which the clear supernatant was decanted from a solid or precipitated oily substance. This solution was then concentrated to provide an amber-coloured oil, which either proved to be the pure product (**1a**, **3a**, **4a**) or was further purified (**2a**, **5a**) by column chromatography on silica gel 60 (230−400 mesh) as follows.

Column Chromatography: In a typical separation, 200 mg of the sample was chromatographed; the sample/sorbent mass ratio was set as 1:50. A glass column (length: 50 cm; i.d.: approximately 15 mm) was selected and filled with a suspension of silica gel (10 g) in chloroform (40 mL) and left to stand overnight for settling and conditioning; next morning it was flushed with fresh chloroform (100 mL) with the help of a slight overpressure of dry nitrogen. The sample was dissolved in 2 mL of chloroform, loaded onto the column, and eluted first with chloroform (100 mL) and then with a chloroform/methanol (85:15, v/v) mixture (100 mL). The elution rate was set at approximately 1 drop/s and 5-mL fractions were collected. Fractions containing the pure product (monitored by TLC) were combined and the solvents were evaporated in a rotary evaporator to give a pale yellow, very viscous oil. Yields of **1a−5a** were in the moderate to good range (approx. 30−70%).

General Synthesis of *N*-[(Carboxy)(2-hydroxyethyl)methyl] Derivatives: Compounds **1a−5a** were hydrolysed to **1b−5b** with stoichi-

Table 5. Reaction conditions, yields and characteristic data of compounds **1a−5b**; yields given are calculated for pure substances (n.q.= near quantitative)

Compound	Solvent	Yield (%)	^{1}H and ^{13}C NMR spectroscopic data (δ values)
1a	CH_3CN	65	^{1}H NMR: 4.45−4.35 (m, 2 H, CH_2O), 4.25−4.15 (m, 2 H, CH_2O), 3.58 (t, 2 H, CH), 2.95−2.80 (d, 4 H, NCH_2), 2.72−2.58 (d, 4 H, NCH_2), 2.40−2.25 (m, 4 H, CH_2). ^{13}C NMR: 174.7 (C=O), 65.18 (CH_2O), 62.08 (CH), 48.97 (NCH_2), 23.34 (CH_2)
1b	H_2O	n.q.	^{1}H NMR: 3.65−3.45 (m, 4 H, CH_2OH), 3.02−2.90 (m, 2 H, CH), 2.63 (s. br, 8 H, NCH_2), 1.95−1.70 (m, 4 H, CH_2). ^{13}C NMR: 177.7 (C=O), 67.55 (CH), 58.64 (CH_2O), 48.53 (br,NCH_2), 31.1 (CH_2)
2a	DMF	15	^{1}H NMR: 4.45−4.32 (m, 2 H, OCH_2), 4.25−4.12 (m, 2 H, OCH_2), 3.83−3.70 (m, 2 H, CH), 3.05−2.90 (m, 4 H, NCH_2), 2.86−2.72 (m, 4 H, NCH_2), 2.44−2.16 (m, 4 H, CH_2), 1.94−1.84 (m, 2 H, CH_2). ^{13}C NMR: 175.67 (C=O), 65.28 (OCH_2), 63.77 and 63.64 (CH), 53.03 and 52.65 (NCH_2C), 51.10 and 50.79 (NCH_2), 29.02 (CCH_2C), 24.88 and 24.60 (CH_2)
2b	H_2O	n.q.	^{1}H NMR: 3.70−3.55 (m, 4 H, $HOCH_2$), 3.21−3.10 (m, 2 H, CH), 2.98−2.73 (m, NCH_2), 1.96−1.64 (m, CH_2). ^{13}C NMR: 178.7 (C=O), 67.55 and 67.37 (CH), 59.18 ($HOCH_2$), 50.60, 50.47, 50.34 and 50.08 (NCH_2), 31.79 and 31.66 (CH_2), 25.67 and 25.57 (CH_2)
3a	CH_3CN	55	^{1}H NMR: 7.70−7.62 (d, 2 H, CH_{arom}), 7.35−7.25 (d, 2 H, CH_{arom}), 4.41−4.32 (m, 2 H, OCH_2), 4.20−4.10 (m, 2 H, OCH_2), 3.96−3.63 (m, 2 H, CH), 3.40−3.00 and 2.96−2.68 (m, 12 H, NCH_2), 2.42 (s, 3 H, CH_3), 2.45−2.35 and 2.30−2.15 (m, 2 H, CH_2). ^{13}C NMR: 176.1 (C=O), 143.0 (C_{arom}), 135.6 (C_{arom}), 129.5 (HC_{arom}), 126.8 (HC_{arom}), 65.22 (OCH2), 62.58 (CH), 54.89, 54.72, 54.07, 53.49, 50.19 and 49.89 (NCH_2), 26.06 and 25.09 (CH_2), 21.03 (CH_3)
3b	H_2O	n.q.	^{1}H NMR: 7.58 and 7.49 (HC_{arom}), 3.59 (s br, 4 H, $HOCH_2$), 3.50−2.55 (m, CH and NCH_2), 2.46 (s, 3 H, CH_3), 1.89 (s br, 4 H, CH_2). ^{13}C NMR: 180.3 (C=O), 144.14, 132.97, 129.39 and 126.35 (C_{arom}), 66.20 (CH), 59.47 and 59.16 ($HOCH_2$), 52.82, 52.07, 51.62 and 50.97 (NCH_2), 32.10 and 31.83 (CH_2), 20.07 (CH_3)
4a	CH_3CN	94	^{1}H NMR: 4.42−4.30 (m,1 H,4′-CH_2), 4.24−4.12 (m,1 H,4′-CH_2), 3.85−3.70 (m,1 H,2-CH), 3.05−2.75 (m,4 H,ring CH_2), 2.50−2.35 (m,1 H,3′-CH_2), 2.32−2.15 (m,1 H,3′-CH_2). ^{13}C NMR ($CDCl_3$): 176.2 (C=O), 65.15 (CH_2O), 63.4 (CH), 53.65 (NCH_2), 25.88, 25.63 and 25.22 (CH_2)
4b	H_2O	n.q.	^{1}H NMR (D_2O, pD = 11.8, TMS): 3.75−3.50 (m, 2 H, 4′-CH_2), 3.20−3.03 (m,1 H, 2-CH), 2.85−2.50 (m, 4 H, ring CH_2), 1.98−1.75 (m, 2 H, 3′-CH_2). ^{13}C NMR (pD = 11.8): 180.9, 180.7 and 180.4 (C=O), 68.39, 67.86 and 67.39 (CH), 59.6, 59.3 and 59.1 (OCH_2), 49.3 (br, NCH_2), 32.26, 31.63 and 30.68 (CH_2)
5a	CH_3CN	18	^{1}H NMR: 4.42−4.33 (m, 2 H, OCH_2), 4.27−4.13 (m, 2 H, OCH_2), 3.95−3.86 (t, 2 H, CH), 3.70−3.60 (m, 8 H, $OCH_{2(ring)}$), 3.63 (s, 8 H, $OCH_{2(ring)}$), 3.10−2.95 (m, 8 H, NCH_2), 2.55−2.30 (m, 4 H, CH_2). ^{13}C NMR: 176.0 (C=O), 70.71 and 70.68 (OCH_2), 65.33 [C(O)OCH_2), 61.77 and 61.69 (CH), 52.31 and 52.28 (NCH_2), 25.96 (CH_2)
5b	H_2O	n.q.	^{1}H NMR: 3.67 (s, 8 H, $OCH_{2(ring)}$), 3.75−3.55 (m, 12 H, $OCH_{2(ring)}$ and CH_2OH), 3.35−3.25 (m, 2 H, CH), 2.99−2.87 (m, 4 H, NCH_2), 2.80−2.70 (m, 4 H, NCH_2), 1.95−1.70 (m, 4 H, CH_2). ^{13}C NMR: 179.5 (C=O), 68.24 and 67.54 (OCH_2), 63.41 (CH), 59.50 ($HOCH_2$), 49.56 and 49.34 (NCH_2), 29.98 (CH_2)

Table 6. Elemental analysis data for compounds **1a−5b**

	Formula	Mass	C calcd. (found)	H calcd. (found)	N calcd. (found)
1a	$C_{12}H_{18}N_2O_4$	254.28	56.68 (57.23)	7.13 (7.33)	11.02 (10.65)
1b	$C_{12}H_{20}N_2Na_2O_6$	334.28	43.12 (42.68)	6.03 (5.78)	8.38 (7.96)
2a	$C_{13}H_{20}N_2O_4$	268.31	58.19 (57.80)	7.51 (7.17)	10.44 (10.22)
2b	$C_{13}H_{22}N_2Na_2O_6$	348.30	44.83 (44.18)	6.37 (6.60)	8.04 (7.58)
3a	$C_{21}H_{29}N_3O_6S$	451.54	55.86 (55.53)	6.47 (6.75)	9.31 (8.87)
3b	$C_{21}H_{31}N_3Na_2O_8S$	531.53	47.45 (47.03)	5.88 (5.95)	7.91 (7.51)
4a	$C_{18}H_{27}N_3O_6$	381.42	56.68 (56.50)	7.13 (6.98)	11.02 (11.13)
4b	$C_{18}H_{30}N_3Na_3O_9$	501.42	43.12 (42.51)	6.03 (6.25)	8.38 (8.01)
5a	$C_{20}H_{34}N_2O_8$	430.49	55.80 (55.34)	7.96 (8.09)	6.51 (6.13)
5b	$C_{20}H_{36}N_2Na_2O_{10}$	510.49	47.06 (46.39)	7.11 (7.27)	5.49 (5.16)

ometric amounts of 0.5 M carbonate-free, aqueous sodium hydroxide, either at room temperature for 1 d or near 100 °C for 5−30 min (except for **3a**, which proved to be fairly insoluble in the aqueous base and required 24 h of reflux time). The hydrolysis mixture was then concentrated to dryness under reduced pressure to yield the target compound as a white to beige solid. Since this still contained a significant amount of water, it was redissolved in absolute ethanol and the solvents were again evaporated to dryness, removing water by azeotropic distillation. Usually, a solid foam was formed; this was triturated with dry diethyl ether, filtered off on a glass filter disc under dry nitrogen and then further dried to constant weight under reduced pressure and over P_2O_5. The sodium salt products are very hygroscopic solids, which readily absorb carbon dioxide from the air; they should therefore be stored under dry nitrogen or argon. NMR and elemental analysis data for all new molecules are summarized in Tables 5 and 6, respectively. All new substances **1a−5b** were judged pure by CHN analysis, ^{1}H and ^{13}C NMR, although the experimentally determined C value error in **1b−5b** exceeded the acceptable ±0.4% accuracy range in the cases of the sodium salts, probably due to the matrix effect of thermally highly stable sodium carbonate.

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