Complexation Properties of 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7-malonate, -7,16-bis(malonate) and -7,16-bis(α-methylacetate)

Ernő Brücher,* Béla Győri, József Emri, Sándor Jakab, Zoltán Kovács, Piroska Solymosi and Imre Tóth

Department of Inorganic and Analytical Chemistry, Lajos Kossuth University, Debrecen, Hungary

The macrocycles 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-7,16-bis(malonate) (oddm), -7-malonate (odmm) and -7,16-bis(α-methylacetate) (oddp) have been synthesized. Their protonation constants and the stability constants of their complexes ML with Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+} have been determined by pH-potentiometry at a 1:1 metal-to-ligand ratio. The macrocycle oddm possesses high selectivity for the large metal ions. The complex $[Sr(oddm)]^{2-}$ is two orders of magnitude more stable than $[Ca(oddm)]^{2-}$ and the stability constant of $[Pb(oddm)]^{2-}$ is six orders of magnitude larger than that of the corresponding zinc complex. The complexes of oddm with large metal ions (Sr^{2+} and Ba^{2+}) possess rigid structures, while the average lifetimes of the metal–donor bonds are relatively large, and this is indicated by the appearance of multiplet signals in the ^1H NMR spectra.

Polyfunctional polyaminopolycarboxylic acids, *e.g.* ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (H_4edta) and diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*″-pentaacetic acid (H_5dtpa) are frequently employed in practice for the complexation of metal ions. They form remarkably stable complexes with di- and tri-valent metal ions, but their selectivity is relatively low due to their flexible structure. Crown ethers[1] and cryptands[2] exhibit much higher selectivity, since the ring size of these mono- and bi-cyclic compounds makes them 'size-match' selective towards the best-fitting metal ions. A drawback of the application of crown ethers however is that their complexes are not stable in aqueous solution. The complexes of cryptands are stable in aqueous media, but they form slowly and dissociate even more slowly because of the presence of the double ring structure, which limits their usefulness in many fields including analytical separation. The stabilities of crown ether complexes can be increased by the replacement of one or two (or occasionally more) oxygen atoms with the more basic nitrogen. With certain transition-metal ions the resulting azaoxa crown ethers form complexes which are quite stable in water, and retain 'size-match' selectivity; however, the complexes with 'hard' metal ions are rather unstable.[3–5]

The stability constants of crown ether complexes can also be increased by the attachment of one or more functional groups to the macrocycle.[6,7] As regards complex formation, however, related substituted crown ethers do not carry the functional groups in appropriate positions, and their preparation is somewhat tedious; thus such compounds are not frequently employed. In contrast, numerous macrocyclic polyazapolyoxa ligands functionalized at the nitrogen atom have been synthesized.[8–10] Of these, the derivatives of the 18-membered 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane ([18]aneN_2O_4) are the most popular; the functional groups are appropriately linked to the two nitrogen atoms and yield the desired complexes.[11–17] The presence of the functional groups can be disadvantageous: in parallel with the increase in stability constants, the extent of complex formation with the donor atoms of the functional groups may become more and more significant, and the role of the macrocycle (and hence the selectivity) decreases.

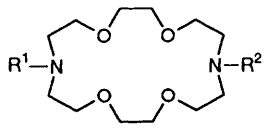
An important field of application of chelate-forming compounds is facilitation of the removal of toxic metal ions (*e.g.* Pb^{2+} and Cd^{2+}) and radioactive isotopes (*e.g.* ^{90}Sr and ^{144}Ce) from living organisms.[18,19] Related medical applications call for the high selectivity of the reagent employed, which must form highly stable complexes with the metal ions to be removed and less stable complexes with those (*e.g.* Zn^{2+}, Cu^{2+} and Ca^{2+}) essential in the vital processes.

Despite considerable efforts, no suitably effective complex-forming agents have so far been found for the mobilization of radioactive strontium isotopes, which form in nuclear fission and if incorporated are localized in the bones. Although the use of chelating agents such as edta and dtpa has been proposed for this purpose, these compounds form more stable complexes with Ca^{2+} (which occurs in considerable concentrations in the body fluids) than with the larger Sr^{2+}, and thus depletion of the latter is not significantly increased.[20]

A macrocyclic ligand of appropriate size may also be selective for larger metal ions. The stability constant of the complex of Sr^{2+} with cryptand 222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) (log K = 8.0)[8] is larger than that of the calcium complex (log K = 4.4). Animal experiments revealed that the cryptand complex of Sr^{2+} is not incorporated into the organism.[21] Nevertheless, this cryptand has not been introduced in medical practice, probably because of its low LD_{50} and the low rate of complexation with Sr^{2+}.

It is well known that [18]aneN_2O_4 produces more stable complexes with larger metal ions; its stability constants (log K) with Sr^{2+} and Ca^{2+} are 2.57 and 1.8, respectively.[3] Under physiological conditions its strontium complex is formed only in small quantities because of the relatively low stability constants and large protonation constants of the macrocycle (log K^H_1 = 9.30, log K^H_2 = 8.15[22]). Following attachment of an acetate group to each of the two nitrogen atoms of the macrocycle the stability constants of the complexes of Sr^{2+} and Ca^{2+} with the resulting [18]aneN_2O_4 diacetate (odda) were found to be appreciably higher: log K_{Sr} = 8.29 and log K_{Ca} = 8.39.[13] Although these values are practically identical, the Sr^{2+}/Ca^{2+} selectivity is considerably more favorable than in the case of the edta complexes, for example, where log K_{Sr} = 8.69 and log K_{Ca} = 10.61.[23]

In the light of the above-mentioned results, the preparation



[18]aneN$_2$O$_4$	$R^1 = R^2 = H$
H$_2$odda	$R^1 = R^2 = CH_2CO_2H$
H$_2$odmm	$R^1 = H$, $R^2 = CH(CO_2H)_2$
H$_4$oddm	$R^1 = R^2 = CH(CO_2H)_2$
H$_2$oddp	$R^1 = R^2 = CHMeCO_2H$

and examination of the complexation properties of novel [18]aneN$_2$O$_4$ derivatives were considered most interesting and desirable. In a short communication we earlier reported[24] an investigation of the complexes of [18]aneN$_2$O$_4$ bis(malonate) (oddm); the present paper describes the synthesis and examination of it and of the corresponding mono(malonate) (odmm) and bis(α-methylacetate) (oddp).

Experimental

Synthesis of the Macrocycles.—Na$_4$(oddm). A stirred suspension of bromomalonic acid (4.76 g, 26 mmol) in a small volume of water was neutralized with 9 mol dm^{-3} NaOH solution in the presence of phenolphthalein. To the resulting solution [18]aneN$_2$O$_4$ (Kriptofix 2,2, Merck) (2.642 g, 10 mmol) was added in portions and the mixture then kept at 60–65 °C for 44–48 h, being adjusted to slightly alkaline (pH 10–11) by the portionwise addition of 9 mol dm^{-3} aqueous NaOH (2.9 cm^3). After completion of the reaction the mixture was treated with NaBr (2.5–3.0 g) and then evaporated to dryness. Unchanged [18]aneN$_2$O$_4$ and the monomalonyl derivative were removed by extraction with CH_2Cl_2 (75 cm^3) and Na$_4$(oddm) was isolated by extraction with absolute ethanol (150 cm^3). The product contained 40–70% of NaBr, which was removed by extraction with 95% ethanol and the residue was dried in vacuum. Yield: 89.6% [Found: $CH(CO_2)_2$, 36.10; N, 4.95. Calc. for $C_{18}H_{26}N_2Na_4O_{12}$: $CH(CO_2)_2$, 36.45; N, 5.05%]. NMR: ^{1}H (sodium 4,4-dimethyl-4-silapentanesulfonate reference, 0.1 mol dm^{-3} NaOD–D$_2$O) δ 3.95 (2 H, s), 3.64 (8 H, s), 3.60 (8 H, t) and 2.85 (8 H, t); ^{13}C (D$_2$O), δ 179.95 (CO_2), 76.45 (NCH), 71.66, 70.84 (OCH_2) and 54.06 (NCH_2). The purity of the product and the quantity of contaminants were checked by means of ^{1}H NMR spectroscopy. The purity was found to be at least 99.5%. The major contaminants were disodium hydroxymalonate (maximum 0.4%; δ 4.32, 1 H) and [18]aneN$_2$O$_4$ (maximum 0.1%; δ 3.10, 2 H).

Bromomalonic acid was prepared in a diethyl ether solution as described earlier,[25] and the pure product was obtained by recrystallization from chloroform.

Na$_2$(odmm). A cooled (ice–water) and intensively stirred suspension of bromomalonic acid (1.47 g, 8 mmol) in water (0.5 cm^3) was neutralized with 9 mol dm^{-3} NaOH solution in the presence of phenolphthalein indicator. Then [18]aneN$_2$O$_4$ (2.0 g, 7.62 mmol) was added, and the mixture was kept at 35–40 °C for 12 h, while continuously adjusted to pH 10–11 by the portionwise addition of 9.0 mol dm^{-3} NaOH solution (0.89 cm^3). It was next kept at 60 °C for 1 h and then evaporated to dryness in vacuum. The crude product was extracted with CH_2Cl_2 (3 × 15 cm^3). The extract was concentrated to 5 cm^3 and the product precipitated by the addition of ether (30 cm^3). The dissolution/precipitation procedure was repeated three times (5 cm^3 of CH_2Cl_2 and 30 cm^3 of ether) and the pure, crystalline product was then filtered off and dried in a nitrogen atmosphere. Yield: 1.65 g, 45.4% [Found (calc.): C, 36.9 (37.8); H, 5.50 (5.50); N, 5.60 (5.85%)]. The product contained a small quantity of NaBr as impurity. ^{1}H NMR (D$_2$O): δ 3.87 (s, 1 H, CH), 3.67 (m, 16 H, OCH_2) and 2.92 (m, 4 H, NCH_2).

Na$_2$(oddp). To a stirred solution of (±)-2-bromopropionic acid (Merck) (2.32 g, 15.2 mmol) in a small volume of water, 7.4 mol dm^{-3} NaOH solution (2.06 cm^3) was added, followed portionwise by [18]aneN$_2$O$_4$ (1.0 g, 3.81 mmol). The mixture was kept at 38–40 °C for 4 h during treatment with 7.4 mol dm^{-3} NaOH solution (1.0 cm^3). Next, portions (0.5 cm^3) of 7.4 mol dm^{-3} NaOH solution were added over a period of 3 h, while the temperature was kept first at 60 and then at 70 °C. The reaction mixture was concentrated under reduced pressure to half its volume, 36% HCl (2.05 cm^3) was added and the evaporation was continued until a crystalline material separated. After cooling to 5 °C, the crystalline material was filtered off, washed with ethanol and water and then dried by air-suction. To a suspension of the dry substance in water (2.0 cm^3), 7.4 mol dm^{-3} NaOH solution (1.0 cm^3) was added and the resulting solution evaporated in vacuum. The product was extracted from the residue with CH_2Cl_2 (3 × 5.0 cm^3), the organic solution was concentrated to one-third of its volume, ether (5 cm^3) was added, and the precipitated product was filtered off, washed with ether (3 × 2 cm^3) and dried in a nitrogen atmosphere. Yield: 1.30 g, 76% [Found (calc.): C, 46.80 (48.00); H, 7.00 (7.15); N, 6.10 (6.20)%]. ^{1}H NMR (D$_2$O): δ 1.36 (d, 6 H, CH_3), 3.15 (m, 8 H, NCH_2) and 3.74 (m, 18 H, OCH_2 and CCH).

Materials and Methods.—The applied salts $MgCl_2$, $CaCl_2$, $SrCl_2$, $BaCl_2$, $MnCl_2$, $ZnCl_2$, $Pb(NO_3)_2$ and $Cd(NO_3)_2$, were of the highest analytical grade. The concentrations of the solutions were determined by complexometric methods, with Eriochrome Black T or methylthymol blue as indicators.

The pH-potentiometric titrations were carried out with a Radiometer PHM 85 pH-meter, using G202B glass and K401 calomel electrodes in vessels thermostatted at 25 °C. The titrated solutions were stirred with a magnetic stirrer and nitrogen gas was bubbled throughout the measurements. In the preparation of the samples, the calculated amount of HCl was slowly added in dilute solution to a vigorously stirred solution of Na$_4$(oddm) or Na$_2$(odmm) in order to avoid decarboxylation of the malonate groups, which occurs in acidic solutions of ethylenediamine-*N*,*N*′-bis(malonic acid).[26]

The hydrogen-ion concentration was calculated from the measured pH values by a known method.[27] The protonation constants were determined at constant ionic strength in 0.15 mol dm^{-3} NaCl, NMe_4Cl or KNO_3 solutions. In the case of oddp, constant ionic strength was ensured with 1.0 mol dm^{-3} KCl solution. For the ionic product of water (log K_w) in 0.15 mol dm^{-3} NaCl, KNO_3, NMe_4Cl and 1.0 mol dm^{-3} KCl, values of 13.96, 13.86, 14.02 and 13.87, respectively, were obtained. The stability constants of the complexes of odmm and oddm were determined in 0.15 mol dm^{-3} NaCl or KNO_3 (Pb^{2+} and Cd^{2+}) solution. Those of the oddp complexes were determined in 1.0 mol dm^{-3} KCl. To obtain the equilibrium data, two to four parallel titrations were carried out.

For calculation of the protonation and stability constants, the program PSEQUAD was used.[28] The NMR spectroscopic measurements were carried out with a Bruker WP 200SY spectrometer, with 3-trimethylsilylpropanesulfonate as internal standard.

Results and Discussion

Since the reaction between [18]aneN$_2$O$_4$ and disodium bromomalonate is fairly slow (approximately 10 times slower than that between [18]aneN$_2$O$_4$ and sodium bromoacetate), the concentrations of the reaction partners should be as high as allowed by the solubilities. Although the rate increases with increasing temperature, the hydrolysis of bromomalonate becomes even faster, leading to the formation of a larger amount of hydroxymalonic acid. However, at 40–50 °C, with a 20–40% excess of bromomalonate, Na$_4$(oddm) can be prepared in good yield and the reaction time is also acceptable. The isolation of Na$_4$(oddm) in pure form was simplified

Table 1 Protonation constants of the macrocycles (25 °C)

Macrocycle	Medium	$\log K_1^H$	$\log K_2^H$	$\log K_3^H$
oddm	0.15 mol dm^{-3} NMe_4Cl	8.62	7.95	4.02
	0.15 mol dm^{-3} KNO_3	7.55	7.44	3.06
	0.15 mol dm^{-3} NaCl	7.95	7.35	3.03
odmm	0.15 mol dm^{-3} NaCl	8.86	7.40	2.34
oddp	1.0 mol dm^{-3} KCl	8.77	8.32	2.10
odda	0.1 mol dm^{-3} NMe_4Cl [a]	8.45	7.80	2.90
	0.1 mol dm^{-3} KNO_3 [b]	8.02	7.89	2.00
	0.1 mol dm^{-3} NMe_4NO_3 [c]	8.93	8.01	2.50

[a] Ref. 13. [b] Ref. 11. [c] Ref. 22.

considerably when it was recognized that, while Na_4(oddm) does not dissolve in ethanol, its double salt with NaBr is highly soluble in absolute ethanol, but insoluble in ethanol–water mixtures containing a small amount of water. Thus, from the solid residue obtained by evaporation of the reaction mixture and subsequent drying, a crude product containing 30–60% of Na_4(oddm) can be obtained, and this can be selectively and quantitatively separated from NaBr by extraction with 96% aqueous ethanol.

Preparation of the tetralithium salt of the [18]aneN_2O_4 bis(malonate) was previously reported by de Jong *et al.*,[14] but the chemical properties of their product, synthesized by the treatment of [18]aneN_2O_4 with methyl bromomalonate in benzene and subsequent hydrolysis with LiOH, differed significantly from those of Na_4(oddm) prepared in our laboratory. In acidic media (pH < 2) oddm is decarboxylated,[26] but the product reported by de Jong *et al.* is not. Further, this substance dissolves $BaSO_4$ to a markedly lower extent than does the corresponding [18]aneN_2O_4 diacetate,[14] whereas the opposite effect would be expected on the basis of the stability constants. It is most probable that de Jong *et al.* isolated a substance in which [18]aneN_2O_4 was acylated with methyl bromomalonate. This assumption is supported by the elemental analytical and ^1H NMR data reported by de Jong *et al.*[14]

Protonation Constants of the Macrocycles.—The protonation constants of the macrocycles ($K^H_i = [H_iL]/[H_{i-1}L][H^+]$) were determined from pH-potentiometric titration data. The titration curves of oddm in physiological NaCl solution (0.15 mol dm^{-3}) in the presence and in the absence of metal ions are shown in Fig. 1. The protonation constants were also determined in 0.15 mol dm^{-3} KNO_3, since the stability constants of the complexes of Pb^{2+} and Cd^{2+} were likewise determined in this solution. The macrocycle odda is known[11,13] to form complexes with Na^+ and K^+ ions too and a similar complexation with oddm was also expected. For the study of the complexation of oddm with these latter ions (Na^+ and K^+), the protonation constants were also determined in 0.15 mol dm^{-3} NMe_4Cl. These protonation constants are listed in Table 1. The values of the fitting parameters[28] obtained during the calculations varied in the range 1×10^{-3}–8×10^{-3}. For comparison, the protonation constants of odda[13] are included.

Of the protonation constants of oddm determined in various media the $\log K^H_1$ values differ most markedly decreasing in the sequence $NMe_4^+ > Na^+ > K^+$, *i.e.* they depend on the cation of the salt employed to ensure constant ionic strength. This sequence clearly shows that the larger K^+ forms a more stable complex with the ligand $oddm^{4-}$ than the smaller Na^+. A similar sequence was observed for $odda^{2-}$, as shown by the stability constants of the complexes of Na^+ and K^+ ($\log K_{Na} = 1.95$[11] and $\log K_K = 3.9$[13]). The $\log K^H_2$ values are nearly the same in the different media, indicating that the interactions of Na^+ and K^+ occur only with the fully deprotonated ligand.

The $\log K^H_1$ and $\log K^H_2$ values of oddp are larger than those of the other macrocycles, probably because of the enhanced basicity of the nitrogen atoms in consequence of the presence of the methyl groups attached to the carbon atoms adjacent to the nitrogens.

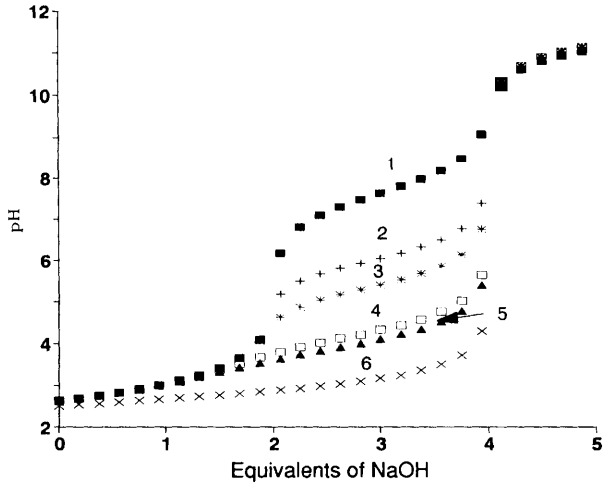


Fig. 1 Titration curves of oddm (1) in the presence of Zn^{2+} (2), Ca^{2+} (3), Sr^{2+} (4), Cd^{2+} (5) and Pb^{2+} (6). The concentrations of the ligand and metal ions were 1×10^{-3} mol dm^{-3}

Stability Constants of the Complexes.—The stability constants of the complexes ($K = [ML]/[M][L]$) were determined by pH-potentiometric titration at a metal to ligand concentration ratio of 1:1. The concentration of the macrocycles in the titrated samples was around 1.0×10^{-3}–2×10^{-3} mol dm^{-3}. The titration curves obtained for oddm in the presence of various metal ions are shown in Fig. 1.

The titration data correlate very well with the presumed formation of 1:1 (ML) complexes, and no improvement in the values of the fitting parameters was observed when the formation of protonated complexes was assumed. The stability constants were calculated by applying the data from two to four parallel titrations; the resulting $\log K$ values are given in Table 2. The relative error (triplicate of the standard deviation) of the $\log K$ values is in the range of 0.05–0.1 $\log K$ unit. For comparison, the stability constants of the odda and edta complexes are included in Table 2.

A comparison of the stability constants revealed the most interesting results for the oddm complexes. The ratios of the stability constants (the differences between the $\log K$ values: $\Delta \log K$) for certain metal ions are quite surprising, most particularly when compared with those of the edta complexes. The stability constant of the complex $[Sr(oddm)]^{2-}$ is two orders of magnitude larger than that of $[Ca(oddm)]^{2-}$, $\Delta \log K = 2.24$, while in the cases of $[Sr(edta)]^{2-}$ and $[Ca(edta)]^{2-}$ an opposite effect was found: $\Delta \log K = -1.93$.[2,3] Owing to its high selectivity for Sr^{2+} over Ca^{2+}, oddm appears to be useful in accelerating the rate of removal of radioactive Sr (*e.g.* ^{90}Sr)

Table 2 Stability constants (log K) of the complexes (25 °C)

		M							
Macrocycle	Medium	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Mn^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}
oddm	0.15 mol dm^{-3} NaCl	2.53	7.55	9.79	9.76	7.41	6.25	10.3	13.0
odmm	0.15 mol dm^{-3} NaCl	< 2	6.58	5.81	—	5.60	4.77	9.71	—
oddp	1.0 mol dm^{-3} KCl	—	7.10	6.81	—	—	7.07	10.08	—
odda	0.1 mol dm^{-3} NMe_4Cl [a]	—	8.39	8.29	7.63	—	8.42	11.07	13.55
	0.1 mol dm^{-3} NMe_4NO_3 [b]	< 2	8.71	—	—	8.66	8.96	—	—
	0.1 mol dm^{-3} KNO_3 [c]	—	7.67	7.69	7.66	—	8.03		
edta [d]	0.1 mol dm^{-3} KCl	8.83	10.61	8.68	7.80	13.81	16.44	16.36	17.88

The error in log K is between 0.05 and 0.1 units. [a] Ref. 13. [b] Ref. 22. [c] Ref. 11. [d] Ref. 23.

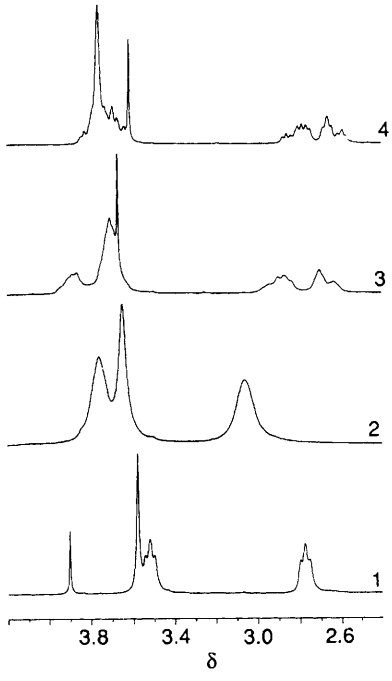


Fig. 2 Proton NMR spectra of $oddm^{4-}$ (1) and the complexes $[Zn(oddm)]^{2-}$ (2), $[Ca(oddm)]^{2-}$ (3) and $[Ba(oddm)]^{2-}$ (4)

from living organisms. This inference, drawn from the difference in the stability constants, is confirmed by the results of animal experiments. A suitable amount of the complex $Na_2[Ca(oddm)]$ injected intravenously 1 h after the incorporation of ^{85}Sr results in the excretion of 90–95% of the radioactive isotope.[29] The selectivity of chelate-forming reagents for toxic metals is often referred to that for the easily removable Zn^{2+}. The data in Table 2 clearly demonstrate the extremely high selectivity of oddm for Pb^{2+} over Zn^{2+} ($\Delta \log K = 6.75$). With edta, extensively used for the treatment of lead poisoning, the selectivity is much lower ($\Delta \log K = 1.44$). There is also a significant difference between the stability constants of the complexes $[Cd(oddm)]^{2-}$ and $[Zn(oddm)]^{2-}$ ($\Delta \log K = 3.99$), whereas the corresponding value for the edta complexes is $\Delta \log K = -0.08$. The difference in the stability constants of $[Mn(oddm)]^{2-}$ and $[Zn(oddm)]^{2-}$ is also unexpectedly high, $\Delta \log K = 1.12$, while a value of $\Delta \log K = -2.63$ is calculated for the corresponding edta complexes.

All of the above results demonstrate that oddm is highly selective for the large metal ions. This behaviour can be explained by the significant role of the interactions between the donor atoms of the large (18-membered) macrocycle and the metal ions, and this effect is expected to be stronger with the larger, better-fitting metal ions.

For the odmm complexes, where there is only a single malonate functional group, the stability constants are markedly smaller. Although the selectivity of this macrocycle for larger metal ions is higher than that of edta, it is still lower than the selectivity of oddm (Table 2). The selectivities of the bis(acetate) derivative odda and of oddp for large metal ions are also lower than those of oddm. In spite of the fact that the presence of the methyl substituents makes the two nitrogen atoms of oddp more basic than those of odda, the stability constants of the oddp complexes are lower by 1–1.5 log K units. The reason for this is probably the steric hindrance due to the methyl groups, so that co-ordination of the acetate groups is somewhat more difficult than in the case of complexation with odda.

A comparison of the stability constants obtained for the different $[18]aneN_2O_4$ derivatives (Table 2) indicates that the differences in the log K values are not determined solely by the size-match selectivity of the macrocycle: other factors too may play a role. The electrostatic interactions of the metal ions with the dinegative malonate groups of oddm are stronger than those with the acetate groups of odda and oddp. However, this difference in interaction may be larger when the hard metal ion is larger and has a higher co-ordination number. In this case, the average number of co-ordinated donor atoms can be larger for the malonate derivative than for the acetate derivative, which leads to an increase in selectivity when a larger and a smaller metal ion form complexes with the malonate derivative.

^1H NMR Spectroscopy of the Complexes.—The ^1H NMR spectrum of the deprotonated macrocycle $oddm^{4-}$ consists of four signals. Owing to spin–spin coupling, the ethylene protons of the OCH_2CH_2N group appear as two triplets (NCH_2, δ 2.85, OCH_2 δ 3.60), while the protons of the OCH_2CH_2O and malonyl CH groups appear as singlets at δ 3.64 and 3.95, respectively. After complexation, the ^1H NMR signals change significantly, depending on the size of the metal ion. Complex formation with smaller metal ions results in broadening and downfield shifts of the signals (Zn^{2+} and Mg^{2+}, though in the latter case both effects are small). For $[Ca(oddm)]^{2-}$ the NCH_2 protons give two broad signals, whereas the other protons exhibit broad overlapping signals (Fig. 2). The multiplet structures of the ^1H NMR spectra of the complexes $[Sr(oddm)]^{2-}$ and $[Ba(oddm)]^{2-}$ are similar, but the chemical shifts are different. Except for the CH proton, all the protons form multiplets; the signal of the NCH_2 protons at higher field is well separated, while those of the OCH_2 and OCH_2CH_2O protons again overlap (Fig. 2).

The signal of the NCH_2 protons of $[Ca(oddm)]^{2-}$ varies with temperature. On elevation of the temperature the two broad signals coalesce into one broad signal. Upon decrease of the temperature, the two signals split and form a multiplet, which is similar to those observed in the spectra of $[Sr(oddm)]^{2-}$ and $[Ba(oddm)]^{2-}$ (Fig. 3).

The ^1H NMR spectra of $[18]aneN_2O_4$, its acetate derivatives and their complexes have not been investigated in detail. In the solid state only the structure of $[Cu(odda)]^{2-}$ has

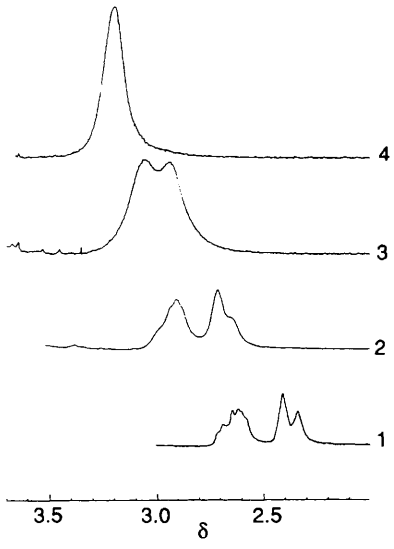


Fig. 3 Proton NMR spectra of $[Ca(oddm)]^{2-}$ at 0 (1), 25 (2), 45 (3) and 65 °C (4)

been studied by X-ray diffraction. Besides the two nitrogen atoms, the two acetate oxygens are co-ordinated to the Cu^{2+} above and below the plane of the four oxygen donor atoms of the macrocycle.[30,31] The similarity of odda and oddm leads to the supposition that in the oddm complexes the two malonate groups are co-ordinated to the metal ion, located inside the macrocycle, on the two sides of the 'plane' of the ring.

The ^1H NMR spectra of the co-ordinated polyfunctional aminocarboxylates depend strongly on the structure of the complex, and also on the average lifetimes of the bonds. If the average lifetimes of the metal–donor atom bonds are relatively long on the NMR time-scale, spectra with a multiplet structure are obtained.[32] In the cobalt(III) complex of *N*-methylethylenediamine-*N*,*N*,*N*′-triacetate the average lifetimes of the Co^{3+}–N and –O bonds are long, the complex possesses a rigid structure, and thus the four protons of the ethylenediamine appear separately in the NMR spectrum, as axial and equatorial protons, which couple with each other to result in an AA′XX′ splitting pattern.[33]

The extensive splitting of the signals of the protons of the group NCH_2CH_2O in the complexes $[Sr(oddm)]^{2-}$ and $[Ba(oddm)]^{2-}$ can also be explained as a result of an AA′XX′-type spin–spin interaction. The disappearance of the intense singlet of the OCH_2 protons and the appearance of the broad overlapping multiplet are similarly due to strong spin–spin interactions. The multiplet structure of the spectra clearly demonstrates that the large Sr^{2+} and Ba^{2+} fit well into the macrocycle, the complexes possess a rigid structure and the average lifetimes of the M–N and –O bonds are long. For the smaller Mg^{2+} and Zn^{2+} the macrocyclic ring is too large, the metal–donor atom interaction is weak, no rigid complex structure is formed and thus no multiplet signals are found in the spectra. The size of Ca^{2+} is larger than that of Zn^{2+}, but it still does not fit sufficiently well into the 18-membered ring, and therefore the properties of its complexes and the character of its ^1H NMR spectrum are between those of the complexes of Zn^{2+} and Sr^{2+}. At higher temperatures the macrocycle is more mobile and the spectrum therefore becomes similar to that of the complex $[Zn(oddm)]^{2-}$ (Fig. 3). On lowering the temperature, this mobility decreases, the average lifetimes of the bonds are longer, and hence signal groups characteristic for the strontium and barium complexes are observed (the signals are occasionally even broader).

In the ^1H NMR spectrum of $odmm^{2-}$ the absence of one malonate group gives rise to two triplet signals for the NCH_2 protons. At the same time no multiplets appear in the spectra of the complexes {*e.g.* for $[Ba(odmm)]^{2-}$ and $[Sr(odmm)]^{2-}$ the signal of the NCH_2 protons adjacent to the malonate group only broadens significantly at 25 °C}, indicating that the structures of the complexes with the larger Sr^{2+} and Ba^{2+} do not become rigid, and the average lifetimes of the metal–donor atom bonds are relatively short on the NMR time-scale.

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