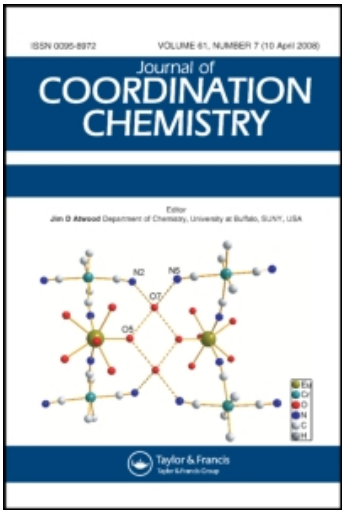

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Synthesis, Potentiometric and ^{1}H NMR Study of Protonation and Complex Formation of 1,4,7-Triazacyclononane-1,4-Diacetate

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SYNTHESIS, POTENTIOMETRIC AND ^{1}H NMR STUDY OF PROTONATION AND COMPLEX FORMATION OF 1,4,7-TRIAZACYCLONONANE-1,4-DIACETATE

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Protonation constants and the protonation scheme of 1,4,7-triazacyclononone-1,4-diacetate (NO2A) have been determined by pH potentiometry and ^{1}H NMR techniques; shielding constants valid for the entire pH range have been calculated. It has been pointed out that the most basic site in the molecule is the unsubstituted secondary amino group. The first two protonation steps belong to ring nitrogens, the third and fourth ones to the carboxylates; the last nitrogen is protonated in very acidic solutions only. Stability constants of complexes of NO2A with selected divalent and trivalent metal ions were determined; with them no indication of kinetic inertness was found. In NO2A complexes the relative contribution of the triazacyclononane ring to the $\log K_{ML}$ values is greater for soft than for hard metal ions, compared to corresponding values for 1,4,7-triazacyclononane-1,4,7-triacetate.

Keywords: Macrocycles; 1,4,7-triazacyclononane; protonation; complexes; NMR; potentiometry; shielding

INTRODUCTION

Macrocyclic complexing agents of the polyazapolyacetate type, whose probably most known representatives are 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (DOTA)[1] and 1,4,7-triazacyclononane-1,4,7-triacetate (NOTA),[2] reached significant theoretical and practical importance in the

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last decade. NOTA complexes of radioactive metal ions have been widely tested for radiolabelling of monoclonal antibodies for tumour imaging and treatment;[3–5] the gadolinium complex of DOTA is used in MRI as a contrast enhancement agent.[6,7] A decade ago, *per-N*-substituted derivatives of polyazacycloalkanes were prepared and their complex formation and NMR properties investigated. Recent developments in the synthesis of regioselectively substituted macrocycles[8–12] and the discovery of the role of kinetically stable protonated intermediates in complex formation processes[13,14] drew our attention to partially substituted triazacyclononane derivatives, first to 1,4,7-triazacyclononane-1,4-diacetate (NO2A). This ligand has been known for several years,[11,15] but to our knowledge most of its complex chemistry remained unstudied. Our aim was to study the effect of a partial *N*-substitution on the protonation mechanism, protonation and complex formation properties of NO2A in order to obtain a better understanding of the contribution of the macrocycle ring and pendant arms to the stability of the complexes and a better prediction of structures for new complexing agents. Here we report protonation constants and protonation mechanism of NO2A determined by both pH potentiometric and ^{1}H NMR techniques as well as its complex formation properties and a novel synthetic procedure for its preparation.

EXPERIMENTAL

All of the solvents and chemicals were of ACS reagent grade or of the commercially available highest quality and used without further purification. The experiments that required anhydrous conditions were carried out in Schlenk-type glassware under a dry nitrogen atmosphere. Continuous and slow addition of the reactants over a long period of time was achieved by a programmable syringe-type electronic pump. NMR spectra were recorded on a Bruker AM360 spectrometer; all chemical shifts are given in ppm relative to either trimethylsilyl propanesulfonate (TSP) in D_2O or tetramethylsilane (TMS) in $CDCl_3$. For pH potentiometric titrations a PHD211 glass electrode, a saturated calomel electrode and a Radiometer PHM85 pH meter equipped with a Radiometer ABU80 automatic burette were used. The titrations were carried out under an argon atmosphere ($I = 1.00\,\text{mol dm}^{-3}$ KCl, 25°C, $pK_w = 13.89$). All pH potentiometric protonation and stability constants were calculated by the computer program PSEQUAD.[16]

1-Trityl-1,4,7-triazacyclononane (1)

This compound was prepared by a method based upon the procedure of Behle *et al.*[10] with the following modifications: 1,4,7-triazacyclononane[2,17] (1.091 g, 8.44 mmol) was dissolved in dry and ethanol-free chloroform (20 cm^3) under a dry nitrogen atmosphere and trityl chloride (2.355 g, 8.44 mmol) dissolved in chloroform (15 cm^3) was added slowly during 1 h at room temperature. The solution was stirred for 16 h, refluxed for 5 min, then evaporated under reduced pressure to give a white solid, which was taken up with 15% sodium hydroxide solution and extracted with chloroform (3 × 50 cm^3). The chloroform solutions were combined, dried over anhydrous magnesium sulfate, filtered and evaporated to give a yellowish oil, which was chromatographed on silica with chloroform–methanol (90 : 10) mixture. The fractions containing the pure product as judged by TLC and NMR were combined and evaporated yielding **1** as a white solid (1.438 g, 3.87 mmol, 45.9%). ^{1}H NMR ($CDCl_3$/TMS): 7.56, 7.20 (m, 15H, arom.H), 3.08 (s, 4H, $-CH_2-N$), 2.98 (t, 4H, $-CH_2-N$), 2.63 (s, 2H, NH), 2.46 (t, 4H, $-CH_2-N-Tr$). ^{13}C NMR ($CDCl_3$): 143.6, 129.8, 127.3, 125.9, 79.37, 53.29, 48.10.

1-Trityl-4,7-di(ethoxycarbonylmethyl)-1,4,7-triazacyclononane (2)

To **1** (1.286 g, 3.46 mmol) dissolved in dry acetonitrile (35 cm^3) was added diisopropyl ethylamine (895 mg, 6.92 mmol) and ethyl bromoacetate (1.156 g, 6.92 mmol) and then the mixture was stirred for 3 days at room temperature. The resulting solution was evaporated under reduced pressure to a yellow oil that was dissolved in ice-cold, dilute sodium hydroxide solution (pH 9.5) and extracted with chloroform (3 × 50 cm^3). The chloroform solutions were combined and dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give a yellow oil, which slowly solidified on standing; this proved to be the pure product **2** as judged by NMR (1.793 g, 3.30 mmol, 95%). ^{1}H NMR ($CDCl_3$/TMS): 7.55, 7.15 (m, 15H, arom.H), 4.14 (q, 4H, $-O-CH_2-$), 3.40 (s, 4H, $-CH_2-COOEt$), 3.05 (m, 8H, $-CH_2-N$), 2.38 (m, 4H, $-CH_2-N(Tr)$), 1.25 (t, 6H, $-CH_3$).

1,4,7-Triazacyclononane-1,4-diacetate trihydrobromid (NO2A)

To **2** (1.24 g, 2.28 mmol) was added to a mixture of 47% hydrobromic acid and glacial acetic acid (16 : 9 volume ratio, total volume 75 cm^3) and the whole mixture was refluxed for 4 h. The solution then was evaporated under

reduced pressure. The residue was triturated with acetone, filtered, washed with acetone and dried under nitrogen to yield NO2A · 3HBr · $5H_2O$ (composition determined by potentiometric titration), which was then further dried *in vacuo* over P_2O_5 at 90°C to constant weight. The product NO2A · 3HBr is a white solid (912 mg, 2.22 mmol, 97%). ^{1}H NMR (NaOD/D_2O): 3.23 (s, 4H, $CH_{2(a)}$), 2.73 (t, 4H, $-CH_{2(d)}$), 2.71 (s, 4H, $CH_{2(c)}$), 2.64 (t, 4H, $CH_{2(b)}$). *Anal.* Calcd. for Br in $C_{10}H_{22}N_3O_4Br_3$ (%): 49.12. Found 48.4.

Calculations

The chemical shift contribution (that is the shift of the chemical shift) ($\Delta\delta_i$) can be expressed by equation (1),[18]

$$\Delta\delta_i = \sum_{j=1}^{N} C_{ij} f_j \tag{1}$$

where C_{ij} is the protonation shift contribution of the ith resonance for total protonation ($f_j = 1$) of the jth protonation site, f_j is the average fraction of time during which the jth site is protonated, and N is the number of the available protonation sites. The chemical shift value of the ith resonance (δ_i) can be given by equation (2);

$$\delta_i = \delta_{i0} + \Delta\delta_i \tag{2}$$

δ_{i0} is determined experimentally from the ^{1}H NMR spectrum for each resonance for $n = 0$; n is the number of proton equivalents added to the molecule and can be given by equation (3),

$$n = \sum \alpha_j f_j \tag{3}$$

where α_j is the number of the equivalent sites of jth type. ^{1}H NMR spectra of NO2A show four resonances, indicating that, due to rapid proton exchange between the different protonation sites, site (1) and (1′) as well as (2) and (2′) are equivalents in pairs; $f_1 = f_{1'}$ and $f_2 = f_{2'}$ and n can be expressed by equation (4):

$$n = 2f_1 + 2f_2 + f_3. \tag{4}$$

The principal object was to determine the f_1, f_2, f_3 and all available C_{ij} values. The number of the C_{ij} values were reduced by assuming that protonation of

a site far enough (four nuclei or more) from the nucleus observed shows no effect on its chemical shift value. Thus C_{a3}, C_{b2}, C_{b3}, C_{c2} and C_{d2} were eliminated and a set of four equations (5)–(8) have been constructed, where subscripted letters *a*, *b*, *c*, and *d* were used for easier identification of variable *i* as shown on Figure 3.

$$\delta_a = \delta_{a0} + C_{a1}f_1 + C_{a2}f_2 \tag{5}$$

$$\delta_b = \delta_{b0} + C_{b1}f_1 \tag{6}$$

$$\delta_c = \delta_{c0} + C_{c1}f_1 + C_{c3}f_3 \tag{7}$$

$$\delta_d = \delta_{d0} + C_{d1}f_1 + C_{d3}f_3 \tag{8}$$

Sum of squares of deviations (D) of the fitted (δ_i) and experimental ($\delta_{i(\text{exp})}$) values were calculated by equation (9).

$$D = \sum(\delta_i - \delta_{i(\text{exp})})^2 \tag{9}$$

During the optimization process D was minimized using the "Optimizer" tool of the computer program Corel Quattro Pro 8. First f_1 and f_2 were fitted (f_3 was determined by equation (4)) while C_{ij} values were kept constant; as an initial estimate C_{ij} values from the literature were used.[18] In the second step C_{ij}s were fitted while f_1, f_2 and f_3 were kept constant. These two steps were performed for each *n* resulting in a matrix of C_{ij}s; we have analysed them in order to find either trends or similar values and selected new C_{ij} parameters supposedly of a broader validity range. The calculation protocol was repeated as many times as necessary to reach a ±0.02 ppm or less maximum deviation for each data point; this was approximately equal to the accuracy of the experimental chemical shifts. Only those C_{ij} values were considered acceptable with which f_1, f_2 and f_3 values reached by the optimization process in step one proved to be independent of their initial value. We found that in the case of NO2A there was no need to handle acidic or basic regions separately from other parts of the titration curves; the set of shielding constants summarized in Table II was found to be valid for the entire pH region. Deviations between the calculated and the experimental chemical shift values are summarized in Table III.

Determinations of the protonation constants have been performed by fitting of equation (10) simultaneously to all data points of the different resonances belonging to the same protonation step using the least-squares

method described previously; results are shown in Table I.

$$\delta = \frac{\delta_A + \delta_{HA} 10^{\log K - pH}}{1 + 10^{\log K - pH}} \quad (10)$$

Equation (10) is constructed for the description of the behaviour of the chemical shifts belonging to one protonation equilibrium only. It can also be used for more than one protonation step if they are quite well separated; if they are close to each other, the chemical shift of the nucleus observed is sensitive to more than one protonation equilibrium, resulting in rapid deterioration of accuracy and erronous results. With NO2A the first and second protonation steps are quite well separated as can be seen in Figure 2 and thus equation (10) can be used for the calculation of $\log K_1$ and $\log K_2$. The higher protonation constants are so close to each other that the results for $\log K_3$ and $\log K_4$ are good as a first estimate only. For $\log K_1$ and $\log K_2$ the deviations of the pH potentiometric and the NMR titration values are approximately 0.2 $\log K$ units, which is around the error level caused by the changing ionic strength and the deuterium effect.

RESULTS AND DISCUSSION

Synthesis

Ligand NO2A has been synthesized according to the reaction scheme shown in Figure 1. The preparation of compound **1** has been achieved by using a modification of the procedure developed by Behle *et al.* for the synthesis of 1,4-dityrityl-1,4,7-triazacyclononane.[10] Coupling of the ethoxycarbonylmethyl side chains to monoprotected triazacyclononane derivative **1** resulted in diester **2**, which was hydrolysed under strongly acidic conditions to the final product NO2A trihydrobromide.

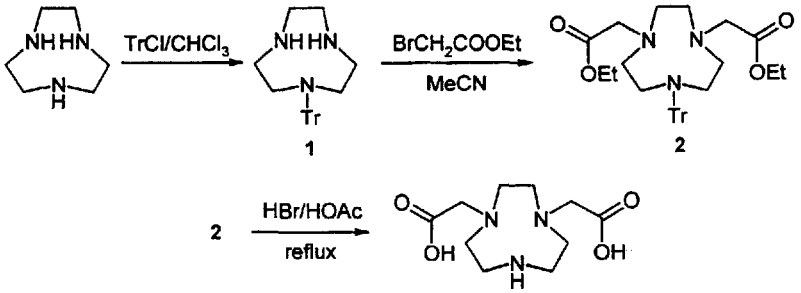

FIGURE 1 Synthetic pathway leading to NO2A.

This procedure is an alternative to known ones, and one of the advantages is the simple synthesis of 1-trityl-1,4,7-triazacyclononane as a useful intermediate, which can be used not only for NO2A but for a variety of other interesting macrocyclic derivatives. The trityl protecting group from **2** can be very easily removed by catalytic hydrogenation over Pd/C in methanol leaving all ester groups unchanged.

Protonation and Complexation Studies

The pH potentiometric studies of NO2A revealed that protonation/deprotonation processes are fairly rapid, and kinetic hindrance has not been observed. The protonation constants of NO2A in comparison with the corresponding values of NOTA are shown in Table I. The first protonation constants of NO2A and NOTA are virtually equal while the second ones show a one order of magnitude higher stability for NO2A; this may be a consequence of the higher flexibility of the NO2A structure, which is the result of less steric bulk and less mutual repulsion of the acetate side chains. The third constants are again fairly close to each other indicating that there is no significant difference in the donor characteristics of the acetates. The moderately lower log K_3 value of NO2A might be the result of the lower number of the pendant arms between which the proton can be shared (Figure 2).

The protonation sequence which can be suggested on the basis of the protonation constants determined by potentiometric titrations is strongly supported by the calculated $f_1 \ldots f_3$ values, showing that the first and the second protons are bound mainly to the ring nitrogen atoms while the third and fourth bind to the carboxylate groups. This scheme is identical with the one found by Geraldes *et al.* for NOTA.[21] The significant difference in the structure of NO2A compared to NOTA is the lack of one acetate group in NO2A and, consequently, the presence of a secondary amino group in the molecule,

TABLE I Protonation constants of NO2A determined by pH potentiometry and ^{1}H NMR techniques in comparison with corresponding values for [9]aneN$_3$ and NOTA

	[9]*aneN*$_3$[a]	*NO2A*[b]	*NOTA*[c]
log K_1	10.42	11.82 [12.05]	11.96
log K_2	6.82	6.70 [6.85]	5.65
log K_3	Very small	2.87 [3.3]	3.17
log K_4		(1.02) [1.6]	n.a.

[a]From Ref. 1. For other values see Ref. 2. [b]Present work, determined by potentiometry, I = 1.0 M KCl. Values in square brackets were determined from ^{1}H NMR titration. [c]From Ref. 19, I = 0.1 M KCl. For other data see Refs. 20–22.

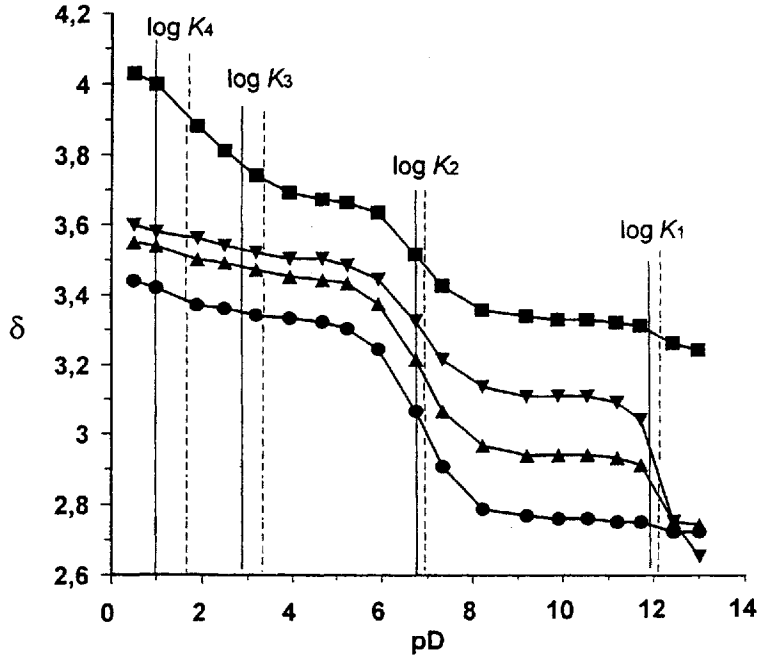

FIGURE 2 ^{1}H NMR titration curve of the individual resonances of NO2A. (■ = *a*, ▼ = *b*, ▲ = *c*, ● = *d*). Solid lines show the protonation constants determined by pH potentiometry; dashed lines indicate the log *K* values calculated from this titraton curve.

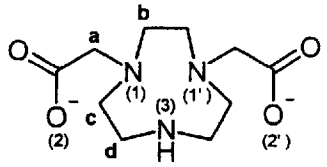

FIGURE 3 Assignment of resonances and protonation sites quoted in the text and in Figure 2 for the fully deprotonated $NO2A^{2-}$ anion ($n = 0$).

under which circumstances the ring nitrogen atoms are not equivalent (Figure 3).

When NO2A is protonated stepwise the first proton is localized on the secondary amino group for the majority of the time (57.2%) and shared with the two carboxylate groups and the remaining two nitrogens of the ring (each 16.0% and 5.4%, respectively). The contribution of the carboxylate groups in the first protonation step is significant; their relatively high protonation ratio indicates that there is hydrogen bonding between the carboxylates and the protonated ring nitrogen atoms. Obviously only one of the

two carboxylates are bound at a time; unfortunately from these results we could not determine whether hydrogen bonds were of intramolecular or intermolecular nature. Introduction of the second proton dramatically changes the hydrogen bonding system resulting in the two protons being shared almost equally by the three ring nitrogens. This might be associated with conformational changes leading to partial deterioration of the hydrogen bonding system between the carboxylates and the ring nitrogens. The third and fourth protons bind to carboxylate groups with negligible change of proton density on the secondary and with a moderate increase on the tertiary amino groups. In summary it has been found that in a regioselectively substituted polyazamacrocyclic polyacetate derivative the basicity of the ring nitrogen atoms differ significantly. In NO2A the secondary amino group is the most basic site of the molecule and the proton density on it does not change significantly with increasing degree of protonation in other parts of the molecule. The contribution of the carboxylates in the hydrogen bonding system varies significantly with the value of n, which might be the consequence of conformational changes of the ring during which a virtually delocalized hydrogen bonded system is formed with the contribution of the ring nitrogen atoms (Tables II and III).

We have determined the stability constants of NO2A with several divalent metal ions and gadolinium(III); the latter one was important for the assumption of potential applicability of the strongly paramagnetic complex

TABLE II Average protonated time fractions and shielding constants calculated for NO2A as a function of the protonation degree n

	$n=1$	$n=2$	$n=3$	$n=4$
f_1	0.054	0.603	0.665	0.740
f_2	0.160	0.037	0.479	0.890
f_3	0.572	0.720	0.738	0.740
Shielding constants:	$C_{a1}=0.75$ $C_{a2}=0.26$	$C_{b1}=0.99$	$C_{c1}=0.83$ $C_{c3}=0.29$	$C_{d1}=0.54$ $C_{d3}=0.74$

TABLE III Comparison of the calculated and experimental chemical shifts using the shielding constants and $f_1 \ldots f_3$ values given in Table II. Experimental shifts are shown in parentheses

Resonance	$n=0$	$n=1$	$n=2$	$n=3$	$n=4$
a	n.a.(3.23)	3.31(3.33)	3.69(3.67)	3.84(3.83)	4.02(4.03)
b	n.a.(2.71)	2.76(2.76)	3.31(3.32)	3.36(3.36)	3.44(3.44)
c	n.a.(2.73)	2.94(2.93)	3.44(3.44)	3.49(3.49)	3.56(3.55)
d	n.a.(2.64)	3.09(3.10)	3.50(3.50)	3.54(3.54)	3.59(3.60)
±max. deviation	n.a.	0.02	0.02	0.01	0.01

TABLE IV Metal ion stability constants of NO2A determined by pH potentiometry in comparison with corresponding values for [9]aneN$_3$ and NOTA

	[9]aneN$_3$	*NO2A*[c]	*NOTA*
Mg^{2+}	n.a.	6.07	9.69[d]
Ca^{2+}	n.a.	5.30	8.92[d]
Zn^{2+}	11.62[a]	17.3	18.3[e]
Cd^{2+}	9.5[b]	13.37	16.0[f]
Mn^{2+}	n.a.	11.56	14.3[g]
Gd^{3+}	n.a.	11.08	13.6[g]

[a]From Ref. 1. For other values see Ref. 2. [b]From Ref. 2. [c]Present work determined by pH-potentiometry, I = 1.0 M KCl. [d]From Ref. 22. For other data see Ref. 20. [e]From Ref. 23. [f]From Ref. 24. [g]From Ref. 25.

[Gd–NO2A] for MR or MRI. The stability constants are summarized in Table IV.

Slow complex formation with the metal ions, especially with gadolinium ions, frequently makes direct potentiometric determinations difficult and therefore we have carefully checked the equilibrium state for each data point and have not found any indication of slow complex formation at all. This was probably a consequence of the open structure of the ligand NO2A compared to NOTA, resulting in a higher flexibility of the acetate pendant arms and the ring.

Several studies pointed out that for 1,4,7-triazacyclononane based ligands the size-preferred alkaline earth metal ion is magnesium, which fits best into the "cavity" of the macrocycle.[11,26–28] Stepwise attachment of well coordinating acetate pendant arms to the triazacyclononane ring gradually increases the stability of the complexes. However, the degree of this increase sharply depends on the nature of the metal ion. With hard magnesium and calcium ions, the $\Delta \log K_{ML(Mg-Ca)}$ value calculated for NOTA and NO2A is the same (0.77 for both) indicating that introduction of a new acetate arm does not change the metal ion selectivity of the ligand. However, NOTA forms (3.5 $\log K$ units) more stable complexes with both magnesium and calcium than NO2A showing that although the selectivity is governed by the macrocycle ring the stability of the complex is determined by the number of the pendant acetate arms. Size-selectivity of the ring as well as "nitrogenophyl" character of the metal ions are dominant for complexes with zinc and cadmium ions; both form fairly stable complexes with NO2A. In these cases the soft nature of the zinc and cadmium ions determines strong binding to the ring nitrogen atoms, as has already been observed with the parent macrocycle [9]aneN$_3$ and is well shown by the high $\log K_{ML}$ values of its complexes.[1,2] In the case of zinc, attachment of two acetate arms to the ring

resulted in a 5.72 log K unit increase in the stability of the NO2A complex compared to [9]aneN$_3$ (that is 2.86 for each acetate), while the third acetate contributed only 1.00 log K unit in NOTA relative to NO2A. With cadmium, each acetate resulted in a 1.93 log K unit contribution to the stability, while the third acetate in NOTA made a 2.63 log K unit increase. This shows that with the smaller zinc ion, which fitted better to the ring, the contributions of the two pendants arms were of almost the same magnitude than the effect of three acetates with the bigger cadmium ion, which required a more densely packed coordination. The role of the pendant arms is somewhat less significant with soft metal ions than with the hard alkaline earth metal ions; in the case of NOTA the increase in stability compared to NO2A is only 2.0 and 2.67 log K unit for zinc and cadmium ions, respectively.

Manganese(II) ions form not only a medium stability complex with NO2A but in the presence of oxygen a redox reaction takes place as well; we have observed the formation of a brown precipitate (probably $MnO(OH)_2$) on contact with the air. This redox-stabilization effect of 1,4,7-triazacyclononane-based ligands (for example 1,4,7-trimethyl-1,4,7-triazacyclononane[29]) is well known for the Mn(III) and Mn(IV) ions. The unexpected thing is that the stability of the [Mn(IV)–NO2A] complex is not high enough to keep Mn(IV) in solution, that is to prevent the precipitation of the low solubility oxide hydroxide.

From the point of view of biomedical applications exceptional importance can be attributed to the paramagnetic gadolinium complex as a potential MRI contrast enhancement agent or MR shift reagent. We found that the thermodynamic stability constant of the [Gd–NO2A] complex is disadvantageously low. In biomedical applications of gadolinium complexes an important factor is the $\log K_{(GdL)}/\log K_{(ZnL)}$ ratio for the estimation of the behaviour of a gadolinium complex *in vivo*; unfortunately, here this value (0.64) proved to be also too low. From these results we estimate that NO2A will not find application in MRI.

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