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PHYSICO-CHEMICAL PROPERTIES OF SOME SEQUESTERING AGENTS RELATED TO ETHYLENEDIAMINE-TETRAACETIC ACID

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The investigations on the chemistry of polyamino-polycarboxylic acids are revieved. Special attention is given to the work going on in the Institute for Medical Research, Zagreb. The proton dissociation constants of EDTA and its C-substituted analoga are discussed and the mode of their ionization according to Tillotson and Staveley is critically reviewed. In the series of C-substituted analoga of the EDTA a lowering of selectivity for calcium is considered. The rare-earth complexes of the above mentioned compounds are considered to be essentially ionic with a certain amount of electrostatic crystal-field stabilization.

Most of the mineral constituents of any animal organism are metals and metaloids. A small number of them can be considered as essential macroconstituents (Na, K, Ca, Mg) because they comprise over 99% of the total metals and metaloids. Other metals are considered microconstituents, some of them being also essential to the normal functioning of the organism (Fe, Mn, Cu, Zn, Mo), mainly because of their catalytic role in biochemical processes.

It is interesting to note that the microconstituents belong to the group of transition-metals, i.e. they possess inner, *d*-orbitals which can be used for the complex formation. Such complexes are generally much more stable than those formed by non-transition metals. All macroconstituents, however, are non-transition metal. Besides these metals, traces of others can be found in the organism, their presence being probably caused by purely ecological reasons (e. g. Pb, Hg, Al).

In certain cases the presence of metal ions can cause pathological changes in the organism. Such cases could be classified as follows: a) presence of a radioactive isotope of any metal, b) the concentration of an essential metal ion is not inside tolerable limits, and c) concentration of a non-essential constituent exceeds a tolerable value.

Pathological conditions classified under a) and c) could, in principle, be treated with complexation therapy if the remedy – the complexant – has sufficiently high affanity towards the toxic metal, and the resulting complexes are soluble and diffusible. Both the complexant and its metal complex should have no – or negligible – toxic properties.

In the present paper a review of the co-ordination chemistry of some potential sequestering detoxificators is given. Special attention is paid to the work done by the collaborators of the Laboratory of Analytical and Physical Chemistry, Institute for Medical Research, Zagreb.

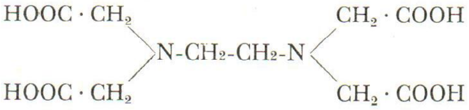
POLYAMINO-POLYCARBOXYLIC ACIDS

The best known representative of the class of chemical compounds named polyamino-polycarboxylic acids is, no doubt, ethylenediamine-tetraacetic acid (EDTA). This compound has been successfully applied in the therapy of a number of metal intoxications (see e. g. ref. 1). The EDTA therapy, however, fails if toxic metals have an affinity towards EDTA comparable to, or lower than, that showed by calcium.

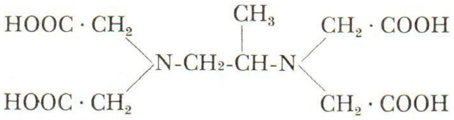
In order to find a chelating substance which would in certain cases (e. g. the ^{90}Sr-contamination) have better pharmacological properties than EDTA, a number of its derivatives and analoga have been synthesized and studied.

The study of C-substituted analoga of EDTA could be of great importance in the co-ordination chemistry of this class of compounds. Especially interesting are such EDTA derivatives that are substituted in the ethylene chain (substitution in the carboxymethyl group would dramatically lower the chelate stability because of steric hindrances).

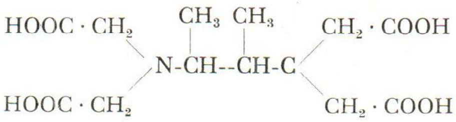
In our Laboratory the following compounds have been prepared: (+)- and (±)-propylenediamine-NN'-tetraacetic acid (PDTA) (2, 3), (±)- and *meso*-1,2-dimethyl-ethylenediamine-NN'-tetraacetic acid (DIMEDTA) (4) and *trans*-cyclopentanediamine-(1,2)-NN'-tetraacetic acid (1,2-CPDTA) (5, 6):



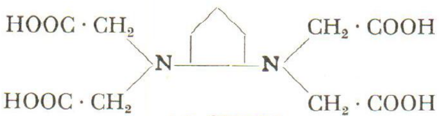
EDTA



PDTA



DIMEDTA



1,2–CPDTA

All the three compounds are C-substituted ethylenediamine-tetraacetic acids (in 1,2-CPDTA the substituent is part of the cyclopentane ring). Also, all the three compounds are optically active. This fact has proved especially important for the structure determination of 1,2-CPDTA: the resolution of this compound into optical antipodes (7) is a fairly strong evidence of its *trans*-configuration, because the corresponding *cis*-compound is a *meso*-form having an axis and a plane of symmetry.

Like EDTA the studied compounds behave as tetrabasic acids. The mechanism of EDTA ionization has been studied by *Schwarzenbach* (8), *Chapman* (9), and *Tilotson* and *Staveley* (10). According to *Tillotson* and *Staveley*, the ionization of EDTA proceeds in several steps: molecular species H_4Y (Y^{-4} denoting the tetranegative anion, ethylendiamine-tetraacetate) has a zwitter-ion structure, one proton being bound to one nitrogen atom and two carboxylate groups being bound by means of a hydrogen bridge.

The ion H_2Y^{-} is formed by the loss of one proton. In this ion each of the two neighbouring carboxylate groups are hydrogen-bridged. The ionic species H_2Y^{-2} is formed by proton detachment from the nitrogen atom. The species H_2Y^{-2} ionizes in such a way that one proton is lost and the other migrates back to the nitrogen atom. The last dissociation step, the formation of Y^{-4} is accomplished by proton detachment from the nitrogen.

Such a mechanism of EDTA ionization has been almost generally accepted because it explains not only the pK values (8) of EDTA but also its IR spectra (9) and heats of neutralization (10). The double zwitter-ion hypothesis proposed by *Schwarzenbach* (8) has been almost fully rejected.

Because the mode of ionization of a ligand has a profound influence on its complexation ability, it is interesting to consider in more detail the results obtained with C-substituted EDTA analoga. pK-values for PDTA, DIMEDTA and 1,2-CPDTA, together with *Schwarzenbach's* values for EDTA (8) and CDTA (cyclohexanediamine-(1,2)-NN'-tetraacetic acid, 11) are shown in Table 1.

The pK values obtained are not easy to explain on the ground of the hypothesis suggested by *Tillotson* and *Staveley* (10) or *Chapman* (9). Exept for CDTA, a significant lowering of pK_1 in respect to EDTA can be observed. According to *Tillotson* and *Staveley*, the substitution in the ethylene chain should affect pK_1 mainly by the inductive effect, but this effect would – for the compounds studied – act in a reverse direction. Similar arguments could be applied for pK_2 values. pK_3

Table 1

pK values and stability constants of alkaline-earth chelates with some polyamino-polycarboxylic acids ($t = 20^0C$, $I = 0.1$ M KCl)

	EDTA[1]	(±)-PDTA[2]	(+)-PDTA[2]	(±)-DIMEDTA[3]	*meso*-DIMEDTA[3]	*trans*-1, 2-CPDTA[4]	*trans*-1, 2-CDTA[5]
pK_1	1.99	1.83	1.88	1.67	1.63	1.87	2.43
pK_2	2.67	2.79	2.75	2.81	2.65	2.44	3.52
pK_3	6.16	6.23	6.24	6.35	6.32	7.48	6.12
pK_4	10.26	10.35	10.34	10.63	10.55	10.09	11.70
$\log K_{MgY}$	8.69	9.49	9.46	8.35	8.30	9.24	10.30
$\log K_{CaY}$	10.70	11.14	11.15	9.09	8.96	11.26	12.60
$\log K_{SrY}$	8.63	9.13	9.16	7.10	7.01	9.42	10.41
$\log K_{BaY}$	7.76	8.12	8.08	5.92	5.86	8.57	8.00
$\log (K_{CaY}/K_{SrY})$	2.07	2.01	1.99	1.99	1.95	1.84	2.19
$\log K_{MgHY}$	2.28	3.11	3.08	2.84	2.56	3.39	—
$\log K_{CaHY}$	3.51	4.30	4.21	3.51	3.63	4.22	5.74
$\log K_{SrHY}$	2.30	2.91	2.58	2.86	2.43	3.09	4.15
$\log K_{BaHY}$	2.07	2.54	2.78	2.14	1.99	2.91	—

[1] Ref. (7)

[2] Ref. (2)

[3] Ref. (3)

[4] Ref. (5)

[5] Ref. (10, 11)

is roughly equal for all the compounds except for CPDTA, which is roughly in accordance with *Tillotson* and *Staveley's* mechanism. Also, pK_4 values, again with the exception of CPDTA, behave as expected.

Although the data presented are not sufficient to give a decisive argument, it seems reasonable to assume the existence of a hydrogen bridge between two nitrogen atoms. In this way the pK_1 and pK_2 values could be partly explained as well as the anomalies shown by CPDTA. The thermochemical studies in the whole series of compounds, as well as spectroscopic investigations, would be extremely useful for a final solution of this question.

ALKALINE EARTH POLYAMINO-POLYCARBOXYLATES

The stability constants of alkaline earth chelates with the sequestering agents studies are shown in Table 1. It can be seen at a glance that the substitution in the ethylene chain profoundly influences the values of stability constants of the complex species $[MY]^{-2}$. An increase of the stability can be found which could be expected because of the inductive effect exerted by aliphatic substituents for DIMEDTA, however, a decrease in stability constants can be observed, probably caused by the steric hindrances exerted by bulky methyl groups. The increase in the chelate stability relative to EDTA as observed with other complexons is not quite well correlated with the increase of basicity.

From the viewpoint of the ^{90}Sr contamination therapy, the relations of the stability constants of strontium chelates to those of corresponding calcium compounds are of interest. Although calcium complexes – in the series studied – are much more stable than strontium ones, the ratio of respective stability constants is, however, decreased from about 120 (for EDTA) to *ca.* 69 (for CPDTA), i. e. for 1.7 times. The diminution of this ratio is caused, we believe, by stereochemical differences in the structure of 1,2-CPDTA relative to EDTA: the substitution in the ethylene chain somewhat increases the nitrogen-nitrogen distance and in such a way the affinity for a somewhat greater ion (strontium) relative to a smaller one (calcium) is slightly increased.

Because the metal-ligand bond in alkaline earth complexonates is mainly electrostatic, one would expect that the chelate stability for a given ligand should increase with the decreasing ionic radius: $Mg > Ca > Sr > Ba$. It can be seen from the values given in Table 1 that this order is partly obeyed in the sequence $Ca > Sr > Ba$ and also, except for CDTA, $Mg > Sr > Ba$. This means that EDTA and closely related complexones possess, to some extent, a selectivity for calcium. This can be observed, although not so evidently, for almost all other complexants. *Weber, Paulić* and *Purec* (6) have found by the regression analysis of data from ref. (13) that there is a correlation between $\log K_{CaY}$ and $\log K_{SrY}$ (Y denoting here any ligand from ref. 13). They have calculated the following regression equation

$$\log K_{SrY} = (0.77 \pm 0.08) \log K_{CaY}$$

(under sign ± the 99% confidence limits of the slope are quoted).

In spite of discouraging conclusions which may be made considering the above equation, there is a possibility, at least a theoretical one, that such an exception from this rule could be found. *Weber* (4) has shown theoretically that the affinity of a complexone towards strontium (relative to that towards calcium) should be mainly dependent on the relative enthalpy of strontium co-ordination (again relative to Ca). This would mean that it would be possible to find a chelating agent selective to strontium to a certain extent, because the relative affinity can be modified e. g. by ligand stereochemical structure.

The stability constants of the so-called »protonated complexes« are also shown in Table 1. This kind of complexes can be represented as $[MHY]^-$ and are considered to be formed from »normal« complexes $[MY]^{-2}$ by detaching and protonating one carboxylate group.

As to the stability constants of these complexes, the same that is said about the $[MY^{-2}]$ complex species, could also be applied to them, although all relations are not so regular, possibly because of a rather large experimental error of K_{MHY}. Slight experimental errors can result in large errors in the K_{MHY} value.

Finally, the stability constants of alkaline earth chelates with (+)- and (±)-PDTA are a contribution to the discussion on the influence of the configuration of an optically active ligand upon the stability of the resulting complexes or – in other words – on the causes of stereoselectivity in co-ordination reactions. It can be seen that the stability constants of both (+)- and (±)-PDTA chelates are equal within the experimental error. This finding is in perfect accordance with the results obtained studying the complexes of natural amino acids with transition metals (15, 16, 17, 18). The contradictory results were obtained in earlier papers (19, 20) and an experimental verification is wanted. A more detailed review of these questions is given elsewhere (1, 21).

RARE EARTH POLYAMINO-POLYCARBOXYLATES

Tripositive ions of the rare-earth metals are known to form extremely stable chelates with EDTA and related ligands (see e.g. ref. 22). These chelates are generally believed to be essentially electrostatic because the tripositive rare-earth ions possess a »closed« electronic configuration: $1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^2 4p^6 4d^{10} 4f^n 5s^2 5p^6$. According to Coulomb's law, the stability of such an ionic compound should increase with the square of the central ion charge and also it should decrease with the increasing radius. For a given metal-ligand pair the ionic chelate stability (measured as log stability constant) should increase linearly with the increasing reciprocal of the central ion radius. Because the ionic radii continuously decrease with the table number increase (»lanthanide contraction«), stability should increase with the table number. *Schwarzenbach et al.* have several times determined the stability constants of all the rare-earth ethylenediamine-tetraacetates (22, 23). They have found that the log stability constants roughly linearly increase with the reciprocal of the ionic radii but that there are some characteristic irregularities.

Schwarzenbach's results for EDTA and CDTA (22) together with the results obtained by *Voloder, Simeon* and *Weber* with PDTA, DIMEDTA and CPDTA are shown in Fig. 1 and in Table 2.

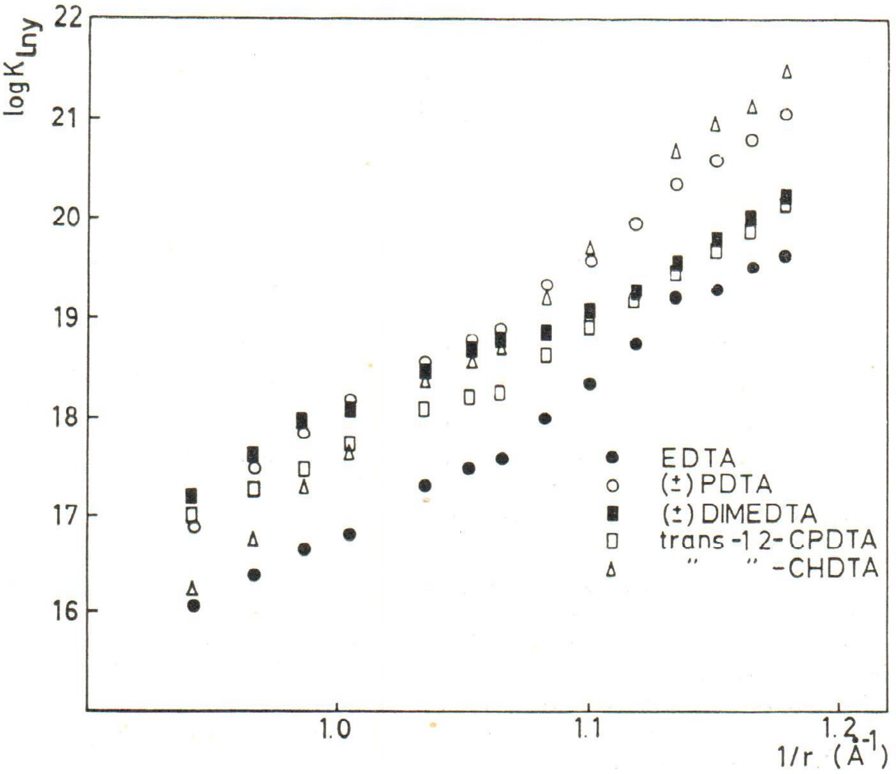


Fig. 1

It can be seen that log stability constants virtually increase with the ionic radius diminution. For EDTA, PDTA, 1,2-CPDTA and 1,2-CDTA the form of this dependence is roughly linear, while the curve for DIMEDTA appears to be of an irregular shape. This could be interpreted by the steric hindrance exerted by the two methyl groups introduced into the ethylene chain which, because of their bukiness, change the geometry of the co-ordination polyhedron somewhere in the middle of the lanthanide series.

Table 2

Stability constants of rare-earth chelates with EDTA and its derivatives
($t = 20^{\circ}C$, $I = 0.1$ M $NaNO_2$)

	EDTA[1]	(±)-PDTA[2]	(±)-DIMEDTA[2]	*trans*-1,2-CDTA[2]	*trans*-1, 2-CPDTA[1]
K_{LaY}	16.05	16.91	17.22	17.01	16.26
K_{CeY}	16.41	17.49	17.60	17.28	16.76
K_{PrY}	16.65	17.84	17.94	17.47	17.31
K_{NdY}	16.82	18.16	18.13	17.72	17.68
K_{SmY}	17.31	18.56	18.56	18.11	18.38
K_{EuY}	17.47	18.78	18.68	18.21	18.62
K_{GdY}	17.53	18.87	18.78	18.24	18.77
K_{TbY}	17.99	19.29	18.85	18.64	19.50
K_{DyY}	18.35	19.56	19.04	18.94	19.69
K_{HoY}	18.73	19.94	19.23	19.24	—
K_{ErY}	19.21	20.34	19.56	19.49	20.68
K_{TmY}	19.27	20.57	19.79	19.71	20.96
K_{YbY}	19.49	20.77	20.00	19.95	21.12
K_{LuY}	19.85	21.05	20.19	20.20	21.51

[1] Ref. (21)   [2] Ref. (23)

From Fig. 1 it can be seen that the points for La, Gd, and Lu lie almost on the same line, while the points denoting other ions are displaced somewhat upwards. To explain the shape of this curve *Schwarzenbach*, *Gut* and *Anderegg* have suggested that EDTA (or other ligands) acts as a sexadentate up to the middle of the series. The geometry according to them should be essentially octahedral. In the middle of the series the lanthanide ions become too small for a six-co-ordination, so that EDTA begins to act as a quinquedentate ligand. *Staveley* and *Randall* (25) suggested an alternative explanation based upon the ligand-field stabilization effects.

Considering the relative magnitudes of lanthanide ions and that of EDTA it can be easily seen that the lanthanides are too large for an octahedral co-ordination. *Hoard* et al. (26,27) have ascertained, by the X-ray diffraction method, that the complexes $H[La(EDTA)(H_2O)_4]$ and $K[La(EDTA)(H_2O_3)]$ possess an essentially dodecahedral geometry, similar to that possessed by the complex ion octacyanomolybdate, $[Mo(CN)_8]^{-4}$ (space group D_{2d}).

To explain the nature of the bond of rare-earth complexonates it would be desirable to calculate the magnitude of the ligand- field stabilization energy (e.g. on the basis of a »Crystal-Field« approximation) and to study UV and visible spectra of these complexes. Considering the data known so far it could be believed that there is a superposition of both phenomena: the ligand-field effect and the change of the mode of co-ordination.

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