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The importance, design and modeling of biodegradable complexants. An extension of the structure-soft character relations

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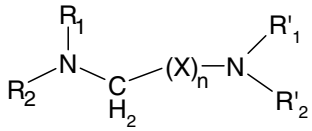
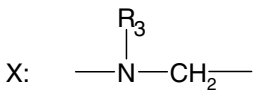
Complexing Chem. or chelating agents are used in plant cultivation to avail of different phytobiologically useful macro- and microelements. The great majority of the traditional chelators (e.g. EDTA) are, however, essentially non-biodegradable, which can lead to environmentally incalculable consequences. In the present work we sum up our results and conclusions on the modeling of the structure-property relationships of some biodegradable complexes in light of modern plant cultivation criteria. We have systematically investigated some new biodegradable ligands with poliamino-polycarboxylic structure, EDTA analogs, using the molecular modeling method and other possibilities of modern computer techniques. These compounds may be considered as a special group of "soft" chemicals. We established mathematical relations between the steric energy of the complexes and the properties of their components. One can conclude that the new complexes with poliamino-polycarboxylic chelators are less stable, therefore easier degradable than the complexes with EDTA. We have drawn conclusions regarding the regression parameters and the stereochemical properties of the complexes and have interpreted the probable causes of the deviations from the theoretically presumable values. The suitability of some general rules known in the complex chemistry (the Dyrssen-Sillen's diparametric compensatory equation, the van Panthaleon-van Eck's, the Schwarzenbach-Ackermnn's, the Irving-Rosotti's, the Larsson's, the Yatsimirsky's relations, the natural stability rank) and the significance of the differences observed were analyzed in detail.

1. Introduction

In some earlier papers (Tőkés et al. 2000, 2005, 2006a, 2006b, 2007) we begun to demonstrate that the retrometabolism concept (Bodor 1996) and especially the soft-hard approach can be extended on phytobiology. Almost ten years ago our first paper (Tőkés et al. 2000) on auxines, namely indole-butyric acid and its soft analogues appeared. The experimentally obtained results on their growth stimulating effect permitted for us to enlarge our knowledge on the mechanism of action of these compounds. The environment and its inhabitants, including humans, are constantly affected by ever increasing amounts of manmade chemicals, which are used for a variety of purposes (Bodor 1996; Boetling 1996; Garrett 1996; Schowanek et al. 1997; Pitter et al. 1999; Száva 1999; Labádi and Száva 2001; Száva 2001). Their design and use are most frequently goal-guided, but the necessity to decrease their toxicity and secondary effects to the possible minimum is stressed rarely, if ever. These effects appear frequently in complex relations and indirectly. From this point of view, it is important to discuss the place and role of numerous complexants in the light of modern plant cultivation as micro- and macroelement (metal) chelators. They are widely used in a variety of consumer products and processes, especially in agriculture. The great majority of traditional chelators (e.g. EDTA) are, however, essentially nonbiodegradable, which can lead to environmentally incalculable consequences. The systematic study of some new biodegradable ligands with polyaminopolycarboxylic structures, projected, synthesized, and patented by our team (Száva 2001a) convinced us that these compounds may be considered as a special group of "soft" and safer chemicals. Their general chemical composition was the following:

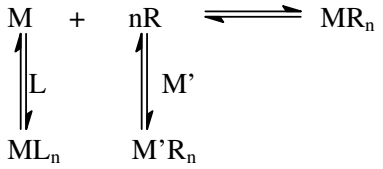


where R_1, R_1', R_2, R_2' are mutually independent hydroxialchyl (C_{2-5}), or carboxialchenyl (C_{2-4}) groups



R_3 may be one from the enumerated before or H, n: 0 or 1. We have studied the structural conditions of biodegradability, especially regarding the new ligands, by the physicochemical characterization of their complexes formed with micro- and macroelements.

The complexity of the investigated competitive equilibriums:



was described (Labádi and Száva 2001; Tőkés et al. 2005, 2006a, 2006b, 2000b) by usual relationships and parameters (absolute and effective stability constants, partial molar fractions, consecutive and overall stability constants, the same parameters for the principal and auxiliary complexing processes etc.).

The biodegradability, that is the reactions that a compound may undergo, is determined by its molecular structure. The studies have resulted in several "rules of thumb" concerning the effects of chemical structure on biodegradability.

The ability to predict relative rates of biodegradation from a chemical structure alone would greatly facilitate the design of safer chemicals. It is easy to observe the analogy between the soft chemicals and the biodegradable ones. There are a few models developed for predicting biodegradability (Boetling 1996). Fragment contribution methods have been used for many years in chemical engineering, and more recently in environmental chemistry. That make semi-quantitative estimates of aquatic biodegradation rates. Data are retrieved from BIODEG, a component of the Environmental Fate Data Base. The models predict biodegradation category correctly for approximately 90%. Both the sign and relative magnitudes of the coefficients are generally consistent with expectation.

Lacking specific knowledge about the environmental behavior of a chemical, the way to design more biodegradable chemicals is to incorporate molecular features such as ester linkage, carboxylic and hydroxyl groups, and exclude halogens, quaternary carbons, nitro groups and other similar groups. The positive and negative features presented in Table 1 are good starting points.

Studies of EDTA-homologues highlighted the fact that the biological stability of these compounds depends on the substituents linked to the nitrogen atoms and a decreasing order of biodegradability could be established:

$-H$, $-COCH_3$, $-CH_3$, $-C_2H_5$, $-CH_2CH_2OH$, $-CH_2COOH$, or: $-NH-CO-CH_3$,

$-N(COCH_3)_2$, and similarly: $-NH-CH_2-COOH$, $-N(CH_2-COOH)_2$.

It was also shown that the biodegradability of heavy metal complexes is better than that of the complexants themselves. For example, the biodegradability of the EDTA$-Fe^{3+}$ complex is about 80% while of EDTA itself is 20–25%. Some complexes from polyaminopolycarboxylic acids are optically active, and their isomers biodegrade to different extent (Schowanek et al. 1997).

Table 1: Structural fragments and coefficients

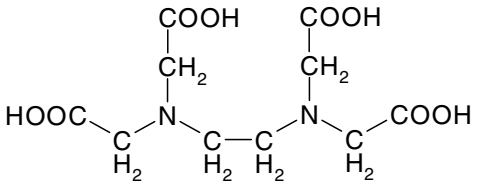
Structural fragment	BIODEG models		Survey models	
	Linear coeff.	Nonlinear coeff.	Primary coeff.	Ultimate coeff.
Aliphatic OH	0.159	1.118	0.129	0.160
Aliphatic NH_2, NH	0.154	1.110	0.043	0.024
Aliphatic O=C−OH	0.073	0.643	0.386	0.365
Tertiary amine	−0.205	−2.223	−0.288	−0.225
Carbon with 4 single bonds and no H	−0.184	−1.723	−0.153	−0.212

2. Investigations, results and discussion

2.1. New biodegradable compounds and their characteristics

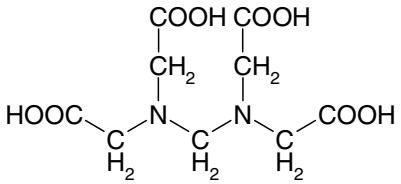
Complexants obtained and investigated by us were the following compounds or some of them:

EDTA:



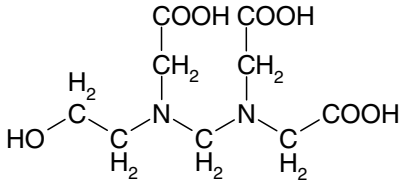
{[2-(Bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}-acetic acid

MDTA:



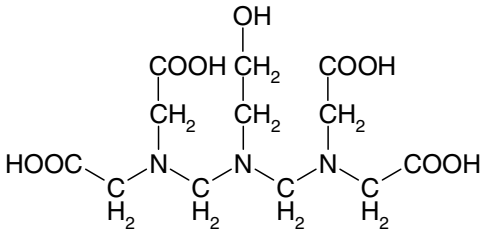
{[(Bis-carboxymethyl-amino)-methyl]-carboxymethyl-amino}-acetic acid

HEMDTA:



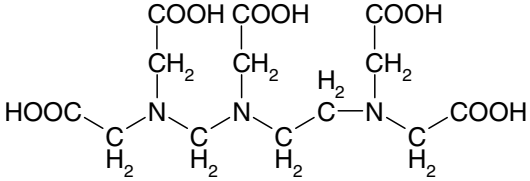
[[(Bis-carboxymethyl-amino)-methyl]-(2-hydroxy-ethyl)-amino]-acetic acid

DMTETA:



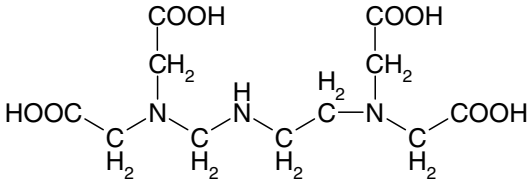
({[[(Bis-carboxymethyl-amino)-methyl]-(2-hydroxy-ethyl)-amino]-methyl}-carboxymethyl-amino)-acetic acid

METPA:



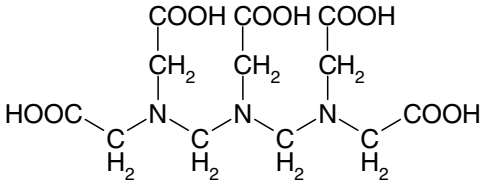
[({[2-(Bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}-methyl)-carboxymethyl-amino]-acetic acid

METTA:



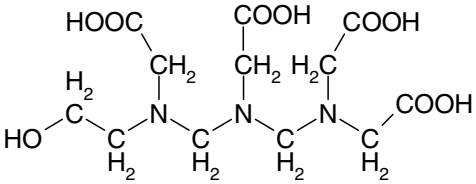
({[2-(Bis-carboxymethyl-amino)-ethylamino]-methyl}-carboxymethyl-amino)-acetic acid

DMTPA:



[({[(Bis-carboxymethyl-amino)-methyl]-carboxymethyl-amino}-methyl)-carboxymethyl-amino]-acetic acid

HEDTTA:



{Carboxymethyl-[(carboxymethyl-{[carboxymethyl-(2-hydroxy-ethyl)-amino]-methyl}-amino)-methyl]-amino}-acetic acid

EDTA = ethylene-diamino-tetraaceticic acid, MDTA = methylene-diamino-tetraacetic acid, HEMDTA = *N*-hydroxy-ethyl-methylene-diamino-threeacetic acid, DMTETA = *N*-hydroxy-ethyl-dimethylene-threeamino-tetraacetic acid, METPA = methylen-ethylene-three-amino-penta-acetic acid, METTA = methylen-ethylene-three-amino-tetra-acetic acid, DMTPA = dimethylene-three-amino-pentaacetic acid, HEDTTA = hydroxy-ethyl-dimethylene-threeamino-tetra-acetic acid.

Table 2: Acidity constants of poly-amino-polycarboxylic acids

Acid	pK_1	pK_2	pK_3	pK_4	pK_5
EDTA	2.00	2.68	6.17	10.27	
DMTETA	2.6	3.0	3.5	7.6	
DMTPA	3.4	4.0	9.8	10.4	10.5
METTA	3.2	3.6	6.6	9.6	
	(2.7	3.5	6.0	9.6)*	
MDTA	3.0	3.2	5.2	9.3	
HEMDTA	3.2	3.6	6.6		

* Reported by an independent laboratory

Parts of results (protonation constants, stability parameters, their pH-dependence) were studied before (Tőkés et al. 2005, 2006a, 2006b). Now, will be examined some interdependences between them and especially the role of the energetic factor. In this context, the proton is considered as a particular term in the complex generator metal ions series (Beck 1965).

The dissociation and the protonation constants of the new, biodegradable polyaminopolycarboxylic acids investigated agree satisfactorily with the corresponding EDTA's values (Table 2).

2.2. Steric energies and correlations

The characteristic steric energies obtained by molecular modeling are composed from the following terms: stretch, bend, torsion, non -1,4-vdW, 1,4-vdW, charge/dipole, dipole/dipole. Steric energies of EDTA as lead compound and of its complexes with different metal ions are presented in Table 3 and compared with some other ions besides the phytophysiologically important micro- and macroelements.

A monotonous relation can only be seen between elements from the same group and dominates the ion-dipole term followed by the dipole-dipole component. Linear correlations for the overall energies are observed mainly with the charge number and the ionic radius, but only for elements from the same group (ex. the group II/A; Table 4).

The overall steric energies for every metal ion-ligand complexes, and a statistical evaluation of some correlations between these energies and certain parameters of metal ions are presented in Table 5.

Energies of these compounds are smaller in every case than those of the adequate ADTA complexes. This result suggests that their reactivity is higher and – consequently – their biodegradability is better than that of EDTA. This conclusion concords with the structural modification applied compared to the reference compound. Therefore, the energy variations may reflect the relative extent of biodegradability.

Looking for the most real interdependences between the steric energy and different characteristics we established acceptable or excellent multiple linear correlations in function of 4 variables of the central ions: ionization energy, ion radius, its charge (valence) and the charge number of elements (11 metal ions).

Table 3: Steric energies of EDTA and its complexes, E (kcal/mol)

	Na^+	K^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	Zn^{2+}
Stretch	1.39	1.43	1.36	1.48	1.67	1.79	1.41
Bend	7.75	9.08	10.24	9.57	8.80	8.66	9.64
Stretch-Bend	0.65	0.71	0.62	0.66	0.71	0.73	0.63
Torsion	−10.30	−7.32	−8.77	−8.90	−10.55	−10.05	−9.18
Non-1,4 VDW	−1.68	−10.38	11.72	11.57	8.09	8.04	11.02
1,4 VDW	8.70	8.84	10.15	9.93	9.02	8.66	9.94
Charge/dipole	−46.27	−31.97	−130.96	−120.88	−102.38	−90.46	−120.46
Dipole/dipole	14.95	10.08	18.67	17.82	16.58	16.25	17.74
Total	−24.80	−19.53	−86.98	−78.75	−68.04	−56.38	−79.27

Table 4: Linear correlations between the overall steric energies (E) and the charge numbers (Z), and ionic radii (R)

Ions	− E (kcal/mol)	Z	R (Å)
Mg^{2+}	86.98	12	0.72
Ca^{2+}	78.75	20	1.00
Sr^{2+}	68.04	38	1.26
Ba^{2+}	56.38	56	1.42
Intersection	−93.76	−119.27	
Slope	0.67	42.48	
Correlation coefficent	0.996	0.982	

The regression equations are as follows:

EDTA

$$E = 22.24 + 0.40^{*}Ip + 5.00^{*}R - 61.84^{*}T + 0.60^{*}Z \quad (1)$$

$$r^2 = 0.984, \quad V = -0.058, \quad S = 4.0, \quad F = 140$$

The reproducibility, residual and other statistical parameters were calculated, as well. The distribution, nearly normal, is reflected by the histogram of residuals and the normal probability plot of residuals, respectively (Figs. 1 and 2).
For the biodegradable complexes:

METTA

$$E = 28.53 + 0.48^{*}Ip + 9.95^{*}R - 65.77^{*}T + 0.53Z \quad (2)$$

$$r^2 = 0.993 \quad V = -0.053 \quad S = 3.5 \quad F = 219$$

MDTA

$$E = 19.87 + 0.16^{*}Ip + 4.05^{*}R - 43.46^{*}T + 0.41^{*}Z \quad (3)$$

$$r^2 = 0.993 \quad V = -0.053 \quad S = 2.4 \quad F = 208$$

DMTETA

$$E = 30.15 + 0.28^{*}Ip + 7.07^{*}R - 51.32^{*}T + 0.45^{*}Z \quad (4)$$

$$r^2 = 0.994 \quad V = -0.060 \quad S = 2.7 \quad F = 228$$

HEMDTA

$$E = 27.66 + 0.41^{*}Ip + 6.98^{*}R - 58.33^{*}T + 059^{*}Z \quad (5)$$

$$r^2 = 0.986 \quad V = -0.078 \quad S = 4.3 \quad F = 109$$

DMTPA

$$E = 26.21 + 0.30^{*}ip + 7.19^{*}R - 59.91^{*}T + 0.57^{*}Z \quad (6)$$

$$r^2 = 0.992 \quad V = -0.058 \quad S = 3.6 \quad F = 177$$

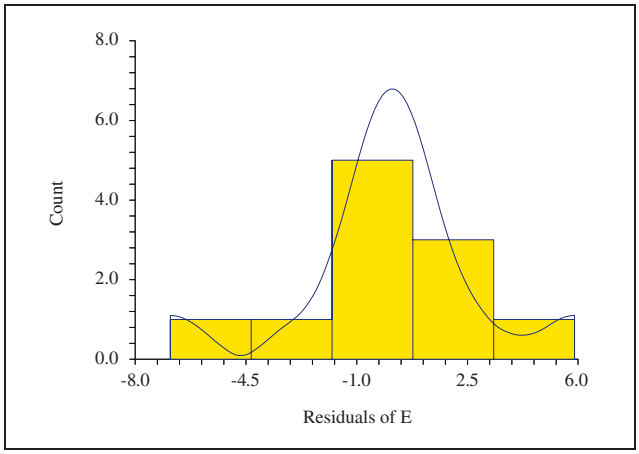


Fig. 1: Histogramm of residuals of E (EDTA, cf. Eq.1)

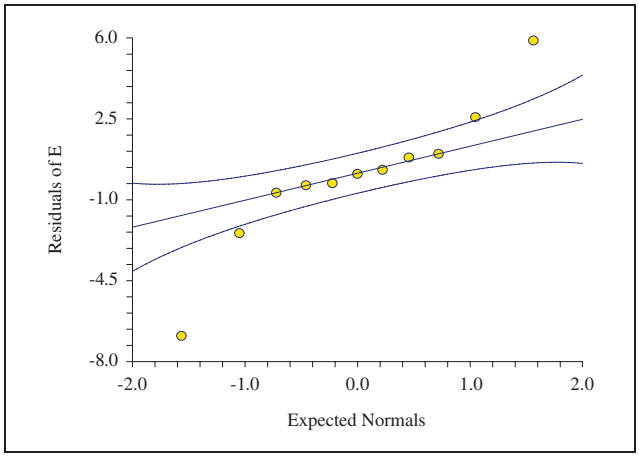


Fig. 2: Normal probability plot of residuals of E (EDTA, cf. Eq. 1)

From the regression equations it is visible that the biggest ponders have the charges and the ionic radii. They are opposites and suggest the validity of the ionic potentials. The correlation coefficients vary parallel to the F values. That permits some supplementary comments on these interdependences. The F parameter has a minimum at HEMDTA and its histogram differs mostly from normal, it is asymmetrical, even bimodal. This distortion is interpreted as an expression of more complexity of the interaction mechanism compared to other ligands.
Some correlations were established between the experimental stability constants and other parameters obtained from structure models, experimental data or from the literature. At first, it is interesting to mention that the logarithms of stability constants vary approximately linearly in

Table 5: Steric energies of some EDTA analogue complexes (E, kcal/mol)

Ions	EDTA	MDTA	HEMDTA	DMTETA	DMTPA	METTA
	4.79	7.49	10.41	12.70	8.40	11.25
Na^{+}	−24.80	−13.72	−12.90	−6.80	−18.02	−17.75
K^{+}	−19.53	−9.60	−8.87	−1.51	−11.93	−10.91
Mg^{2+}	−86.97	−58.50	−74.52	−59.96	−80.59	−84.85
Ca^{2+}	−78.75	−52.34	−63.88	−52.69	−70.81	−76.22
Sr^{2+}	−68.04	−43.28	−51.40	−42.08	−58.44	−63.35
Ba^{2+}	−56.38	−37.46	−42.99	−35.36	−50.20	−55.33
Mn^{2+}	−77.06	−52.34	−63.88	−52.69	−70.81	−76.22
Cu^{2+}	−69.53	−47.08	−54.95	−46.83	−63.41	−68.43
Fe^{3+}	−132.18	−93.03	−115.27	−99.74	−127.08	−134.53
Fe^{2+}	−69.53	−47.08	−56.75	−47.03	−64.74	−68.43
Zn^{2+}	−79.27	−52.34	−65.65	−52.95	−72.38	−76.22

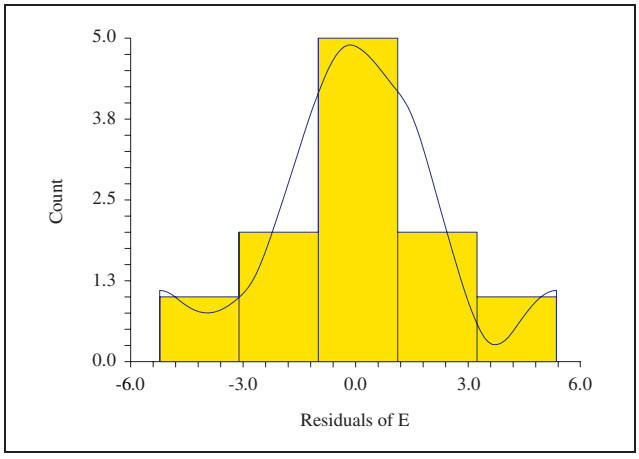


Fig. 3: Histogram of residuals of E (METTA, cf. Eq. (2))

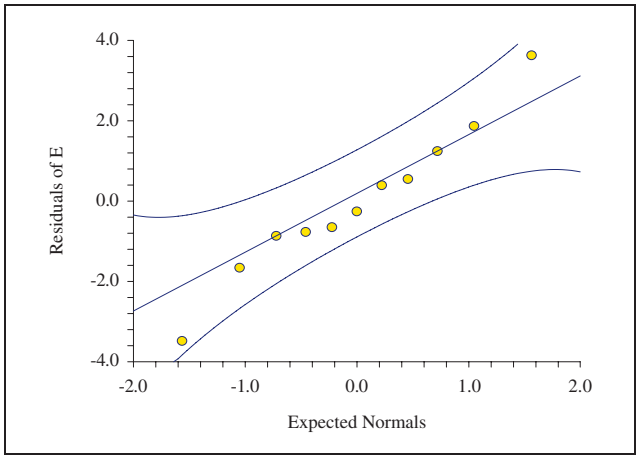


Fig. 6: Normal probability plot of residuals of E (MDTA, cf. Eq. (3))

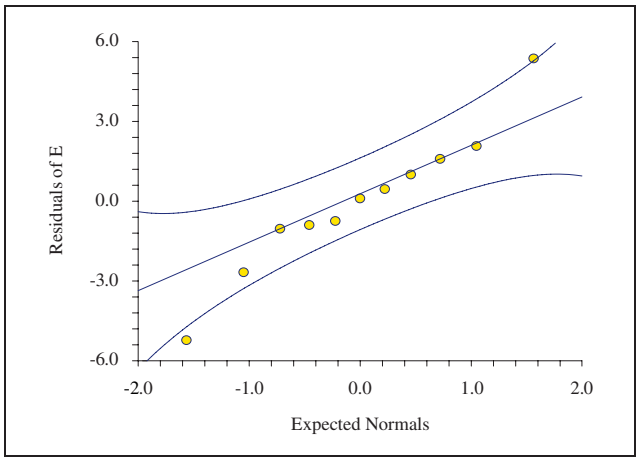


Fig. 4: Normal probability plot of residuals of E (METTA, cf. Eq. (2))

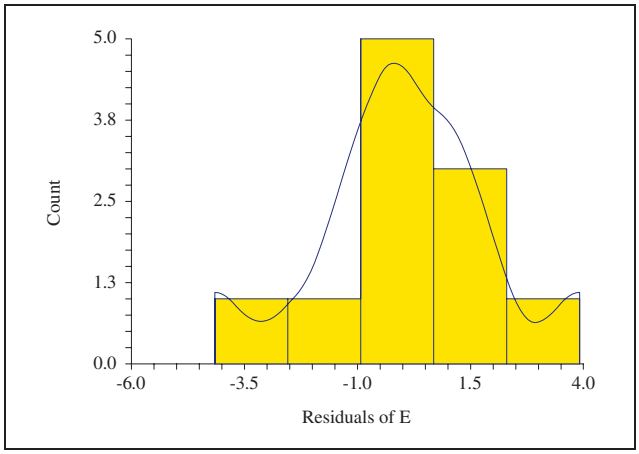


Fig. 7: Histogramm of residuals of E (DMTETA, cf. Eq. (4))

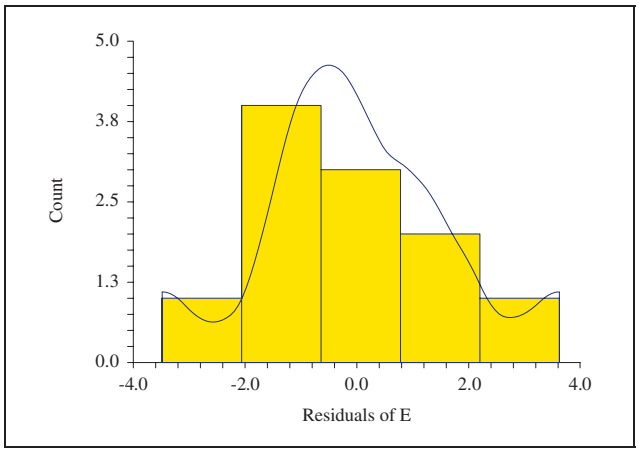


Fig. 5: Histogramm of residuals of E (MDTA, cf, Eq. (3))

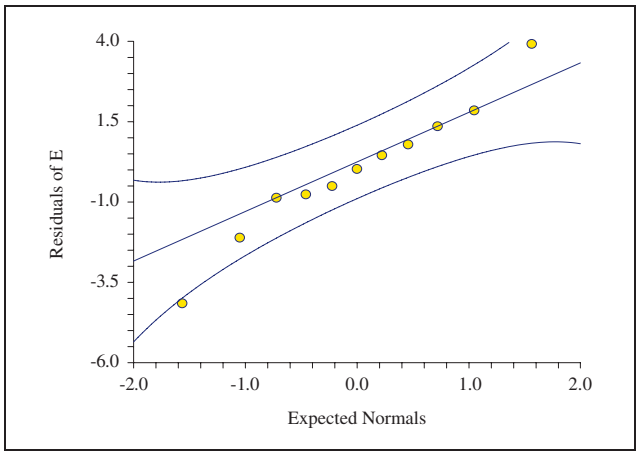


Fig. 8: Normal probability plot of residuals of E (DMTETA, cf. Eq. (4))

function of the same 4 characteristics, but in this case the ponders are more equilibrated. This statement is exemplified by EDTA (Fig. 13).

$$\lg \mathrm{Kst} = 3.4873 + 1.2148 \cdot \mathrm{Ip} + 1.2699 \cdot \mathrm{R} - 5.9774 + 5.5134 \cdot 10^{-2} \cdot \mathrm{Z} \quad (7)$$

$$r^2 = 0.946\ \mathrm{V} = -0.100\mathrm{S} = 6.2\ \mathrm{F} = 17.4$$

It is interesting but explainable, that although both of $\lg K_{st}$ and the overall steric energy correlate linearly with the same variables, the correlation between them is more or less convincable. It must however be kept in mind that in these regression equations the coefficients are essentially different and reflect structural particularities of molecules.

2.3. The Dyrssen-Sillen's equation

It seems useful to take a look at the rule of successive complexation constants (the diparametric compensatory equation of Dyrssen-Sillen):

$$\frac{K_n}{K_{n-1}} = \frac{K_{n+1}}{K_n} \quad (8)$$

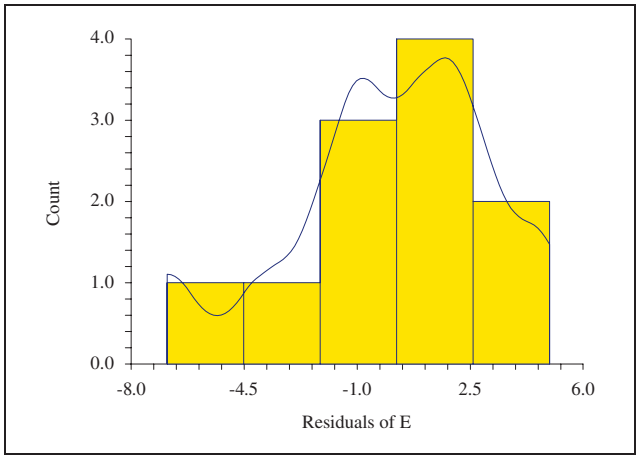


Fig. 9: Histogram of residuals (HEMDTA, cf. Eq. (5))

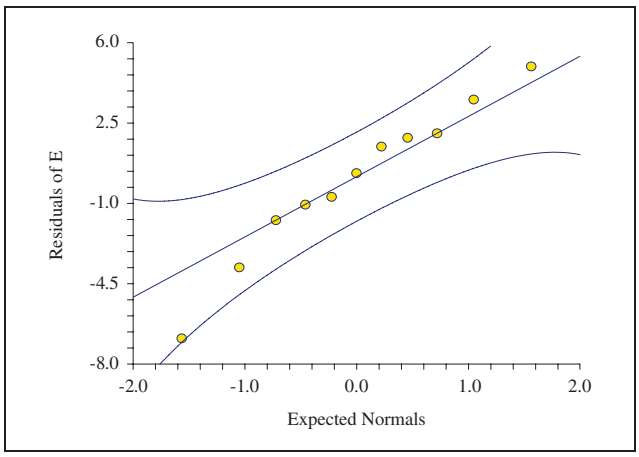


Fig. 10: Normal probability plot of residuals of E (HEMDTA, cf. Eq. (5))

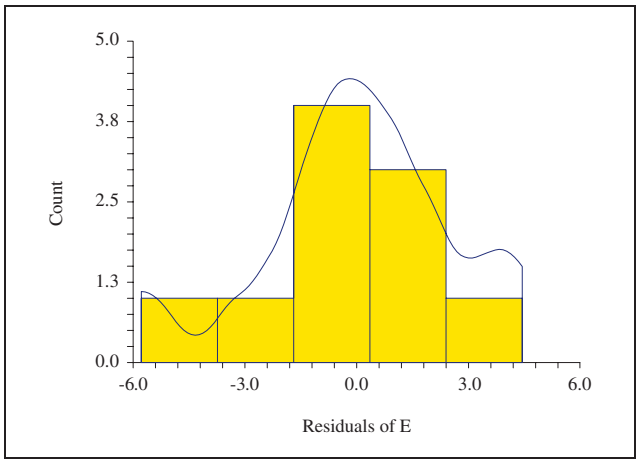


Fig. 11: Histogram of residuals of E (DMTPA, cf. Eq. (6))

or

$$K_n = \sqrt{K_{n-1}K_{n+1}} \qquad (9)$$

respectively

$$\lg K_n = (1/2)\,(\lg K_{n-1} + \lg K_{n+1}) \qquad (10)$$

This rule is not applicable to EDTA analgues because their complexation ratio is almost always 1 : 1. But, in the particular case of protonation constants, these relations, in principle, may be valid. We will examine comparatively the calculated and the experimental values:

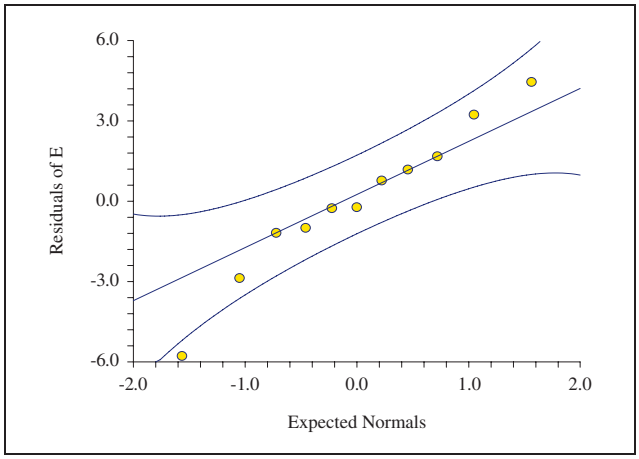


Fig. 12: Normal probability plot of residuals of E (DMTPA, cf. Eq. (6))

EDTA — experimental

$$\lg K_3 = (1/2)(2.00 + 6.17) = 4.08 \quad \lg K_3 = 2.68 \qquad (11)$$

$$\lg K_2 = (1/2)(2.68 + 10.27) = 6.97 \quad \lg K_2 = 6.17 \qquad (12)$$

It is visible that between the compared constants there are significant differences. In general, this statement refers to all compounds.

DMTETA

$$\lg K_3 = (1/2)(2.6 + 3.5) = 3.0 \quad \lg K_3 = 3.0 \qquad (13)$$

$$\lg K_2 = (1/2)(3.0 + 7.6) = 5.1 \quad \lg K_2 = 3.5 \qquad (14)$$

DMTPA

$$\lg K_4 = (1/2)(3.4 + 9.8) = 6.6 \quad \lg K_4 = 4.0 \qquad (15)$$

$$\lg K_3 = (1/2)(4.0 + 10.4) = 7.2 \quad \lg K_3 = 9.8 \qquad (16)$$

$$\lg K_2 = (1/2)(9.8 + 10.5) = 10.1 \quad \lg K_2 = 10.4 \qquad (17)$$

METTA

$$\lg K_3 = (1/2)(3.2 + 6.6) = 4.9 \quad \lg K_3 = 3.6 \qquad (18)$$

$$\lg K_2 = (1/2)(3.6 + 9.6) = 6.6 \quad \lg K_2 = 6.6 \qquad (19)$$

MDTA

$$\lg K_3 = (1/2)(30 + 5.2) = 4.1 \quad \lg K_3 = 3.2 \qquad (20)$$

$$\lg K_2 = (1/2)(3.2 + 9.3) = 6.2 \quad \lg K_2 = 5.2 \qquad (21)$$

HEMDTA

$$\lg K_2 = (1/2)(3.2 + 6.6) = 4.9 \quad \lg K_2 = 3.6 \qquad (22)$$

A probable explanation of differences is based on the particular character of the proton compared to other cations, furthermore to complex phenomena conditional to steric structure of ligands and to possible conformational modifications due to successive binding of protons, that determining in different way the following protonation or complexation steps.

2.4. The van Panthaleon van Eck's equation

Van Panthaleon and van Eck proposed the following relation for complexation research:

$$\frac{\lg \beta_n}{n} = \lg \beta_1 - \lambda(n-1) \qquad (23)$$

From this it follows that the ($\lg \beta_n$/n, n) values must situate on a straight line and its slope is -λ. For our ligands see Figs. 13–18.

The correlation equations emphasize some structural effects. For example, in the presence of 5 carboxyl groups

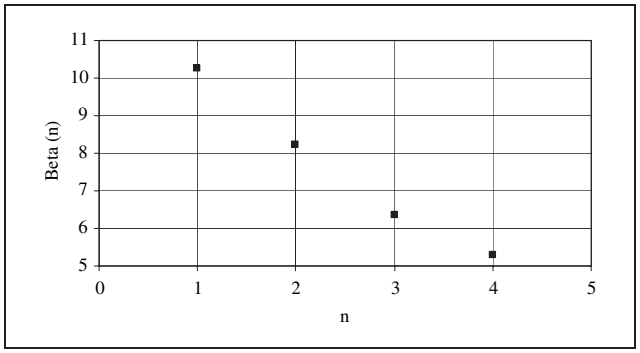


Fig. 13: Correlation y = f(x) at EDTA: n = 4, $lg\beta_1 = 11.74$, $\lambda = -1.68$, r = −0.991

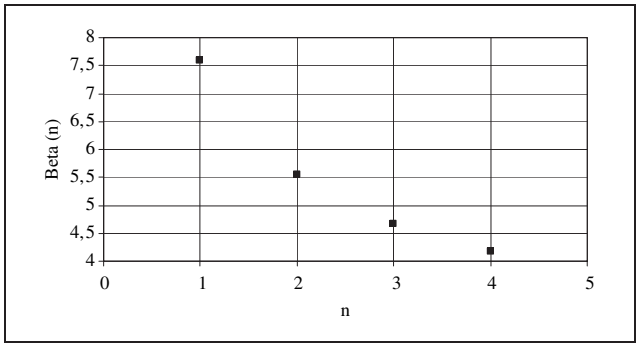


Fig. 14: Correlation y = f(x) at DMTETA: n = 4, $lg\beta_1 = 8.29$, $\lambda = -1.12$, r = −0.952

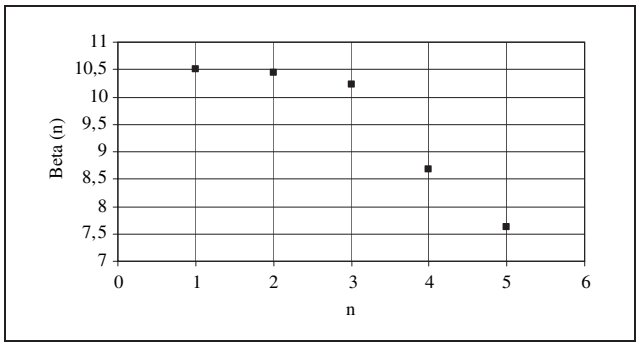


Fig. 15: Correlation y = f(x) at DMTPA: n = 5, $lg\beta_1 = 11.76$, $\lambda = -0.75$, r = −0.923

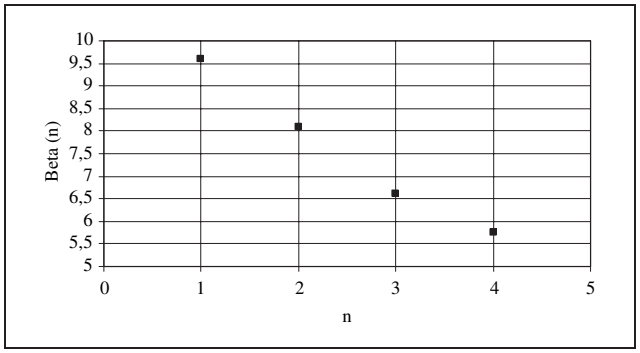


Fig. 16: Correlation y = f(x) at METTA: n = 4, $lg\beta_1 = 10.78$, $\lambda = -1.30$, r = −0.993

(DMTPA) the drawn line deviates visibly from linearity, it seems to be formed from right lines intersected at n = 3. Similarly, in the presence of a hydroxyethyl group, the slope is decreased significantly compared to the other compounds.

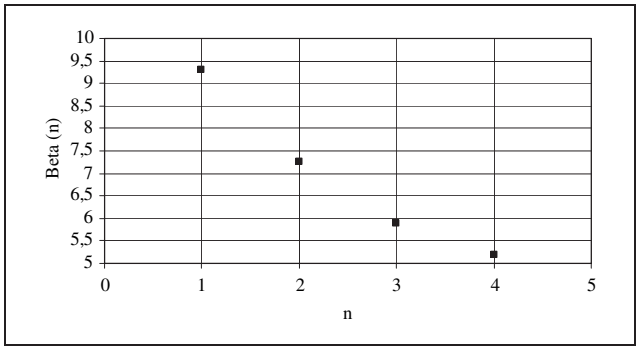


Fig. 17: Correlation y = f(x) at MDTA: n = 4, $lg\beta_1 = 10.34$, $\lambda = -1.37$, r = −0.977

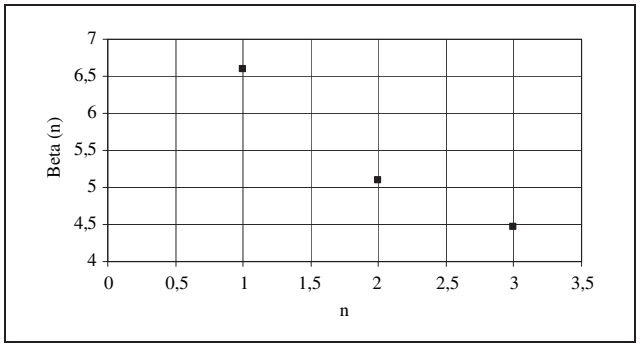


Fig. 18: Correlation y = f(x) at HEMDTA: n = 3, $lg\beta_1 = 7.53$, $\lambda = -1.07$, r = −0.974

2.5. Correlations between the stability and protonation constants. The Irving-Rosotti's rule

As demonstrated before, the logarithms of the protonation constants of the EDTA analog biodegradable ligands correlate linearly with the similar data of EDTA. The linearity is most weak for DMTPA. The slopes for succesive steps are smaller than for EDTA. This fact is explainable also with stereochemical particulartities of terms; the slope is the smallest for DMTETA, where the dissociable carboxyl groups are situated mutually at the biggest distances and at HEMDTA where the structure of the neighbouring groups is dramatically modified.

$$pK_{a(DMTETA)} = (0.45 \pm 0.05)pK_{a(EDTA)} + (3.02 \pm 0.26) \quad (24)$$

$$n = 4; \quad r = 0.988; \quad s_0 = 0.44$$

$$pK_{a(DMTPA)} = (0.90 \pm 0.26)pK_{a(EDTA)} + (2.12 \pm 1.64) \quad (25)$$

$$n = 4; \quad r = 0.925; \quad s_0 = 1.73$$

$$pK_{a(META)} = (0.785 \pm 0.021)pK_{a(EDTA)} + (1.60 \pm 1.34) \quad (26)$$

$$n = 4; \quad r = 0.992; \quad s_0 = 0.14$$

$$pK_{a(MDTA)} = (0.760 \pm 0.086)pK_{a(EDTA)} + (1.15 \pm 0.53) \quad (27)$$

$$n = 4; \quad r = 0.988; \quad s_0 = 0.12$$

$$pK_{a(HEMDTA)} = (0.829 \pm 0.037)\, pK_{a(EDTA)} + (1.46 \pm 0.15) \quad (28)$$

$$n = 3; \quad r = 0.990; \quad s_0 = 0.12$$

Since EDTA complexes were thoroughly investigated, and there is a rich corresponding database in the literature (Anderegg 1997; Pettit and Powell 1997), the above equations allow the prediction of the stability of analog complexes for the present experimentally unknown cases. It is interesting that the same correlations between the parameters of the new ligands are better compared to EDTA:

$$\lg K_{St(MDTA)} = (0.929 \pm 0.092)\, \lg K_{St(HEMDTA)} + (0.061 \pm 1.43) \quad (29)$$

$$n = 5; \quad r = 0.981; \quad s_0 = 0.88$$

$$\lg K_{St(MDTA)} = (2.00 \pm 0.16)\, \lg K_{St(DMTETA)} - (8.06 \pm 1.84) \quad (30)$$

$$n = 5; \quad r = 0.994; \quad s_0 = 0.58$$

$$\lg K_{St(MDTA)} = (1.19 \pm 0.13)\, \lg K_{St(METPA)} - (3.45 \pm 2.00) \quad (31)$$

$$n = 5; \quad r = 0.976; \quad s_0 = 0.99$$

$$\lg K_{St(DMTETA)} = (0.468 \pm 0.045)\, \lg K_{St(HEMDTA)} + (4.28 \pm 0.73) \quad (32)$$

$$n = 5; \quad r = 0.986; \quad s_0 = 0.36$$

$$\lg K_{St(HEMDTA)} = (1.27 \pm 0.13)\, \lg K_{St(METPA)} - (3.40 \pm 1.96) \quad (33)$$

$$n = 5; \quad r = 0.974; \quad s_0 = 0.97$$

$$\lg K_{St(DMTETA)} = (0.550 \pm 0.105)\, \lg K_{St(METPA)} + (3.31 \pm 1.63) \quad (34)$$

$$n = 5; \quad r = 0.950; \quad s_0 = 0.68$$

According to a generally known rule (Irving and Rosotti), the stability constants ($\lg K_{st}$) of complexes formed between different ligand series and the same metal ions in each, separately, are correlated linearly with each other. This rule is valid inversely too: between metal ion series and selected ligands. One must underline, that the linearity is satisfied for cations with the same valence. For example:

$$\lg K_{st(Cu)} = (1.50 \pm 0.26)\, \lg K_{st(Zn)} - (1.65 \pm 4.06) \quad (35)$$

$$n = 5; \quad r = 0.981; \quad s_o = 0.88$$

but

$$\lg K_{st(Cu)} = (0.55 \pm 0.16)\, \lg K_{st(FeIII)} + (6.8 \pm 3.0) \quad (36)$$

$$n = 5; \quad r = 0.86; \quad s_o = 1.35$$

2.6. The Yatsimirsky's rule

Yatsimirsky compared the stability constants of complexes formed with metal ions having the same radii and valences (for ex. Mg^{2+}, Zn^{2+}). The differences

$$\lg K_{Zn} - \lg K_{Mg} = \Delta\lg K_{ZnMg} \quad (37)$$

denote the contribution of the covalent character of coordinative bonds. The presence at this bond of oxygen and nitrogen atoms involves constant increments in $\Delta\lg K_{ZnMg}$ values:

$$\Delta\lg K_{ZnMg} = 2.8n_N + 0.6n_O \quad (38)$$

This relation permits to identify the nature and number of functional groups coordinatively binding with metal ions. For example:

$$\text{EDTA}: \ \Delta\lg K_{ZnMg} = 16.5 - 8.7 = 7.8 \quad (39)$$

$$2.8n_N + 0.6n_O = 7.8 \quad (40)$$

That is aproximated by $n_N = 2$ and $n_O = 4$ values ($2.8^*2 + 0.6^*4 = 8.0$) which acceptablelly corresponds to formation of 5 penta-cycles.

$$\text{METTA}: \ \Delta\lg K_{ZnMg} = 12.6 - 5.5 = 7.1 \quad (41)$$

$$2.8n_N + 0.6n_O = 7.1 \quad (42)$$

that is $n_N = 2$ and $n_O = 2$ ($288^*2 + 0.6^*2 = 6.8$), and suggests the possibility of formation of a binuclear complex.

It is important to see that the affinity of interactions contains – besides the reaction heats – the changes of entropies, also. From this point of view, the leaving of water molecules has an entropy increasing effect (favorable for the affinity), while the formation of chelat-cycles causes (unfavorable) entropy-diminuation.

2.7. The natural stability rank

Comparing the results it is visible that steric energies and stabilities of complexes with different metal ions reflect the natural stability rank, conditioned by the electron-structures, namely: Mn < Fe(II) < Co(II) < Ni < Cu > Zn. For example see Table 6.

Table 6: Natural stability rank order of EDTA-metall ion complexes

Ion:	Mn(II)	Fe(II)	Co(II)	Ni(II)	Cu(II)	Zn(II)
$\lg K_{st}$:	13.47	14.45	16.10	18.45	18.80	16.50
E (kcal/mol):	−77.07	−69.53	–	–	−69.53	−79.27

3. Experimental

3.1. Materials

A series of biodegradable, EDTA analog compounds, having the general formula presented in chapter 1 was investigated. For comparison, the determinations were completed with EDTA having a biodegradability of 20–25% only. All biodegradable ligands were designed, synthesized and biologically tested by Dr. E. J. Szava Ingenieurbüro (München, Germany). Their biodegradability (measured by the OECD 301B method, in closed system) was at least of 80% (Száva 2001a).

The complex generator metal ions (Ca^{2+}, Mg^{2+}, Cu^{2+}, Mn^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+}) were added to the system as their water soluble salts. All chemicals were of the Merck p.a. quality.

3.2. Instruments

The determinations were completed by a Multimeter, model Consort 835, a potentiometer (pH-meter) Jenway, glass-electrodes P10NB, and a spectrophotometer Jenway 6405 UV-VIS. For the study of complexes, selection of the stable conformations and calculation of the steric energies, and molecular dynamics parameters a Chem3D © Cambridge Soft 10.0 Ultra program was used. The statistical calculations were performed by means of a program elaborated within our research team (Regress, Regressm, © Ferencz L.).

3.3. Methods

The most important methods applied to determination of biodegradable ligands and complex' parameters were diverse potentiometric and spectro-

photometric techniques (Dudutz 1976; Labadi and Szava 2001). To optimization and uniformity of operations adequate algorithms were elaborated.

This research paper was presented during the 6th Conference on Retrometabolism Based Drug Design and Targeting, June 3–6, 2007, Göd, Hungary.

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