

«normalen» Wert 1,394 Å ab. Auffällig im siebengliedrigen Ring sind der stark gespreizte Winkel C3–C4–C5 von 132° ($\pm 0,9$), und die ungleichen Torsionswinkel C3–C4–C5–C6 von 14° und C5–C6–C7–C12 von 72° ($\pm 1,4$). Die Doppelbindung C13–C14 und die anschliessenden Atome C3, C12 und C15 liegen ebenfalls in einer Ebene (mittlere Abweichung von der LS.-Ebene 0,01 Å). Die Länge der Doppelbindung, 1,33 Å ($\pm 0,01$), entspricht einer isolierten Doppelbindung ohne Konjugation mit den benachbarten aromatischen Systemen. Die Winkel zwischen der Doppelbindungsebene und der Benzolringebene einerseits und der Thiophenringebene andererseits betragen 55° bzw. 36°, der Winkel zwischen Thiophen- und Benzolringebene 48°.

Die in *trans*-Stellung zum Thiophenring stehende Seitenkette C15–C16–N–C18 bildet eine gestreckte Kette, deren mittlere Ebene einen Winkel von etwa 45° mit der Ebene der Doppelbindung einschliesst (siehe Torsionswinkel in Figur 3). Aus der Figur 1 ist ferner ersichtlich, dass auch die H-Atome der Methylgruppen die energetisch günstige «staggered» Konformation einnehmen.

Die N–H...Cl Wasserstoffbrücke ist nahezu vollkommen linear, N–H 0,73 Å, H...Cl 2,25 Å und N...Cl 2,98 Å. Die sehr kurze N–H-Bindung ist wohl als zufällig zu betrachten, es ist hingegen interessant, dass auch der N...Cl-Abstand recht kurz erscheint im Vergleich mit andern Wasserstoffbrücken dieser Art, wo der Abstand zwischen 3,06 und 3,20 Å [6] liegt.

Die Überprüfung der intermolekularen Abstände ergab eine relativ lockere Packung des Kristalls. Keine intermolekularen Abstände zwischen C-, N-, S- und Cl-Atomen sind kürzer als 3,5 Å. Der kürzeste H...H-Abstand beträgt 2,6 Å.

LITERATURVERZEICHNIS

- [1] 18. Mitteilung: *J.-M. Bastian, A. Ebnöther & E. Jucker*, *Helv.* 54, 283 (1971).
 [2] *J.-M. Bastian, A. Ebnöther, E. Jucker, E. Rissi & A. P. Stoll*, *Helv.* 49, 214 (1966).
 [3] «International Tables for X-ray Crystallography, vol. III, 202 (1967).
 [4] *C. K. Johnson*, ORNL-3794, Oak Ridge National Laboratory 1965.
 [5] *B. Bak, D. Christensen, J. Rastrup-Andersen & E. Tannenbaum*, *J. chem. Physics* 25, 892 (1956).
 [6] *W. C. Hamilton & J. A. Ibers*, «Hydrogen Bonding in Solids», S. 183, 1968; *J. D. Dunitz & H. P. Weber*, *Helv.* 47, 951, 1138 (1964).

27. Stereoselective Effects in Reactions of Metal Complexes, II Selectivity in the Complex Formation of Nickel(II)-, Copper(II)-and Zinc(II)-(D)-propylenediaminetetraacetate with Racemic 1-phenylethyl-amine [1]

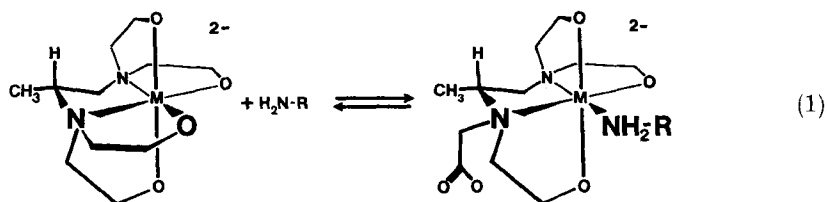
by **K. Bernauer, M.-F. Jeanneret** and **D. Vonderschmitt**

Laboratoire de chimie inorganique et analytique, Université de Neuchâtel

(19. XI. 70)

Summary. The selectivity in the formation of mixed complexes of optically active meta-propylenediaminetetraacetates with 1-phenylethyl-amine has been investigated by chromatography and by liquid-phase distribution measurements for the three metal ions Ni²⁺, Cu²⁺ and Zn²⁺. The selectivity is found to be sufficiently high to allow the chromatographic resolution of the racemic amine.

In a previous communication [1] we reported the partial resolution of amino acid derivatives into their stereoisomers by means of an exchange resin containing an optically active anionic iron chelate. There are two prerequisites for this chromatographic method: 1. The complex with the optically active ligand (auxiliary ligand) must be labile in order to allow fast ligand exchange; 2. It must maintain its asymmetric structure around the metal ion. With such a system we were able to demonstrate for the first time stereoselective effects with unidentate ligands (exchange ligands). The major drawback of this method was the necessity of using alcohol as an eluant. In this solvent, the chelate with the auxiliary ligand was only partially accessible to ligand exchange and the diffusion rate was substantially decreased because of insufficient swelling of the resin. Consequently, the bands in the elution pattern were too broad to give complete separation of the stereoisomers, despite the significant differences in the stabilities of the two diastereomeric mixed complexes. The present communication deals with an aqueous system. Propylenediaminetetraacetic acid (PDTA) was employed as the auxiliary ligand, Ni^{II} as the metallic center, and 1-phenylethyl-amine (PEA), as example of a variety of metal ions and monodentate exchange ligands. It was hoped that the optically active form of the multidentate auxiliary ligand would react entirely stereospecifically in the formation of the metal complexes and that the central ion would retain the imposed configuration even after fixation of a unidentate amine base. The exchange ligand probably replaces a carboxyl group in the girdle plane of the complex (1) [2].



To determine the stereoselectivity of reaction (1) an anion-exchange column was saturated with the complex and a frontal analysis with the racemic mixture of the exchange ligand was performed¹⁾. Fig. 1 shows the remarkably high enrichment obtained. To eluate the amine bound to the complex in the resin, the column was merely rinsed with water. The zone between water and amine (inverse front) showed an enrichment of the other antipode and within the limits of experimental error, its amount was equal to the enrichment obtained at the beginning.

The enrichment of the isomers can be determined with high accuracy by measuring the optical activity of the eluate. In order to calculate the difference of the equilibrium constants of reaction (1) for the two optical isomers of RNH_2 , however, it is necessary to know the exact amount of amine attached to the metallic center. Determination of this quantity proved to be difficult because of *Donnan* equilibrium effects. A detailed analysis of the amine distribution between aqueous solution and resin phase showed that the amine concentration is much higher in the resin than in solution.

¹⁾ The eluate from the M-PDTA column was passed through an other short column containing Dowex 1-X2 in the OH^- -form in order to avoid the appearance of small amounts of $(\text{M-PDTA})^{2-}$ in the samples to be analyzed.

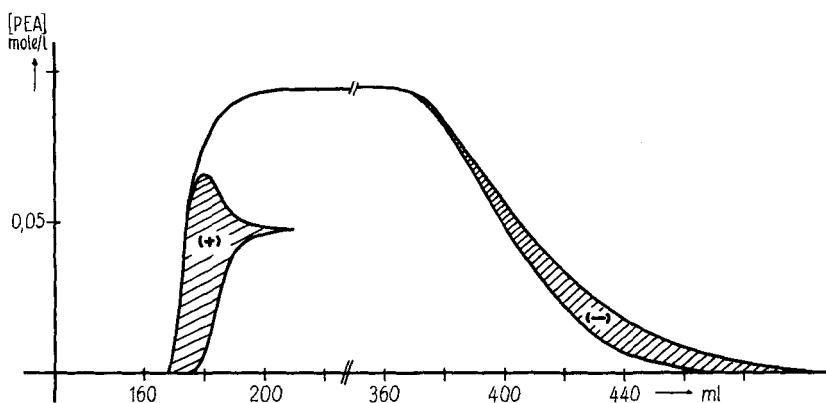


Fig. 1. Frontal analysis of racemic 1-phenylethyl-amine on Dowex 1-X2, saturated with $[\text{Cu-D-PDTA}]^{2-}$. Column length 37 cm; elution with water

Furthermore, the amount of amine absorbed by the resin depends on the nature of the anion with which the column is loaded. Magnesium ethylenediaminetetraacetate, the metallic center of which is unable to coordinate with an amine, was used as a substitute for those M-PDTA complexes which react with phenylethyl-amine, in order to estimate the concentration of uncomplexed amine in the resin phase. Using these estimates, values of the ratios of the equilibrium constants for the two isomeric amines were calculated. Values obtained in this manner are given in Table 1.

Because of the high affinity of the exchange resin for the aromatic amine, the values determined for $(K_{(-)}/K_{(+)})_{\text{resin}}$ are not relevant to the conditions inherent to aqueous solutions. It seemed, therefore, reasonable to estimate the degree of selectivity of complex formation by an alternative method. To this end, distribution equilibria of racemic phenylethyl-amine between an organic solvent (heptane) and an aqueous solution of the metal-D-PDTA were studied. The free amine is enriched in one of the

Table 1. Enrichment of D-1-phenylethyl-amine by frontal analysis on Dowex 1-X2 saturated with different optically active metal complexes

Bed volume 37 ml

complex	amount of complex (mmoles)	concentration of PEA in the aqueous phase (M)	PEA bound to the complex ^{a)} (mmoles)	optically active PEA in the eluate ^{a)} (mmoles)	$\left(\frac{K_{(-)}}{K_{(+)}}\right)_{\text{resin}}$
$[\text{Ni-D-(-)PDTA}]^{2-}$	25	0.092	1.7	0.44	1.7 ± 0.1
$[\text{Cu-D-(-)PDTA}]^{2-}$	25	0.094	4.1	0.89	1.6 ± 0.1
$[\text{Zn-D-(-)PDTA}]^{2-}$	20	0.098	0.6	0.095	1.4 ± 0.2

^{a)} After establishment of equilibrium in the column.

two isomers according to the stereoselectivity of the complex formation. Since the free amine is distributed between the aqueous and the organic phase, regardless of its

chirality, the enrichment can be conveniently determined by measuring the optical activity of the organic layer.

To calculate the ratio $K_{(-)}/K_{(+)}$, we used relation (2)

$$\frac{K_{(-)}}{K_{(+)}} = \frac{(\text{PEA})_{\text{tot}} - (x - y) (1 + 1/A) (x + y)}{(\text{PEA})_{\text{tot}} - (x + y) (1 + 1/A) (x - y)} \quad (2)$$

where $(\text{PEA})_{\text{tot}}$ is the total amount of 1-phenylethyl-amine introduced, x is its amount in the organic layer, y is the enrichment of the (+)-isomer of phenylethyl-amine in the organic phase and A is the distribution coefficient of the amine between the aqueous phase and heptane ($A = [\text{PEA}]_{\text{organic}}/[\text{PEA}]_{\text{aq}}$).

The distribution coefficient A was found to be strongly dependent on the concentration of electrolyte. A was therefore determined separately for each concentration

Table 2. *Selectivity of exchange equilibria with 1-phenylethyl-amine by liquid phase distribution with different optically active metal complexes*

Equal volumes of water and heptane (10 ml)

complex	total electrolyte concentration (M)	total amount of PEA (mmoles)	x (mmoles)	y (μ moles)	λ	$\frac{K_{(-)}}{K_{(+)}}$
[Ni-D-(–)PDTA] ^{2–} 0.136 M	0.14	6.61	4.55	30.6	2.7	1.27
	0.76	6.71	5.80	15.9	7.5	1.29
[Cu-D-(–)PDTA] ^{2–} 0.252 M	0.81		3.35	45.3	7.0	1.25
	0.67		3.17	52.6	5.7	1.26
	0.54	4.36	3.08	52.6	4.6	1.28
	0.40		2.96	52.0	3.9	1.27
	0.26		2.83	52.6	3.1	1.26
[Zn-D-(–)PDTA] ^{2–} 0.228 M	0.48	8.58	6.86	18.4	5.1	1.17
	0.43		4.63	16.5	4.1	1.07
	0.38	6.42	4.68	17.8	3.9	1.10
	0.33		4.89	20.2	3.7	1.22
	0.28		4.50	19.6	3.3	1.10

of complex either by substituting another 2:1 electrolyte (Na_2SO_4) of equal concentration for the complex, or by measuring the coefficient in presence of an excess of electrolyte. The amount of phenylethyl-amine in the organic layer was estimated by titration in H_2O -ethanol with hydrochloric acid. From the optical rotation of the heptane solution y was obtained using a specific rotation value ($[\alpha]_{365}^{25}$) of 135° . The values for $K_{(-)}/K_{(+)}$ as well as the values for x , y , and the total electrolyte concentrations are summarized in Table 2²⁾.

Absolute values for the two constants $K_{(-)}$ and $K_{(+)}$ of equilibrium (1) can be estimated in principle either by frontal analysis or by analysis of the liquid-phase

²⁾ To eliminate atmospheric CO_2 which tends to form 1-phenylethyl-ammonium hydrogen-carbonate, the solutions were shaken in an atmosphere of nitrogen.

distribution equilibria. These methods were not satisfactory, however, the standard deviations being much too high. Nevertheless, the estimated values (0.2 to 0.5 in aqueous solution) as well as the high selectivity and the rapid establishment of the exchange equilibria suggested the use of the complex form of the resin to resolve racemic mixtures by elution chromatography. Figure 2 shows that the separation of the optical antipodes can be effected in a very simple manner. Even a relatively short column containing $[\text{Cu-D}(-)\text{-PDTA}]^{2-}$ gives approximately 60% resolution of 1-phenylethyl-amine. Since pure water is used as the eluant the method is very convenient, and the optically active substances obtained are pure and devoid of additional reagents. It should be possible to resolve a great number of racemic amines into optically active components by the same procedure.

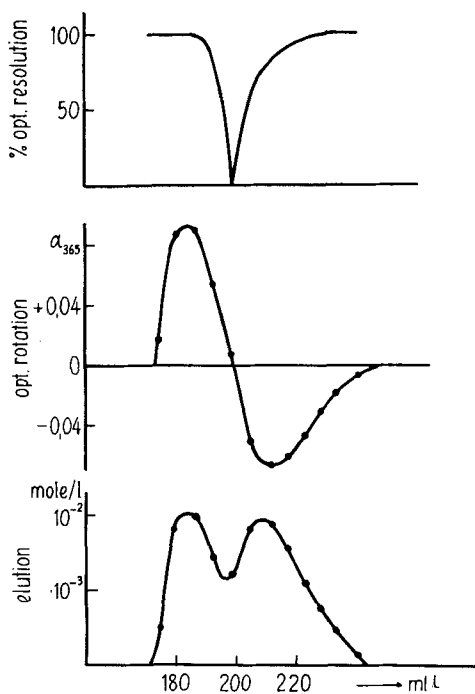
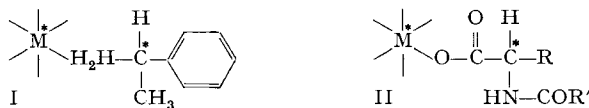


Fig. 2. Separation of optical isomers of 1-phenylethyl-amine by elution chromatography on Dowex 1-X2 saturated with $[\text{Cu-D-PDTA}]^{2-}$

Column length 37 cm; elution with water

The value of the ratio $K_{(-)}/K_{(+)}$ is a quantitative measure for the selectivity of reaction (1). The two stereoisomeric mixed complexes differ in free energy by about 140 cal/mole (300 cal/mole in the resin). Selectivities for amino acid derivatives determined by an analogous procedure [1] were much inferior, the two diastereomers differing in energy only by about 50 cal/mole. The structures of the two mixed complexes suggest an explanation of these results: the distance between the asymmetric carbon atom of the exchange ligands and the metal ion is two bond lengths in

structure I, but three bond lengths in structure II. The existence of a measurable stereoselectivity in structure II was thought to be due to interactions in the secondary



coordination sphere [1], *e.g.* differences in solvation. The exchange ligand in structure I is much closer to the first coordination sphere, and nonbonding interactions between the asymmetrically arranged chelate and the amine may be responsible to a great extent for the rather high specificity. Nevertheless the differences of selectivities in the resin phase and in aqueous solution imply that interactions with the secondary sphere are also important.

While conformational analyses of ring systems adequately explain the configuration of many chelates [3] (including M-PDTA [4]) it seems much more difficult to rationalize the behavior of unidentate ligands in terms of nonbonding interaction, hydrogen bonding, and especially solvation. The determination of very small differences in free energy with the two methods presented here may contribute much to the understanding of these effects [5].

Financial support of this research by the *Fonds National Suisse de la Recherche Scientifique* is gratefully acknowledged.

Experimental. – a) *Products:* 1-Propylenediaminetetraacetic acid mono-hydrate was prepared after [3]. The recrystallized substance was analyzed by potentiometric titration; $[\alpha]_D = -48,4^\circ$ ($c = 0,5$; H_2O).

Solutions of the complexes of Ni^{2+} , Cu^{2+} , and Zn^{2+} containing no additional electrolyte were prepared as previously described [1].

1-Phenylethyl-amine (*FLUKA, pract.*) was purified by distillation and kept over NaOH.

b) *Optical rotations* were measured in a 1 dm tube with a *Perkin-Elmer* 141 polarimeter.

BIBLIOGRAPHY

- [1] *F. Humbel, D. Vonderschmitt & K. Bernauer, Helv. 53, 1983 (1970).*
 [2] *G. S. Smith & J. L. Hoard, J. Amer. chem. Soc. 81, 556 (1959); J. R. Bhat, D. Radhamma & J. Shankar, J. inorg. nucl. Chemistry 27, 2641 (1965); F. P. Emmenegger & G. Schwarzenbach, Helv. 49, 625 (1966).*
 [3] *E. J. Corey & J. C. Builar, J. Amer. chem. Soc. 81; 2620 (1959); R. D. Gillard & P. R. Mitchell, in «Structure and Bonding», Vol. 7, Springer, Berlin 1970.*
 [4] *F. P. Dwyer & F. L. Garvan, J. Amer. chem. Soc. 81, 2955 (1959).*
 [5] *A. T. Advani, D. S. Barnes & L. D. Pettit, J. chem. Soc. (A) 1970, 2691.*