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Kinetic Stereoselectivity in Tetraamine Co(III) Aminoacid Complexes: The Effect of Methyl Groups in the 2,9 Positions of the Triethylenetetraamine Ligand upon Acid Catalyzed Decarboxylation of β_1 and β_2 Bound α,α-Aminomethylmalonic Acid

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The acid catalyzed decarboxylation of $\Delta(+)_{436}$-β_1-[*(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III)-S-aminomethylmalonate*] $ClO_4 \cdot H_2O$ *(1) and* $\Lambda(-)_{436}$-β_2-*(triethylenetetraaminecobalt(III)-R-aminomethylmalonate)*ClO_4 *(2) each lead to unequal amounts of R- and S-alanine products. A systematic dependence on steric bulk is evident upon decarboxylation, of a series of 2,9-methyl substituted triethylenetetraminecobalt(III)-aminomethylmalonate complexes, where the excess of S-alanine over R-alanine varies from 10 to 30%.*

Introduction

Because of the well defined nature of both reactants and products, the study of chirality phenomena pertaining to organic substrates bound to substitutionally inert transition metal complexes has received considerable attention. Recent high pH equilibrium studies exchanging a solvent hydrogen or deuterium ion for the α-proton of alanine bound to optically active Co(III) tetraamines have shown the product to contain no enantiometric excess of R- over S-alanine or of deuterated R- over deuterated S-alanine [1, 2]. This is in contrast to the significant asymmetric yields obtained upon base equilibration of an optically active bis(ethylenediamine) Co(III) complex of valine (26% enantiomeric excess) [1] and of aspartic acid (54% enantiomeric excess) [3]. The increased stereospecificity in the valine case has been attributed to the steric requirements of the bulky isopropyl side chain while considerable stability may be lent to one of the diastereomers of the aspartate complex by facile formation of a hydrogen bond between the free carboxylate group and one of the ethylenediamine nitrogens (as in similar complexes involving glutamate and aminomethylmalonate) [4, 5]. More recent work has shown that longer equilibration times tend to produce more nearly racemic deuterated amino acids [6]. Thus the above asymmetric product yields could be attributed to a rapid proton transfer to a postulated sp^2 intermediate and therefore be partially kinetically controlled.

It has been shown that an acid catalyzed route can lead to an asymmetric yield of alanine bound to a dissymmetric Co(III) moiety [7]. A preliminary investigation of the acid catalyzed decarboxylation of Λ-β_2-[(2S,9S)-diamino-4,7-diazadecanecobalt(III)-R-aminomethylmalonate]$^+$ (*1*b) had shown that a 30% excess of S- over R-alanine could be obtained [8]. Since there is no appreciable lability of the alanine species in acid solution, this should represent a purely kinetic product ratio. Because of the previously obtained yield of S-alanine the asymmetric synthesis of alanine via acid catalyzed decarboxylation of bound α,α-aminomethylmalonate was considered worthy of further investigation. Changing the bulkiness of the substituents as well as the chirality at the 2,9 positions of the triethylenetetraamine ligand of 1 should offer a convenient avenue of study of steric effects on the decarboxylation reaction. Accordingly, the synthesis and decarboxylation via H^+ in H_2O of the new homologs *1* and *2* were carried out. The rates of the decarboxylation reactions were obtained under pseudo first order conditions and the degree of induced asymmetry determined.

Experimental

NMR spectra were obtained on Varian T-60 and EM 360 and Jeol MH-100 spectrometers. CD spectra were obtained in 1 *M* HCl on a Cary 60 spectropolarimeter and deconvoluted with the aid of a Hewlett-Packard 9821 desk calculator. Rotations were taken on Perkin-Elmer 241 and Jasco DIP-180 polarimeters. I.R. spectra were obtained on a Perkin-Elmer 457 grating spectrophotometer. Absorption spectra were obtained on a Cary 17 uv–vis spectrophotometer. The cation exchange resin was Bio-Rad

AG50WX2, 200 - 400 mesh The construction of the pH-stat used in the syntheses is described elsewhere [9] α,α-aminomethylmalonic acid (*3*), Λ-α-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III)Cl_2] Cl (*4*) and Λ-β_2-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III)-R-aminomethylmalonate] ClO_4 (*5b*) were synthesized as reported previously [8] Λ-β_2-[triethylenetetraaminecobalt(III)-R-aminomethylmalonate] Cl (*2*) was synthesized and resolved as reported elsewhere [10]

Δ(+)$_{436}$-β_1-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III)-S-aminomethylmalonate] $ClO_4 \cdot H_2O$ (1)

3 (0 759 g, 5 71 mmol) and *4* (2 04 g, 5 71 mmol) were slurried with 12 ml of H_2O in a 50 °C water bath A pH-stat charged with 1 0 *M* NaOH was attached and set to maintain the pH between 7 0 and 7 1 Base addition had ceased after 36 hours stirring After 48 hours the red-orange reaction mixture was removed from the heat and sorbed onto a 1–1/4″ × 25″ cation exchange column (Na^+ form) and elution begun with 0 2 *M* $NaClO_4$ After one faint pink band eluted rapidly and was discarded, five bands of significant intensity eluted at rates consistent with +1 ions [6] The first two (*a* and *b*) were eluted with 0 2 *M* $NaClO_4$, the third (*c*) with 0 3 *M* $NaClO_4$ and the last two (*d* and *e*) with 0 4 *M* $NaClO_4$ The order of abundance was $c > a > d, e > b$ The principal product, fraction *c*, was identified as the previously synthesized Λ-β_2 -complex (*5*) on the basis of its CD spectrum Since *a* exhibited a CD spectrum most nearly approximating compound 6_S it was the only fraction of interest to this work, therefore the other fractions were not further characterized Fraction *a* was evaporated to 50 ml and treated with 300 ml of ethanol to precipitate 0 50 g (18%) of pink-orange microcrystals which were recrystallized from H_2O with a small excess of $NaClO_4$ to yield orange crystals

Δ(+)$_{436}$-β_1-[(2S,9S)-2,9-diamino-4,7-diazadecanecobalt(III)-R or S-alaninate] $Cr_2O_7 \cdot H_2O$ (6_R or 6_S)

4 (2 17 g, 6 06 mmol) and alanine (0 54 g, 6 06 mmol) were treated as above in 10 ml of H_2O After four hours, base addition was complete to yield a red solution Continued (overnight) stirring on the warm water bath produced a deep orange solution which was sorbed onto a 1″ × 40″ cation exchange column and eluted with 1 67 *M* HCl The eluate, which consisted of two bands, was collected in 165 × 6 4 ml portions A plot of the ratio of the rotations at 546 and 436 nm showed that the intermediate fraction consisting of 6% of the tubes contained some mixture of both bands The second fraction was characterized as the previously synthesized Λ-β_2 complex on the basis of its CD spectrum [5] The first fraction was assigned the Δ conformation on the basis of its strong negative Cotton effect near 500 nm in the CD spectrum The entire pure first fraction was evaporated to dryness to yield 1 02 g of red-orange powder (38%) The complex was recrystallized from hot H_2O with an excess of $Na_2Cr_2O_7$ to yield large brown needles

Decarboxylation of 1

100 mg of *1* was dissolved in 2 ml of 1 *M* HCl with a few mg of sodium dimethylsilapentanesulfonate (DSS) as internal NMR standard and placed in a 79 ± 1 °C hot water bath The decarboxylation was followed by periodically quenching the sample in cold water and monitoring the decreased intensity of the methyl singlet at δ = 1 88 ppm in the NMR spectrum The calculated first order rate constant was k = 0 29 ± 0 01 min^{-1} After 33 minutes (14 half-lives) on the hot water bath, the sample was sorbed onto a 1″ × 30″ cation exchange column and the first fraction eluted with 0 8 *M* HCl After a significant volume of clear eluate had passed the second band was brought out with 1 5 *M* HCl Each fraction was reduced in volume then diluted to 250 0 ml and the CD spectra obtained Fraction #1 was identical to Δ-β-S-alanine complex 6_S and fraction #2 was identical to the Δ-β-R-alanine complex 6_R

Comparison of the molar ellipticities showed the R-alanine complex to be 1 33 times as concentrated as the S-alanine complex

Decarboxylation of 2

50 mg of *2* was dissolved in 1 ml of 1 *M* HCl The decarboxylation was followed as above by monitoring the disappearance of the NMR methyl singlet at δ = 1 80 ppm After decarboxylation was complete, the ratio of the areas under the 100 MHz peaks for the S- and R-alanine complexes was found to be 1 23 (after subtracting out the small amount of overlap) The same procedure was followed for 12 *M* HCl (ratio = 1 23) The product from a second decarboxylation under the same conditions was chromatographed as above to yield only two fractions The CD spectrum of the first fraction matched that published for Λ-β-triethylenetetraamine Co(III)-R-ala^{+2} and that of the second matched that for Λ-β_2-triethylenetetraamine Co(III)-S-ala^{+3} [11] The decarboxylation was also followed polarimetrically at 81 °C by observing the increasing rotations, at 546 nm, of 1–2 m*M* solutions in 1 *M* HCl (k = 0 29 ± 0 02 min^{-1})

Results

The analytical data for the newly prepared complexes is presented in Tables I–III

Fraction *a* (compound *1*) is the second most prevalent product from the treatment of *4* with α,α-aminomethylmalonic acid It was assigned the Δ configuration on the basis of the strong negative Cotton effect near 500 nm and pro-S conformation

TABLE I. Molar Rotations (M_α) (C ≅ 1.5 × 10^{-3} *M*, 1 *M* HCl).

	546 nm	436 nm
l	−2819°	3856°
δ_R	−4438	5752
δ_S	−4930	5934

TABLE II. NMR Parameters in 1 *M* HCl.[a]

	amino acid methyl group		tetraamine methyl groups	
	δ	j	δ	j
l	1.88	0	1.42	6.4
			1.45	6.2
δ_R	1.54	7.0	1.40	6.1
			1.44	5.6
δ_S	1.53	7.0	1.40	6.1
			1.44	5.6

[a]δ in ppm downfield from sodium dimethylsilapentanesulfonate; j in Hz.

of the malonate ligand on the basis of the strongly negative vicinal effect near 450 nm [5].

The CD spectra of δ_S and δ_R in the visible region are shown in Figs. 1 and 2 along with the principal gaussian components. Except for peak heights, the CD spectrum of *l* closely resembles that of δ_S [12].

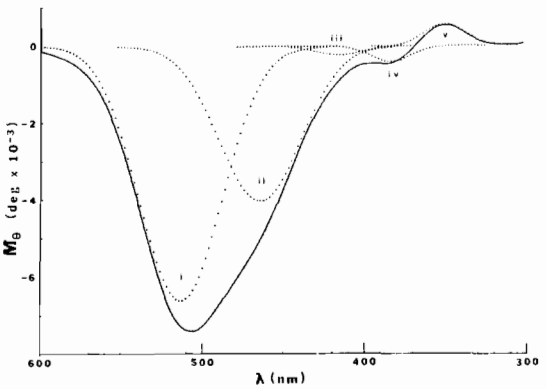


Fig. 1. The circular dichroism spectrum of Δ(+)$_{436}$-β_1-[(2S, 9S)-2,9-diamino-4,7-diazadecanecobalt(III)-S-alanine]Cr_2O_7 and its component gaussian Cotton effects.

The parameters of the component gaussian Cotton effects, the summation of which reproduce the experimental spectra to within the accuracy of the instrument, are presented in Table IV (the symbols are as defined previously) [5]. Note that *vii* is cosmetic and added only to produce a fit at the high frequency edge of the spectra.

l has been confirmed as a$\Delta\beta_1$ complex via an X-ray structure determination. Previous results, confirmed by X-ray structure determination have shown that a positive principal Cotton effect near 500 nm in the visible spectrum is indicative of a Λ configuration of the tetraamine ligand [5]. The same result has been demonstrated for triethylenetetraamine complexes [13]. The sign of the principal Cotton

TABLE III. Elemental Analyses.

	l		δ_R		δ_S
	theor	found	theor	found	found
C	29.91	29.90	23.79	23.46	23.48
H	6.07	6.17	5.45	5.48	5.55
N	14.54	14.56	12.61	13.06	12.54
Co	12.2	12.6	–	–	–

TABLE IV. Parameters of the Component Cotton Effects.*

Complex		*i*	*ii*	*iii*	*iv*	*v*	*vi*	*vii*
δ_R	a	496	–	430	384	345	560	263
	b	42.2	–	19	19	21	40	26
	C	−7847	–	−114	−227	796	−258	1345
δ_S	a	513.4	464	415	383	349	571	235
	b	36	36	19	17.5	18	35	28
	C	−6118	−3729	−217	−378	519	−255	14150

*a is peak location in nm, b is halfwidth at 1/e of maximum in nm and C is molar ellipticity in degrees.

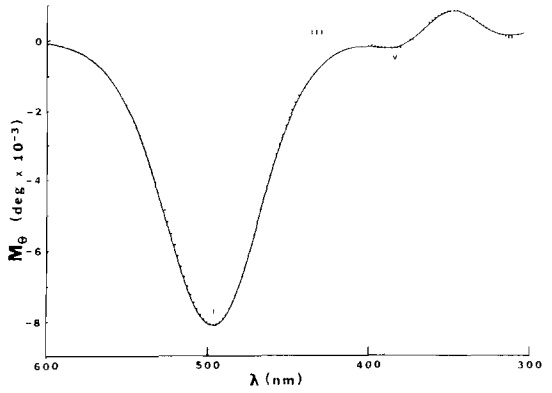


Fig 2 The circular dichroism spectrum of $\Delta(+)_{436}$-β_1-[(2S, 9S)-2,9-diamino-4,7-diazadecanecobalt(III)-R-alanine] Cr_2O_7 and its component gaussian Cotton effects

effect in complexes 6_R and 6_S is quite unambiguously negative (Figs 1 & 2) leading to their assignment as Δ complexes The I R spectrum in the range of 990–1100 cm^{-1} has been successfully used to differentiate various β-complexes from α-complexes [13, 14] This region of the IR spectra of *1* and 6_S are compared as well as that of the previously characterized β_2-complex *5* and its *S*-alanine decarboxylation product in Fig 3 The patterns of the β_2-complexes are nearly identical to each other as are those of *1* and 6_S, leading to the conclusion that 6_S is also a β_1 complex Previous workers have demonstrated a definite difference between the CD spectra of β_1 and β_2 complexes, both in character and location of peaks [11, 13] Another confirmation of β_1 for 6_R and 6_S comes upon examination of the difference CD curve between 4_S and 4_R, *i e*, the S-alanine vicinal effect This has been shown to be radically different for β_1 and β_2 complexes [10, 15] The vicinal effect obtained by taking half the difference between the CD curves of 4_S and 4_R is nearly identical to that obtained previously for the β_1 bound aminomethylmalonate of compound *1* [12] and different from that observed for β_2 bound alanine [11, 15] Congruency of the NMR spectra of 6_R and 6_S with that of the decarboxylation product from *1* demonstrated that *1* was the proper precursor for *6* Similarly, CD spectra of the isolated decarboxylation products of *2* proved them to be the previously characterized β_2 R- and S-alanine triethylenetetraamine Co(III) complexes [11]

Previous workers have observed, in the uv-vis spectra of tetraamine Co(III) amino acid complexes, that the ratio of the absorbance of the band at long wave length (near 500 nm) to that at shorter wavelength (near 350 nm) is greater than 1 0 for β_1 complexes and less than 1 0 for β_2 complexes [11] We find here that for the chloride and perchlorate salts of *1*, 6_R, 6_S and the corresponding Δ-β_1-glycine complex this ratio lies between 1 08 (for *1*) and 1 24 (for

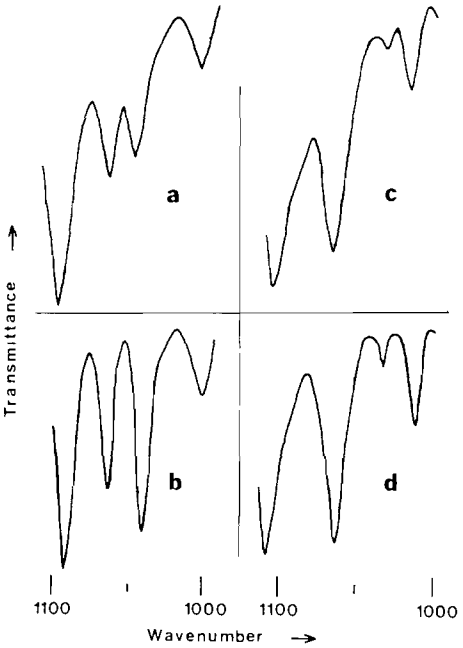
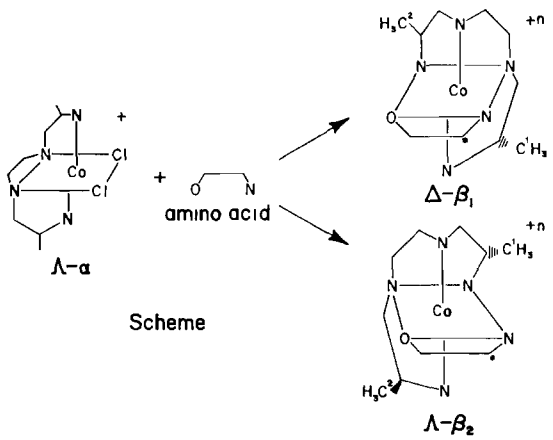


Fig 3 Infrared spectra, in KBr discs, of the halide (Cl^- and Br^-) salts of a) *5*, b) S-alanine decarboxylation product of *5*, c) *1*, d) 6_S

6_S) and elsewhere that for a series of β_2 amino acid complex this ratio varies from 0 91 to 0 97 [16]

Discussion

There are effectively only two products from the reaction of alanine with compound *4* in water at



Scheme

pH 7 (Scheme) The $\Lambda\beta_2$ complex has been discussed previously and corresponds (as demonstrated spectrally) to the principal product from the treatment of *4* with α,α-aminomethylmalonic acid under the same conditions [8] Spectral evidence (IR, CD,

TABLE V. Decarboxylation Yields.

Complex	Excess of S-alanine over R-alanine
1	−14
2	10.3
5	30[a]

[a]Reference 7.

UV–VIS) shows that compound *6* corresponds to the second most abundant product from the treatment of *4* with α,α-aminomethylmalonic acid and on the basis of the X-ray structural determination of *1* [12] has been assigned the Δ-β_1 configuration. In order to gain some insight into steric effects of substituents at the 2,9 positions of the triethylmetetraamine ligand, *1* and *2* were subjected to acid catalyzed decarboxylation. The decarboxylations were carried out under pseudo-first order conditions, at 80 ± 2 °C and acid concentrations which had previously been shown to be on the plateau of the pH-rate profile for bound aminomethylmalonate [8]. The rates were followed by NMR and polarimetry and the calculated first order rate constants found to be equal, within experimental error, to that previously determined for *5* ($k = 0.29 \pm 0.02$ min^{-1}). For each decarboxylation, only two products (one S- and one R-alanine complex) were formed, as indicated by NMR and cation exchange chromatography. The products from the decarboxylation of *2* exhibited a significant difference between the locations of the methyl resonances in the NMR spectrum. Accordingly, the product ratio was readily obtained by integration of the NMR peaks. For 6_R and 6_S there was not sufficient difference between either the NMR or the CD spectra to allow for accurate determination of the relative proportions of R- and S-alanine products from the decarboxylation of 1. It was therefore necessary to separate the products chromatographically and estimate their quantities individually. The decarboxylation results are expressed in terms of excess of S-alanine over R-alanine in Table V.

Examination of the β_1 and β_2 complexes in the Scheme reveals two situations for the substituent methyl groups; one in which the group may be thought of as being shielded from the amino acid by the bulk of the tetraamine moiety (C^1) and one in which the methyl group is exposed (C^2). Complex *2*, with no substituent methyl groups represents the simplest case. Production of alanine is seen upon attack of a proton at the planar sp^2 α-carbon of the decarboxylated aminiomethylmalonate substrate [5]. In the absence of additional steric bulk, the decarboxylation is found to yield an excess of 10.3% S- over R-alanine. Therefore, for the $\Lambda\beta_2$ complex, the decarboxylation slightly favors production of the S-alanine complex. As bulkiness is added to the 2,9 positions of the tetraamine (compound *5*) the predilection towards S-alanine is increased to the extent that a 30% excess of S- over R-alanine is realized upon decarboxylation of *5*. In the Δ-β-case (compound *1*) at least a 10% excess of R-alanine should be expected (just the mirror image of the Λ-β case). Inspection of the scheme reveals that because the substrate is now β_1 the exposed methyl group (C^2) is now located further from the site of proton attack and would not be expected to exert the degree of enhancement observed upon decarboxylation of complex *1*. This expectation is borne out when the excess of R- over S-alanine upon decarboxylation of *1* is found to be 14%.

Although the results of this study may be rationalized as due to steric effects inherent in the tetraamine ligand in the above qualitative fashion, the spread of isomer ratios in this kinetic differentiation represents a difference in activation energy differences of only about 0.6 Kcal/mol. Thus the observed product ratio variation may conceivably be a consequence of small differences in solvation effects or even differences in the configuration at the secondary tetraamine nitrogen in solution.

Acknowledgements

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