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Preparation of N-Arylmethylglycinato-bis-(ethane-1,2-diamine)cobalt(III) Complexes. Comparison of their Exchange Reactions at pD 9.7

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*The preparation and characterisation of N-arylmethylglycinatobis-(ethane-1,2-diamine)cobalt(III) complexes, where aryl = phenyl (*1a*) 2-methylphenyl (*1b*) and naphthyl (*1c*), are described. In contrast to (*1a*), exchange of the diastereotopic glycinate methylene protons in (*1b*) and (*1c*) in borax buffer (pD 9.7) is shown to proceed non-stereoselectively.*

Introduction

Under mild basic conditions, glycinate co-ordinated *via* its amino and carboxylate group to certain metal ions, reacts with simple aldehydes [1]. After reductive work-up of the reaction mixture a derived α-amino-acid or mixture of diastereoisomeric amino-acids is obtained [2–4]. For example, condensation of glycinato-*bis*-(ethane-1,2-diamine)cobalt(III) iodide with aqueous acetaldehyde gives rise to threonine and allothreonine in proportions depending on the pH of the solution [2, 3]. With aqueous formaldehyde, glycinato-bis-(ethane-1,2-diamine)-cobalt(III) yields two cobalt-containing products [5]. Both are derivatives of α-hydroxymethylserine, one with two bidentate ethane-1,2-diamine ligands and the other with a 6,13-dioxacyclam tetradentate ligand formed by condensation of formaldehyde with ethane-1,2-diamine.

The pathway by which these and similar condensations occur is clearly far from simple [1]. As a basis for the exploitation of this chemistry for the synthesis of unusual amino-acids, we have prepared N-substituted glycinato chelates of cobalt(III) with N-substituent of varying steric bulk (*1a–1c*). We have investigated the stereoselectivity of exchange of the hydrogens H_a and H_b (*1*) by deuterium with the aim of finding a group R which gives an optimum extent of stereoselection. If such a group could be found, then the possibilities of using a metal complex as a reagent for enantioselective syntheses would be greatly enhanced. We have previously described the preparation of complex (*1a*), its crystal structure analysis and a study of its stereoselective exchange in phosphate buffer at pH 10.9 [6]. Complexes (*1b*) and (*1c*) are formulated as ΛR/ΔS isomers by analogy with (*1a*) [6]. Recently, Fujita and his coworkers [7] have shown that although sarcosinato-bis-(ethane-1,2-diamine)cobalt(III) favours the ΛR/ΔS isomers, small amounts of ΔR/ΛS isomers can be detected by ^{13}C n.m.r. spectroscopy. These isomers were separated chromatographically and the ΔS isomer was shown to equilibrate in aqueous solution with the ΔR isomer, the rate of this reaction depending on hydroxide concentration. The equilibrium at 25 °C contains 85% of the ΔS isomer and 15% of the ΔR isomer [7].

Results and Discussion

N-substituted glycinato-bis-(ethane-1,2-diamine)-cobalt(III) chelates (*1a*)–(*1c*) are formed by treatment of either *trans*-$[Co(en)_2Cl_2]Cl$ in basic solution or of *cis*-$[Co(en)_2OH(H_2O)](OH)_2$ with the corresponding amino-acid. Because *trans*-$[Co(en)_2Cl_2]Cl$ is more readily prepared, the route using this complex as starting material is preferred. For both routes, an equilibrium mixture is eventually produced, containing *mono-*, *bis-* and *tris* (ethane-1,2-diamine) complexes, and prolonged heating of the reaction mixtures results in the preferential crystallisation of the least soluble of these, namely $[Co(en)_3]Cl_3$. However, under kinetically controlled conditions, the *bis*-chelate precipitates from solution and may be isolated in acceptable yield.

The solubility of *bis*-complexes (*1a*)–(*1c*) in water depends markedly on the nature of the counter-anion present, decreasing in the sequence $AcO^- \gg Cl^- > Br^-$. Thus, for applications using largely aqueous solvents, the acetates are preferable. Indeed, when the N-substituted glycinato ligand possesses a very lipophilic group (*e.g.* N-(1-naphthylmethyl)), the bromides and chlorides are virtually insoluble in cold

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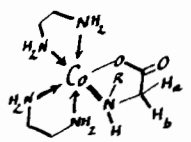

(*1*)*

(*1a*) R = benzyl
(*1b*) R = 2-methylbenzyl
(*1c*) R = naphthylmethyl

water, whereas the acetates are readily soluble. All the water soluble complexes form deep red solutions characterised by two absorption maxima in the visible spectrum. The wavelengths of these maxima and their extinction coefficients are practically independent of the nature of the chelating glycinato ligand. Thus, N-(benzyl)glycinato-bis-(ethane-1,2-diamine)cobalt-(III) acetate has λ_{max} 487 nm (ϵ = 114 M^{-1} cm^{-1}), 344 nm (ϵ = 132 M^{-1} cm^{-1}) in water (*cf.* [Co(en)$_2$-(gly)](ClO$_4$)$_2$ λ_{max} 489 nm (ϵ = 100 M^{-1} cm^{-1}), 347 nm (ϵ = 110 M^{-1} cm^{-1}) [8]). Additionally, complexes of ligands containing aromatic rings exhibit bands of large (>10^4 M^{-1} cm^{-1}) extinction coefficient in the u.v. spectrum.

The cobalt(III) complexes (*1a*)–(*1c*) are diamagnetic and exhibit sharp resonances in their ^{1}H n.m.r. spectra. For all complexes, the CH_2 α to carboxylate appears as an AB quartet because these protons are diastereotopic. Additionally, the chelated aminocarboxylate possesses a CH_2 group α to N (γ to Co^{2-}) and this resonance also appears as an AB quartet.

Coordination of an α-aminocarboxylate to a metal ion as a bidentate chelating ligand, causes an enhancement of the lability, with respect to proton (or deuteron) exchange, of the α-methylene protons. Thus, treatment of glycinato-bis-(ethane-1,2-diamine)cobalt(III) with OD^- at 295 K causes rapid deuteration of the α-methylene protons (monitored by the disappearance of the CH_2 triplet in the ^{1}H n.m.r. spectrum) [9]. We have reported [6] observations of the exchange of the α-methylene protons with deuterons for N-(benzyl)glycinato-bis-(ethane-1,2-diamine)cobalt(III). For this reaction, the exchange, followed by ^{1}H n.m.r. spectroscopy, exhibited a degree of stereoselectivity. This stereoselectivity was explained on the basis of steric effects: the bulky benzyl substituent on the glycinate nitrogen performs the dual role of preserving configuration at the metal-bound nitrogen and influencing the direction of approach of the entering electrophile (D^+). We now describe further studies of this reaction and also the effect of replacing the benzyl group by other bulky groups (2-methylbenzyl and naphthylmethyl).

*All compounds used in this work were racemates [ΛR isomer shown in (*1*)].

Our original observations were restricted to N-(benzyl)glycinato-bis-(ethane-1,2-diamine)cobalt(III) [6]. The ^{1}H n.m.r. spectrum of this complex in D_2O shows *inter alia* an AB quartet, due to the glycinate CH_2 group, with components at δ 3.21, 3.29, 3.54 and 3.62 p.p.m. For solutions buffered in the pD range 9.5 < pD < 11.0 (DCO_3^-, borate, phosphate), there is a time-dependent collapse of this quartet, the rate of disappearance depending on the pD of the solution, increase in pD promoting more rapid disappearance. During the initial stages of this exchange there is the appearance of and an increase in intensity of a singlet resonance at δ 3.23. A singlet of *lower* intensity appears at δ 3.55, indicating that the exchange of H for D is stereoselective. Towards the end of the reaction, these singlets disappear with the formation of di-deuteriated species. If the origin of the stereoselectivity were primarily due to the bulk of the benzyl group bound to N, then it would be expected that a similar or perhaps even more pronounced stereoselectivity might be noted with groups of increasing steric bulk. Accordingly, we have synthesised N-(2-methylphenylmethyl)- and N-(naphthylmethyl)-*bis*-(ethane-1,2-diamine)cobalt-(III) complexes [(*1b*) and (*1c*), respectively] and followed their exchange behaviour. The ^{1}H n.m.r. spectra of both complexes (*1b*) and (*1c*) in D_2O show *inter alia* an AB quartet due to a diastereotopic methylene glycimate. Under conditions for which stereoselective exchange was observed for N-(benzyl)-glycinato-*bis*(ethane-1,2-diamine)cobalt(III), there was no indication (in the ^{1}H n.m.r. spectrum) of stereoselective exchange. Indeed, the sole time-dependent changes were the disappearance of the α-CH_2 quartet, whilst singlets of similar intensity appeared and later disappeared between the A and B components of this quartet.

In order to investigate this surprising observation more fully, the exchange reaction was monitored by ^{2}H n.m.r. spectroscopy. Solutions of the three complexes were prepared in D_2O buffered to pD = 9.7 by addition of disodium tetraborate dihydrate (0.025 *M*). Partial exchange was allowed to occur (19 h at 304 K) as monitored by ^{1}H n.m.r. spectroscopy. The reaction was stopped by addition of 1 *M* acetic acid, the cobalt complexes were precipitated by addition of acetone and the ^{2}H n.m.r. spectra of the partially exchanged complexes in D_2O, recorded. The ^{2}H n.m.r. spectrum of each complex contained only two resonances at *ca.* δ 3.85 and δ 3.55 due to the two diastereotopic deuterons α to CO_2^-. Comparison of the relative intensities of these peaks was complicated because of partial overlapping of the lower field resonance by that due to solvent D_2O. However, for N-(2-methylphenylmethyl) and N-(naphthylmethyl)-glycinato-*bis*(ethane-1,2-diamine)cobalt(III) complexes the ^{2}H resonances were of approximately equal intensity, whereas for N-(benzyl)glycinato-*bis*-

(ethane-1,2-diamine)cobalt(III) the lower field resonance at δ 3.84 was of slightly enhanced intensity (quantitative comparison was not possible). These observations confirm those of the ^1H n.m.r. experiments, *i.e.* exchange in N-(benzyl)glycinato-*bis*-(ethane-1,2-diamine)cobalt(III) is stereoselective.

The inference from the results presented in this paper is that our original interpretation [6] of the steric role of the benzyl group was an oversimplification. The possible involvement of ΔR/ΛS isomers, present in small equilibrium concentrations in the processes described, needs to be evaluated.

Experimental

Materials

trans-$[Co(en)_2Cl_2]Cl$ was prepared from *cis*-$[Co(en)_2(CO_3)]Cl$ [10]. $LiOH \cdot H_2O$ was reagent grade (May and Baker) and all other chemicals were analytical reagent grade. Dowex IRA-400(Cl) resin (standard grade) was packed into a column (60 × 2 cm) and converted into the acetate form by prewashing with 1 *M* sodium acetate solution (5 l) and water (2 l).

Physical Measurements

^1H n.m.r. spectra were recorded on a Perkin-Elmer R 34 (220 MHz) instrument at ambient temperature (*ca.* 296 K). ^2H n.m.r. spectra were recorded on a Bruker WH-400 instrument operating at 61.4 MHz, using a capillary of $CDCl_3$ to provide an external reference signal. ^2H n.m.r. resonances reported are uncorrected for susceptibility effects. Samples for both ^1H and ^2H n.m.r. measurements were prepared in D_2O (99.8 atom%) containing 1% w/w TSS internal standard (for ^1H n.m.r. measurements). U.v.–visible absorption spectra were recorded on a Perkin Elmer 552 instrument at ambient temperature. Combustion microanalyses (for C, H, N) were performed by CHN Analysis Ltd., South Wigston, Leicester, U.K. *N-Benzylglycine hydrochloride* was prepared as described [11].

Bis-N-(2-methylbenzyl)glycine

To a boiling solution of glycine (6.1 g, 81 mmol) and potassium hydroxide (15.4 g, 275 mmol) in ethanol (46 cm^3) and water (46 cm^3) was added over 30 min 2-methyl(chloromethyl)benzene (25 g, 178 mmol). The mixture was refluxed for 30 min and then solvent (*ca.* 40 cm^3) was distilled off. After acidifying with acetic acid (8 cm^3) and cooling to room temperature, the mixture was extracted three times with ethyl acetate. The combined extracts were dried (Na_2SO_4) and the ethyl acetate was removed to give a white solid (19.1 g). Recrystallisation was achieved by dissolving this solid in boiling chloroform (300 cm^3) and adding 600 cm^3 petrol (b.p. 40–60 °C). After cooling for 3–4 h at 0 °C, filtering and drying gave bis-N-(2-methylbenzyl)-glycine as a white powder, m.p. 162–3 °C. Yield 11.6 g (51%). *Anal.*: Calc. for $C_{18}H_{21}$, NO_2: C, 76.29; H, 7.47. Found: C, 75.21; H, 7.44%.

N-(2-methylbenzyl)glycine hydrochloride

To a suspension of 10% palladium/charcoal (2 g) in methanol (20 cm^3) under nitrogen was added a suspension of bis-N-(2-methylbenzyl)glycine (11.5 g, 41 mmol) in methanol (150 cm^3) containing conc. hydrochloric acid (7 cm^3). After hydrogenolysis in a Parr hydrogenator (1 h, ΔP = 11 p.s.i.) the suspended organic material had gone into solution and the mixture was filtered through Celite. Evaporation of the filtrate gave a solid that was recrystallised from ethanol (200 cm^3) [cool to −20 °C for 12 h]. The crystals of N-(2-methylbenzyl)glycine hydrochloride were collected and dried. Yield 7.75 g (88%). No sharp m.p. *Anal.*: Calc. for $C_{10}H_{14}ClNO_2$: C, 55.68; H, 6.54. Found: C, 55.62; H, 6.45%. ^1H n.m.r. (D_2O): δ 2.41 (S, 3H), 4.01 (S, 2H), 4.39 (S, 2H) and 7.5 (S, 4H) p.p.m.

N-(1-naphthylmethyl)glycine hydrochloride

This was prepared from 1-(chloromethyl)naphthalene in the manner described for N-(2-methylbenzyl)-glycine. Yield: 17% overall from glycine. M.p. 255–8 °C dec. (from ethanol). *Anal.*: Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.60. Found: C, 61.76; H, 5.62%. ^1H n.m.r. (D_2O): δ 4.03 (S, 2H), 4.75 (S, 2H) and 7.5–8.5 (m, 7H) p.p.m.

Preparation of Complexes

N-substituted glycinato-*bis*-ethane-1,2-diamine cobalt(III) dichlorides were prepared by a general method described for N-(2-methylbenzyl)-glycinato-*bis*-(ethane-1,2-diamine)cobalt(III) dichloride. The corresponding diacetate was obtained by two methods: either by treatment of an aqueous solution of the dichloride with a suspension of silver acetate or by means of an anion-exchange resin.

N-(2-methylbenzyl)glycinato-bis-*(ethane-1,2-diamine)cobalt(III) dichloride*

N-(2-methylbenzyl) glycine hydrochloride (2.2 g, 10 mmol) was dissolved in methanol (150 cm^3) and $LiOH \cdot H_2O$ (805 mg, 20 mmol) was added. The mixture was heated on a steam bath under reflux for 30 min during which time the lithium hydroxide dissolved. To this solution was added solid *trans*-$[Co(en)_2Cl_2]Cl$ (2.85 g, 10 mmol) in portions over 5 min. Most of this material dissolved to give a deep violet solution. The volume of solvent was increased to 250 cm^3 by addition of methanol and the mixture was boiled for *ca.* 30 min until a pink solid (the crude dichloride) started to deposit. The suspension was allowed to cool slowly to room temperature (*ca.* 2 h)

and then in ice (2 h). The crude dichloride was separated by filtration using suction, and was recrystallised by dissolving in water (20 cm^3) on a steam bath, filtering and cooling in ice for 12 h. The solid was filtered and washed with methanol (20 cm^3) and ether (20 cm^3) and dried at 1 mm Hg. Yield 1.1 g (26%). *Anal.*: Calc. for $C_{14}H_{28}Cl_2CoN_5O_2$: C, 39.26%, H, 6.59%, N, 16.36%; found C, 38.91%, H, 6.46%, N. 16.09%. *^1H n.m.r. (D_2O)*: δ 2.45 (s, 3H), 2.90 (m, 8H), 3.21, 3.30, 3.49, 3.58 (ABq, 2H), 3.83, 3.90, 4.21, 4.28 (ABq, 2H), 7.3–7.55 (m, 4H), p.p.m.

N-(2-methylbenzyl)glycinato-bis-*(ethane-1,2-diamine)-cobalt(III) diacetate (AgOAc method)*

N-(2-methylbenzyl)glycinato-*bis*-(ethane-1,2-diamine)cobalt(III) dichloride (461 mg, 1.08 mmol) was dissolved in water (10 cm^3) with stirring at 40–50 °C. A suspension of silver acetate (360 mg, 2.16 mmol) in warm water (30 cm^3) was added, dropwise, over 10 min and the resulting dense suspension was stirred for 5 min. The precipitated AgCl was removed by filtration through a short column of Celite 545 with the aid of suction. The clear red filtrate was evaporated to small volume at *ca.* 50 °C and then cooled to room temperature. An equal volume of methanol was added and the solution stirred in ice whilst acetone (80 cm^3) was added, dropwise, over 5 min. The suspension of diacetate was stirred in ice for a further 10 min and the solid separated by suction filtration. It was sucked dry, washed with a little acetone and finally freed from occluded solvent by heating at 70 °C and 0.1 mm Hg for 14 h. Yield 496 mg.

N-(2-methylbenzyl)glycinato-bis-*(ethane-1,2-diamine)cobalt(III) diacetate (anion exchange method)*

The dichloride (580 mg) was dissolved in water (20 cm^3) and the solution was passed down an IRA-400 (AcO^-) column at *ca.* 4 cm^3 min^{-1}. The eluate (*ca.* 50 cm^3) was evaporated to small volume and cooled in ice. Acetone (150 cm^3) was then added, dropwise, to the stirred solution. The precipitated diacetate was filtered, washed and dried as described above. Yield 600 mg. *^1H n.m.r. (D_2O)*: δ 1.92 (s, 6H), 2.45 (s, 3H), 2.90 (m, 8H), 3.21, 3.30, 3.48, 3.56 (ABq, 2H), 3.83, 3.90, 4.20, 4.27 (ABq, 2H), 7.3–7.5 (m, 4H) p.p.m.

Preparation of Samples for ^2H N.m.r. Spectroscopy

N-(benzyl)glycinato-*bis*-(ethane-1,2-diamine)-cobalt(III) diacetate (60 mg) was dissolved in 0.025 M borax/D_2O buffer (1 cm^3). The progress of the reaction was monitored by ^1H n.m.r. spectroscopy. After 19 h at 304 K, the exchange was adjudged to have proceeded sufficiently (as indicated by the resonance at δ 3.23), and was stopped by pouring the mixture into 1 *M* aqueous acetic acid (final pH *ca.* 5). The diacetate was precipitated at 0 °C by addition of acetone (120 cm^3). The solid was filtered off, washed with acetone and dried. The solid was dissolved in D_2O (*ca.* 1 cm^3) in an n.m.r. tube and the spectrum recorded.

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