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Stereochemistry in the Macrocyclic (1,4,7,11,14,17-Hexaazacycloeicosane)-cobalt(III) Ion and Force Field Calculations

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For the title complex $[Co(hace)]^{3+}$ *three geometric isomers are possible, two of which can have NH diastereoisomeric forms, giving a total of six geometrically distinct species. All these are sterically quite crowded and reasonable conformational possibilities are limited. The most reasonable conformation for each diastereoisomer was selected for energy minimization. The experimental evidence (particularly* ^{13}C *NMR) indicates that the isolated complex is one diastereoisomer only, with* C_2 *symmetry, and from the energy calculations this is assigned as the lowest energy diastereoisomer* Λ-mer, cis-*RR*/Δ-mer, cis-*SS racemate. The next most stable form* Λ-mer, *cis, RS* (C_1 *symmetry) is 14 kJ mol*$^{-1}$ *higher in energy which would account for the stereospecific coordination. The other four diastereoisomers are considerably higher in energy.*

Introduction

In the preparation of the *trans* and *cis* geometric isomers of $[Co(tacd)_2]^{3+}$ (tacd = 1,4,7-triazacyclodecane) by the reaction of $[Co(NH_3)_5Br]Br_2$ with tacd·3HBr over charcoal at 80 °C, a third complex was formed in 9% proportion of the total CoN_6^{3+} products [1]. This complex had properties closely similar to those of *cis*-$[Co(tacd)_2]^{3+}$ (elemental analyses, ^{13}C and ^1H NMR spectra, visible absorption spectrum, ion-exchange chromatographic behaviour) but the absence of detectable isomerization indicated that it was a different complex species. Only the formulation $[Co(hace)]^{3+}$, where hace is the sexadentate macrocyclic ligand 1,4,7,11,14,17-hexaazacycloeicosane, was consistent with all these properties, and the presence of hace·6HBr in the tacd·3HBr sample was subsequently confirmed by ion-exchange separation.

We now report an analysis of the stereochemistry for the $[Co(hace)]^{3+}$ system, and deduce the structure of the most stable isomer from NMR spectra and energy minimization calculations.

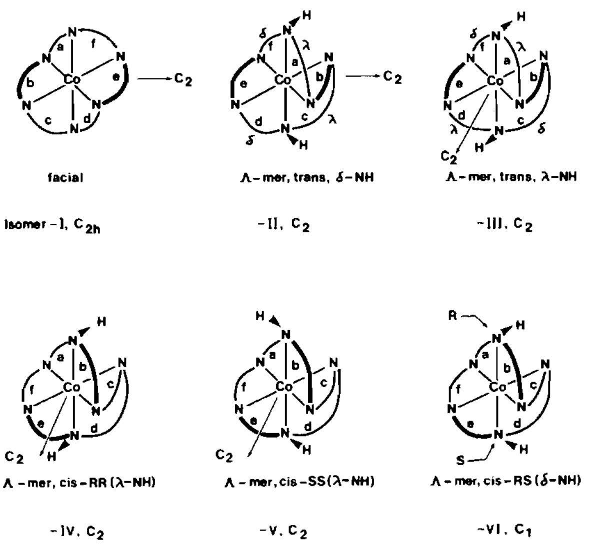

Fig. 1. Possible isomers and diastereoisomers for $[Co(hace)]^{3+}$ with their designations and stereochemical specifications. The tn-type chelate rings are shown as thickened curves. The molecular symmetries shown are those based on planar chelate rings. Ring conformations shown for (II) and (III) are those preferred.

Results and Discussion

Stereochemistry of $[Co(hace)]^{3+}$

Six geometrically distinct structures are possible for $[Co(hace)]^{3+}$, and these are shown with their stereochemical designations as structures (I) to (VI) in Fig. 1. Structure (I) has the ligand in an *all-facial* topology, and structures (II) to (VI) have the dissymmetric *mer* topology; for these *mer* structures only one absolute configuration Λ (defined according to the IUPAC rules [2]) is shown. Within the *mer* topology, *trans* and *cis* geometric isomers arise from the different relative dispositions of the two tn rings.

In the *mer* topology also, the N–H bonds from the nitrogens which couple the pairs of *mer* rings are

TABLE I. Relationships between Isomers and Diastereoisomers in Different Complexes. Symmetries for Planar Rings are parenthesized.

$[Co(dien)_2]^{3+}$ Isomers		$[Co(hace)]^{3+}$ Isomers			$[Co(hexacyclen)]^{3+}$ Isomers
symm-facial (C_{2h})	→	(I) *facial* (C_{2h})		→	*facial* (D_{3d})
mer, δ-NH (C_2)	→	(II) Λ-*mer, trans*, δ-NH (C_2)		→	Λ-*mer*, δ-NH (C_2)
mer, λ-NH (C_2)	→	(III) Λ-*mer, trans*, λ-NH (C_2)		→	Λ-*mer*, λ-NH (C_2)
Λ-*unsymm-facial* (C_2)		(VI) Λ-*mer, cis*-RR (C_1)	[δ-NH]	↗	
		(IV) Λ-*mer, cis*-RS (C_2)	[λ-NH]	↗	
		(V) Λ-*mer, cis*-SS (C_2)			

chiral as in *mer*-$[Co(dien)_2]^{3+}$ [3] (dien = diethylenetriamine), and this gives two NH diastereoisomers (II) and (III) for the *mer, trans* geometry, and three NH diastereoisomers (IV), (V) and (VI) for *mer, cis*. This chirality of the NH bonds can be specified as λ-NH or δ-NH as in *mer*-$[Co(dien)_2]^{3+}$ [3]. These nitrogens are asymmetric in the *mer, cis* structures where they couple en and tn chelate rings and for this geometry the R or S absolute configurations at these nitrogens need to be specified to completely define the structures. The λ-NH/δ-NH terminology is insufficient here because the Λ-*mer, cis*-RR and -SS have the same chirality λ of the *mer*-NH bonds.

The molecular point-group symmetries shown in Fig. 1 are those based on planar chelate rings. However the conformation of the various en rings may be λ or δ, and chair or λ-skew or δ-skew are possible for the tn rings. A number of combinations of these are possible for each of the structures (I) to (VI). The conformations of the *mer*-coupled en rings in the *mer, trans* structures (II) and (III) are expected to be constrained to some extent by the dispositions of the NH bonds, as in *mer*-$[Co(dien)_2]^{3+}$ [3]; the conformations preferred on this basis are shown in Fig. 1, and maintain the C_2 symmetries. The conformations of the *mer*-coupled rings in the *mer, cis* structures (IV) to (VI) are not so constrained.

Under basic conditions where NH exchange can occur [4], diastereoisomers (II) and (III) would be expected to interconvert, as would structures (IV) to (VI).

The $[Co(hace)]^{3+}$ system is related to the $[Co(dien)_2]^{3+}$ system in that structures (I) to (VI) can be constructed by variously bridging the en-ring arms of the geometric and optical isomers of $[Co(dien)_2]^{3+}$ in pairs by trimethylene bridges. The relationships between the isomers of the two systems are listed in Table I, together with correspondences to the analogous macrocycle system $[Co(hexacyclen)]^{3+}$ (hexacyclen = 1,4,7,10,14,16-hexaazacyclooctadecane) [5, 6] having all en-type rings.

Experimental Properties of $[Co(hace)]^{3+}$

The complex was prepared and chromatographed (SP-Sephadex) under basic conditions [1], so that all possible isomers and diastereoisomers should have resulted in their thermodynamic equilibrium proportions at 80 °C. In the subsequent ion-exchange work-up and isolation under acidic conditions no change in the equilibrium proportions of the geometric isomers would be expected.

In the Sephadex chromatography with Na_3PO_4 eluent, NH diastereoisomers should be interconvertible under the basic conditions. It is possible therefore that each geometric isomer (*facial, mer-trans*, and *mer-cis*) moves only as the NH diastereoisomer most favoured by ion-association with PO_4^{3-}, so that the NH diastereoisomer(s) in the isolated product might not be in equilibrium proportions.

The ^{13}C NMR spectrum of the isolated $[Co(hace)](ClO_4)_3$ in D_2O (pH 3) showed seven sharp resonances, and the ^1H NMR (d_6-Me_2SO) showed three NH proton resonances [1]. These spectra give the maximum molecular symmetry as C_2, thereby excluding structures (I) and (VI).

^{13}C NMR spectra are generally sensitive to geometric isomerism [7, 8], and for the systems $[Co(hexacyclen)]^{3+}$ [5, 6] and $[Co(linpen)]^{3+}$ [9] (linpen = 1,14-diamino-3,6,9,12-tetraazatetradecane) the different NH diastereoisomers (for each geometry) also give unique ^{13}C NMR resonances. Thus the seven resonances in the ^{13}C NMR spectrum of $[Co(hace)](ClO_4)_3$ indicate that only one of the six geometric/diastereoisomeric species is present.

Two experiments were carried out which demonstrate that the coordination of hace is stereospecific: (1) the isolated $[Co(hace)](ClO_4)_3$ was exposed to

TABLE II. Calculated Conformational Structures and Energy Terms for $[Co(hace)]^{3+}$ Isomers.

Diastereoisomer	Symmetry Constraint[A]	Calculated conformations[B]	Bond length deformations	Non-bonded interactions	Valence-angle deformations	Torsional terms	Total strain energy kJ mol^{-1}
(I) *facial*	none	δ^{D}, λ-skew^{D}, δ^{D}, λ^{D}, δ-skew^{D}, λ^{D}	18.0	79.4	77.4	63.0	237.7[E]
(II) Λ-*mer*, *trans*, δ-NH	C_2	λ, λ-skew, λ, δ, λ-skew, δ		>3000			>4000
	none	envelope, chair, δ^{D}, δ^{D}, λ-skew^{C,D}, δ	18.4	66.1	86.5	59.9	230.9
(III) Λ-*mer*, *trans*, λ-NH	C_2	λ^{D}, λ-skew, δ, λ^{D}, λ-skew, δ	15.4	57.0	76.6	45.8	194.8
(IV) Λ-*mer*, *cis*-RR	C_2	δ, chair, λ, δ, chair, λ	14.5	61.4	42.5	28.4	146.7
(V) Λ-*mer*, *cis*-SS	C_2	δ^{D}, δ-skew^{D}, λ^{D}, δ^{D}, δ-skew^{D}, δ^{D}	13.3	67.8	43.9	59.9	184.9
(VI) Λ-*mer*, *cis*-RS	none	δ, chair, δ, δ^{D}, δ-skew, λ	14.9	56.1	48.2	41.8	161.0

[A] This is the symmetry constraint imposed for the coordinate (and hence energy) calculations and is the symmetry of the conformational structure initially selected. The initial (and final) structures for isomers (I), (II) and (VI) were C_1 symmetry. [B] Conformations of the chelate rings in order a to f around the macrocycle. Rings are designated a to f as in Fig. 1. [C] This end of the molecule (one end of pseudo-C_2 axis, Fig. 1) of (II) is inevitably more crowded. [D] Conformation is distorted: the two N–C carbons are markedly shifted from being equidistant on opposite sides of the N–Co–N plane. [E] Calculations did not converge but eventually oscillated on iteration, between C_i (lower energy) and C_1.

conditions under which isomerizations of cobalt(III)-amine complexes occur (*i.e.* charcoal and/or base), and Sephadex chromatography of the resulting solutions gave only a single band. In closely related systems [5, 10, 11] the different geometries are readily separated by this means, and we conclude that only one geometry of $[Co(hace)]^{3+}$, but not necessarily a single diastereoisomer, was present. (2) the ^{13}C NMR of $[Co(hace)](ClO_4)_3$ in D_2O was rerun with added NaOH (pH 12). Under these conditions, configurations at *mer*-NH centres can invert readily following proton exchange [4]; but after 9 hr the resultant spectrum was identical to that in D_2O at pH 3. Thus only one NH diastereoisomer is present in conditions where specific ion-association effects (as possibly in the phosphate chromatographic elution) do not obtain.

The close similarity of the ^{13}C NMR spectrum, the visible spectrum, and the chromatographic behaviour to those of *cis*-$[Co(tacd)_2]^{3+}$ are indicative that the tn rings are *cis* [1], consistent with the *mer, cis* structures (IV) and (V). In support of this, the 2:1:1 ^{13}C NMR peak pattern which is apparently characteristic of two en rings meridionally coupled in *mer*-$[Co(dien)_2]^{3+}$ [7, 12], *unsymm*-$[Co(hexacyclen)]^{3+}$ (two NH diastereoisomers) [5, 6], and $[Co(linpen)]^{3+}$ (two of the geometric isomers and their NH diastereoisomers) [9] is absent.

Force Field Calculations and Energy Minimized Structures

The purpose of the energy minimization calculations was to determine the stable isomer, which was indicated to be (IV) or (V) by the chemical and spectroscopic evidence, and to account for the observed stereospecificity in the system.

The energy minimization procedure was outlined previously [13]. Because of the several different conformational arrangements possible for each isomer a complete series of calculations was not feasible. For each diastereoisomer, Dreiding models were used to decide a reasonable conformation based upon a compromise between ring strain and H- - -H nonbonded interactions, and its measured coordinates were initial data in the minimization program. Particular attention was given to structures having C_2 symmetry. For five of the diastereoisomers, typically with 625 interactions, the calculations converged and the minimum energy data are given in Table II.

Despite the limitations of the fixed angles of the Dreiding models, we believe that in the present system they can give a reliable assessment of the least favourable conformations of a given geometry, but give a less reliable comparison between conformations of different diastereoisomers. The particular value of strain energy minimization is that differences between conformations of diastereoisomers are quantified in terms of all the interdependent contributions to the total strain energy. Experience has shown [13, 14] that this minimization program finds the minimum in the conformation of the initial coordinates.

For isomer (I), it is not possible to accommodate both tn rings in the chair conformation. Although one chair and one skew can be accommodated, it seems that skew conformations for both tn rings lead to least strain. Significant interactions in the potential C_{2h} symmetry model or its degraded forms C_2, C_i, or C_s, notably non-bonded contacts down to 1.5 Å, cannot readily be relieved within their respective symmetries. The most reasonable model is that generated from the C_{2h} structure by inversion of one en ring. During refinement a pattern was observed in which the structure had alternating C_i and C_1 symmetries of which the C_i structure had the lower energy. Notwithstanding this C_i symmetry, isomer (I) would be expected to give a 2:2:2:1 peak pattern in the ^{13}C NMR spectrum due to spectrum averaging [5, 13, 15–19]. It seems that, as in *symm*-[Co(hexacyclen)]$^{3+}$ [5] and *s-fac*-[Co(dien)$_2$]$^{3+}$ [14, 20], detailed structures with mirror symmetry are not favoured due largely to higher non-bonded interactions.

In the Λ-*mer, trans* structures (II) and (III), each coordinated *mer*-dien prefers to have the en rings in opposite conformations as in *mer*-[Co(dien)$_2$]$^{3+}$, with the tn rings each adopting the λ-skew conformation for least ring strain. For (II), the resulting C_2 structure λ, λ-skew, λ, δ, λ-skew, δ (rings in order a to f as in Fig. 1) is not only strained but has at least two very serious H- - -H interactions at one end of the molecule (*i.e.* one end of C_2 axis), and no minimum could be found in this symmetry. The crowding could be relieved by changing one tn conformation to chair, and the resulting C_1 structure was then refined. The energy-minimized structure was quite distorted, and the ring strain evident from the Dreiding model shows as a very high valence angle deformation contribution, with non-bonded interactions still substantial.

With diastereoisomer (III), the model of the preferred C_2 structure λ, λ-skew, δ, λ, λ-skew, δ has less ring strain and crowding than any model for (II), and this is evident in the lower values for all the energy contributions in the calculated structure.

Apart from the δ, chair, λ, δ, chair, λ with C_2 symmetry, other models for diastereoisomer (IV) can be constructed having other conformations of the four en rings, and while several of these seem relatively strain free they all introduce further close contacts between the tn rings. Skew tn rings cannot easily fit into this diastereoisomer without distorting towards symmetrical-boats.

Maintaining the two chair tn conformations into diastereoisomer (V) introduces considerable ring strain, twists two en rings into near envelope conformations, and adds a number of severe non-bonded contacts. In this instance δ-skew tn rings are preferred. Arrangements alternate to that in Table II incur further H- - -H interactions (*e.g.* λ, δ-skew, λ, λ, δ-skew, λ) and/or ring strain *e.g.* envelope, δ-skew, δ, envelope, δ-skew, δ).

Diastereoisomer (VI), which could be considered intermediate between diastereoisomers (IV) and (V), shares the disabilities of each in that two δ-skew tn conformations cannot be accommodated and neither can two chairs. The optimum appears to be chair + δ-skew, midway between (IV) and (V). Likewise the optimum en conformations are similar.

The experimentally observed stereospecificity is consistent with the energy minimization results which indicate that the isolated [Co(hace)]$^{3+}$ has structure (IV). If a second diastereoisomer were present, its population must have been below the limit of detection (1%) which would require a free energy difference of *ca.* 11 kJ mol^{-1}. The calculated energy difference 14 kJ mol^{-1} between structure (IV) and the next most stable diastereoisomer (VI) is sufficiently large that we feel errors in the strain energy formalism [13] could not invert the order. Experimentally, isomer (VI) does not satisfy the criterion for C_2 symmetry as required by the ^{13}C NMR spectra, and structure (V) which is of C_2 symmetry can be eliminated with confidence on the basis of its strain energy, 38.2 kJ mol^{-1} above (IV).

It is of interest that our deduced structure for [Co(hace)]$^{3+}$ is the same as that found subsequently for [Ni(hace)](ClO$_4$)$_2$·Me$_2$NCHO [21], although the apparent stereospecificity in the latter complex may be due in part to crystal forces.

The stereospecificity observed in the present system contrasts with that in the analogous macrocyclic hexamine systems [Co(hexacyclen)]$^{3+}$ [5, 6] (all en rings) where the equilibrium proportions are *facial* : Λ-*mer*-δ-NH : Λ-*mer*-λ-NH *ca.* 1:50:50, and Co(III) with [21] crown-N$_6$ (alternating en and tn rings) where the most preferred isomer is *facial* [22].

An X-ray crystal structure analysis of the isolated [Co(hace)]$^{3+}$ is in progress [23].

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