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Isomers of the Bis(1,4,7-triazacyclodecane)cobalt(III) Ion, and the Occurrence of Higher Cyclic and Non-Cyclic Amines in the Richman–Atkins Synthesis for Cyclic Amines

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In seeking to prepare the two geometric isomers of $[Co(tacd)_2]^{3+}$ (Fig. 1) to continue our studies of isomerization reactions [1], we obtained the ligand tacd (tacd = 1,4,7-triazacyclodecane) through the Richman–Atkins procedure [2, 3] involving cyclization of $\overset{+}{Na}\overset{-}{N}(Ts)CH_2CH_2CH_2\overset{-}{N}(Ts)\overset{+}{Na}$ (I) and (Ts)-$OCH_2CH_2N(Ts)CH_2CH_2O(Ts)$ (II) (Ts = p-CH_3-$C_6H_4SO_2$–). The tacd·3HBr thus prepared was expected to be quite pure since: the $HN(Ts)CH_2$-$CH_2CH_2N(Ts)H$ from which (I) was prepared *in situ*, and (II), each gave clean ^{13}C n.m.r. spectra; the immediate cyclized product $tacd(Ts)_3$ was recrystallized (although melting points were variable over batches); and the tacd·3HBr from detosylation of $tacd(Ts)_3$ was crystallized in restricted yield, 55–65% (although melting points were variable over 241–250°, decomp.) The ^{13}C n.m.r. spectrum of tacd·3HBr seemed to confirm its high purity (three peaks in ratio 2:4:1; δ 45.3; 43.9, 21.4 respectively in D_2O; referenced to *t*-butyl alcohol capillary at δ 30.79 for CH_3; 20.10 MHz broad-band proton decoupled), although various batches always showed some small additional CH_2 resonances.

This tacd·3HBr was employed to synthesize the bis-complex of cobalt(III) by the standard substitution procedure

$$[Co(NH_3)_5Br]Br_2 + 2tacd\cdot 3HBr + LiOH \xrightarrow[4hr]{charcoal,\ 80\ ^\circ C} [Co(tacd)_2]^{3+}$$

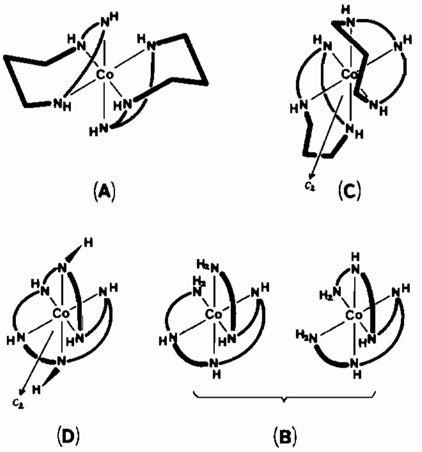

Fig. 1. Products in the synthesis of $[Co(tacd)_2]^{3+}$. (A), *trans*-$[Co(tacd)_2]^{3+}$, 96%. (C), *cis*-$[Co(tacd)_2]^{3+}$, 4%. (D), Λ-*mer*, *cis*,RR-$[Co(hace)]^{3+}$. (B), Λ-*mer*,*cis*-$[Co(dtah)]^{3+}$. Six-membered rings (tn) are shown thickened. The designations *trans* and *cis* refer to the relative geometric dispositions of the tn rings. One optical form is shown for each of the racemates (C), (D) and (B).

On cation-exchange chromatography of the product solution (SP-Sephadex with 0.1 M Na_3PO_4 eluent) three bands of CoN_6^{3+} complexes separated, from which the complexes were isolated by cation-exchange and crystallized as perchlorate salts. The ^{13}C n.m.r. spectra in D_2O showed that the products (A) and (B) from the first two bands respectively were pure single complex species. The product from the third eluted band gave two sets of seven resonances, showing it to be a mixture of two complexes (C) and (D) in ratio *ca.* 1:3, Table I [4]. Pure (D) was subsequently separated and isolated from this mixture (*vide infra*), and pure (C) from the equilibrium mixture formed by isomerization of (A) (*vide infra*).

Complexes (A) and (C) as perchlorate salts could be interconverted with charcoal or base (80°) to give the same equilibrium mixture (A):(C) = 96:4, in agreement with the preparative proportions, Table I (under conditions where ion-association is insignificant). These are therefore the expected geometric isomers of $[Co(tacd)_2]^{3+}$.

The clean ^{13}C n.m.r. spectra of (A) and (C) reflect the symmetries of the structures based on planar chelate rings so that the geometric configurations can be assigned unequivocally: the 2:2:2:1 peak pattern of (A) shows that it is the *trans* isomer of symmetry C_{2h}, whereas (C) gives seven equal peaks indicating C_2 symmetry and is therefore the *cis* isomer [4].

The solution spectra do not yield information on the conformations of the interconnected chelate rings (the en-rings could be δ-gauche or λ-gauche,

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the tn-rings could be chair of δ-skew or λ-skew). The conformations could be locked, or could be labile within the n.m.r. time scale giving spectrum averaging, but on the basis of Dreiding models and experience with other systems [5–7] we would expect that the latter applies. The detailed conformational stereochemistry for this system is complicated: various combinations of all the ring conformations are possible, and N–H diastereoisomers are also possible in principle. However Dreiding models and energy minimization calculations indicate that the most favoured form has *trans* geometry with the tn-rings in chair conformations (Fig. 1), and the ^{13}C n.m.r. assignment of the experimentally favoured isomer (A) as *trans* with identical (averaged) ring conformations in the two ligands is consistent with this. The less favoured isomer (C) of *cis* geometry should also have chair-tn conformations.

In the presence of PO_4^{3-}, (A) becomes even more favoured over (C) due to the greater ion-association of (A) with this anion (as evidenced by its first elution in cation-exchange chromatography with Na_3PO_4 eluent [8]). Thus in Na_3PO_4 at 80 °C (but not under the conditions of the chromatography at ambient temperature) (C) isomerizes completely to (A) experimentally and this property was used to obtain pure (D), *i.e.*

$$\text{(C)} + \text{(D) mixture} \xrightarrow{Na_3PO_4,\ 80\ ^\circ C} \text{(A)} + \text{(D)},$$

these products being easily separable chromatographically.

Complex (D) has properties similar to those of *cis*-$[Co(tacd)_2]^{3+}$ (C): (D) and (C) give similar elemental analyses; they give similar ^{13}C n.m.r. spectra of seven equal resonances indicating C_2 symmetry; (C) and (D) have almost identical visible absorption spectra, which are markedly different from that of the differently coloured *trans* isomer (A), Table I; the ^1H n.m.r. spectrum (d_6-Me_2SO) of (D), like (C), shows no NH_2 resonances indicating macrocyclic ligand(s); and the two complexes elute almost together on chromatography. However (D) remained unchanged under conditions where isomerizations of CoN_6^{3+} complexes occur [1] so that it could not be another isomer of $[Co(tacd)_2]^{3+}$ (*i.e.* not a conformational isomer of NH diastereoisomer). Thus we deduce that (D) is a single diastereoisomer of $[Co(hace)]^{3+}$ (hace = 1,4,7,10,13,16-hexacycloeicosane), for which six geometrically distinct diastereoisomers are possible. This conclusion accords with the recent report by Margulis and Zompa that a particular sample of synthesized tacd·3HBr gave crystals of one diastereoisomer of $[Ni(hace)](ClO_4)_2 \cdot Me_2NCHO$, found by X-ray crystallography [9]. Our energy minimization calculations show that the lowest energy diastereoisomer of $[Co(hace)]^{3+}$ is Λ-*mer*, *cis*, RR/Δ-*mer*, *cis*, SS racemate (Fig. 1) which

TABLE I. Proportions and Properties of Complexes.

Complex	Preparative proportions, %	Colour	Visible absorption max. ϵ_{nm} in M^{-1} cm^{-1}	^{13}C n.m.r. in D_2O*	
(D) Λ-*mer,cis*,RR-$[Co(hace)]^{3+}$ (racemate)	9	Orange	$\epsilon_{349} = 105.6$, $\epsilon_{486} = 110.9$	7 equal resonances	
(C) *cis*-$[Co(tacd)_2]^{3+}$	3	Orange	$\epsilon_{347} = 117.3$, $\epsilon_{482} = 111.0$	7 equal resonances	chromatographic elution order†
(B) *mer,cis*-$[Co(dtah)]^{3+}$	<1	Orange	$\epsilon_{349} = 102.5$, $\epsilon_{485} = 109.0$	12 equal resonances	
(A) *trans*-$[Co(tacd)_2]^{3+}$	88	Yellow	$\epsilon_{341} = 84.5$, $\epsilon_{467} = 75.0$	2:2:2:1	

*20.10 MHz broad-band proton decoupled, run on a Bruker WP-80 spectrometer using 8192 data table. The spectra are referenced to the CH_3 signal δ 30.79 from a *t*-butyl alcohol capillary. Chemical shift falues are, for (D): δ 56.5, 55.6, 53.9, 53.6, 50.4, 48.5, 22.8. (C): δ 52.6, 52.0, 51.7, 49.7, 47.1, 44.7, 18.4. (B): 57.0, 55,4, 55.1, 54.0, 53.3, 50.0, 49.0, 47.6, 41.7, 39.2, 26.2, 23.0. (A): 53.5, 49.6, 44.9, 16.3 in ratio order respectively.

†(C) elutes only marginally ahead of (D), insufficient for their separation.

is the analogous diastereoisomer to that isolated in the nickel(II) complex [9], and which is one of the two possibilities indicated by the ^{13}C n.m.r. spectrum (*i.e.* C_2 symmetry) and the visible absorption spectrum (*i.e.* *cis* topology as for (C)) and the chromatographic behaviour (*i.e.* *cis* topology as for (C)).

The minor complex (B) contains twelve carbons (by elemental analyses and ^{13}C n.m.r. spectrum), and the ^{1}H n.m.r. spectrum has broad peaks from NH_2 showing that the ligand is non-macrocyclic. The complex remains unchanged with charcoal or base. The visible absorption spectrum is almost identical with those of (D) and (C) (Table I). These properties indicate that (B) is one of the diastereoisomers of *mer, cis*-$[Co(dtah)]^{3+}$, Fig. 1 (dtah = 1,16-diamino-3,7,10, 13-tetraazahexadecane). Two topologies are possible for a *mer, cis* arrangement of the tn rings in $[Co(dtah)]^{3+}$ (Fig. 1), and a total of six NH diastereoisomers are possible between these two topologies (both topologies are C_1 symmetry).

These findings prompted our reexamination of the tacd•3HBr product. One batch was subjected to cation-exchange chromatography when two fractions were cleanly separated on elutions with HCl. Crystallization of the first effluent from elution with 1.5 M HCl gave pure tacd•3HCl (m. pt. 245–250 °C decomp.), which showed a clean ^{13}C n.m.r. pattern of three reasonances only (D_2O: δ 45.0, 43.5, 21.1 in ratio 2:4:1). The product from crystallization of the subsequent 4 *M* HCl effluent was in substantial amount and gave a ^{13}C n.m.r. spectrum showing ten other resonances. These correspond to the small peaks noted in the synthesized tacd•3HBr samples, and they can be attributed to hace•6HCl (three resonances, ratio 4:8:2) and dtah•6HCl (seven resonances, ratio 1:2:5:1:1:1:1). These hexamines appear to be present in comparable amounts, and the elemental analysis results of this second fraction are intermediate between the calculated figures for these two compounds. When this product was used to prepare the cobalt(III) complex, only (B) and (D) were obtained.

It is now clear that the Richman–Atkins cyclization procedure is not specific, at least for cyclic triamines. Dimeric cyclic amines (hace) and higher linear polyamines (dtah) can be co-products with the required simple cyclic amine (tacd). The condensations occur by nucleophilic attack of $-(Ts)N^-$ in (I) at the C–O(Ts) carbon centres of (II). Formation of the linear product dtah presumably results from an elimination reaction by $-(Ts)N^-$ in the linear precursor of hace. Other non-cyclized by-products, such as $NH(Ts)(CH_2)_3N(Ts)(CH_2)_2N(Ts)(CH_2)_2$-O(Ts), are also conceivable from the condensation reaction.

The tosyl derivatives and hydrobromides of the higher amine co-products will presumably have lower solubilities than $tacd(Ts)_3$ and tacd•3HBr respectively, which probably accounts for the difficulties in purifying $tacd(Ts)_3$ and tacd•3HBr by recrystallization procedures without incurring substantial losses. These losses may be minimized by carrying out only one recrystallization of $tacd(Ts)_3$. Subsequently, ion-exchange provides an efficient means of removing the higher amines from the cyclic triamine tacd•3HBr.

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