On the Stability of the O–T Linkage in 17-Hydroxyprogesterone

Sir:

In a recent publication on the role of reduced nicotinamide–adenine dinucleotide phosphate (NADPH) in steroid hydroxylations,[1] the author, in studying the enzymatic hydroxylation of progesterone, arrives at the conclusion that the tritium atom from labeled NADPH becomes firmly bound to the oxygen atom introduced at C-17. This implies that the tritium atom of the 17-OT group does not exchange during lengthy incubation and isolation procedures. Since this is contrary to experience with hydroxyl groups in general[2,3] and the 17α-hydroxyl in particular,[4] we felt the example merited reexamination. A deuteriochloroform solution of 17α-hydroxyprogesterone (I) shows a broad hydroxyl absorption at δ 2.96 integrating for one proton, compared to the peak at δ 5.74 due to the proton at C_4 (Figure 1). Shaking the chloroform solution with two drops of deuterium oxide results in the immediate loss of the band at δ 2.96 with no other change in the spectrum, conclusively proving that the 17-hydroxyl group does indeed exchange rapidly.

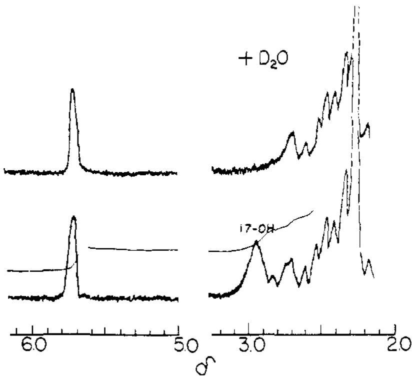

Figure 1.

In a second experiment, designed to eliminate the possibility of an unusual isotope effect due to tritium, 200 mg of I was treated with 1 ml of tritiated water in 30 ml of dioxane. The solvents were then removed under vacuum, and the product, dissolved in ethanol–toluene–PPO–POPOP, was counted. Approximately 1 equiv of tritium (corresponding to the OH group) was incorporated in this fashion. When the sample in toluene was washed once with ordinary water 95% of the activity was lost. Under the same conditions negligible activity was incorporated in progesterone itself.

The author states that acetylation of the 17-hydroxyl group caused total loss of activity. However, under the conditions of the reaction (acetic acid–acetic anhydride–toluene-*p*-sulfonic acid) tritium activity located at the 21-methyl group might well be expected to be lost if the mechanism suggested by Turner,[5] involving enolization of this group, operates. In fact, when I is dissolved in deuterioacetic acid with toluene-*p*-sulfonic acid and allowed to stand overnight, the sharp band originally present at δ 2.25 due to the 21-methyl group disappears, proving complete exchange of the protons at this position.[6]

It seems clear that Kadis' results are more simply explained as involving attachment of tritium label at the 21-methyl group, either enzymatically or through related exchange phenomena, and the mechanistic implications previously presented must be discounted.

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(4) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p. 5.

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(6) Under these conditions the proton at C-4 also undergoes partial exchange.

J. Holtzman, J. R. Gillette, Henry M. Fales
Laboratories of Chemical Pharmacology and Metabolism
National Heart Institute, Bethesda, Maryland

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Correlations of Nuclear Magnetic Resonance and Optical Rotatory Dispersion Spectra for Establishing the Absolute Configurational Assignment of Cobalt(III)-Chelated Optically Active Triethylenetetramine Homolog–α-Amino Acid Adducts

Sir:

The fact that optically active molecules which can act as ligands coordinate in a stereoselective manner is well known.[1,2] The original concept of this stereopreference was based partly on the apparent stereospecific coordination of D-cyclohexanediamine,[3] but part of this work has been shown to be incorrect.[4] The conclusions drawn by Jaeger, however, have some merit but must be updated in light of the theoretical predictions of Corey and Bailar[1] which were confirmed experimentally by Dwyer, *et al.*[5] Most of the work on ligand stereospecificity so far has involved bidentate molecules. It was only recently that a tetradentate molecule was shown to be stereoselective in its coordination.[6] The ligand, 2,9-diamino-4,7-diazadecane [called L,L-α,α'-dimethyltrien, to illustrate its analogy to triethylenetetramine (abbreviated trien)], has been shown to prefer the absolute configuration, D-*cis*-α.[6,7] However, it also forms the L-*cis*-β and *trans* isomers in small amounts.[6,7] None of the isomers D-*cis*-β or L-*cis*-α was observed. Discussions of the theoretical reasons behind this ligand's stereoselective coordination are to be found in ref 6 and 7.

In this communication a correlation between the nuclear magnetic resonance (nmr) and optical rotatory dispersion (ORD) spectra of several amino acid adducts of D-*cis*-α- and L-*cis*-β-[Co(L,L-α,α'-dimethyltrien)Cl_2]$^+$ ions is reported. The new compounds D-*cis*-α-[Co(L,L-α,α'-dimethyltrien)(aa)]$^{2+}$ and L-*cis*-β-[Co(L,L-α,α'-dimethyltrien)(aa)]$^{2+}$, where (aa) is one of the following amino acid anions, glycinate, L-alaninate, and D-alaninate, were synthesized. Their nmr and

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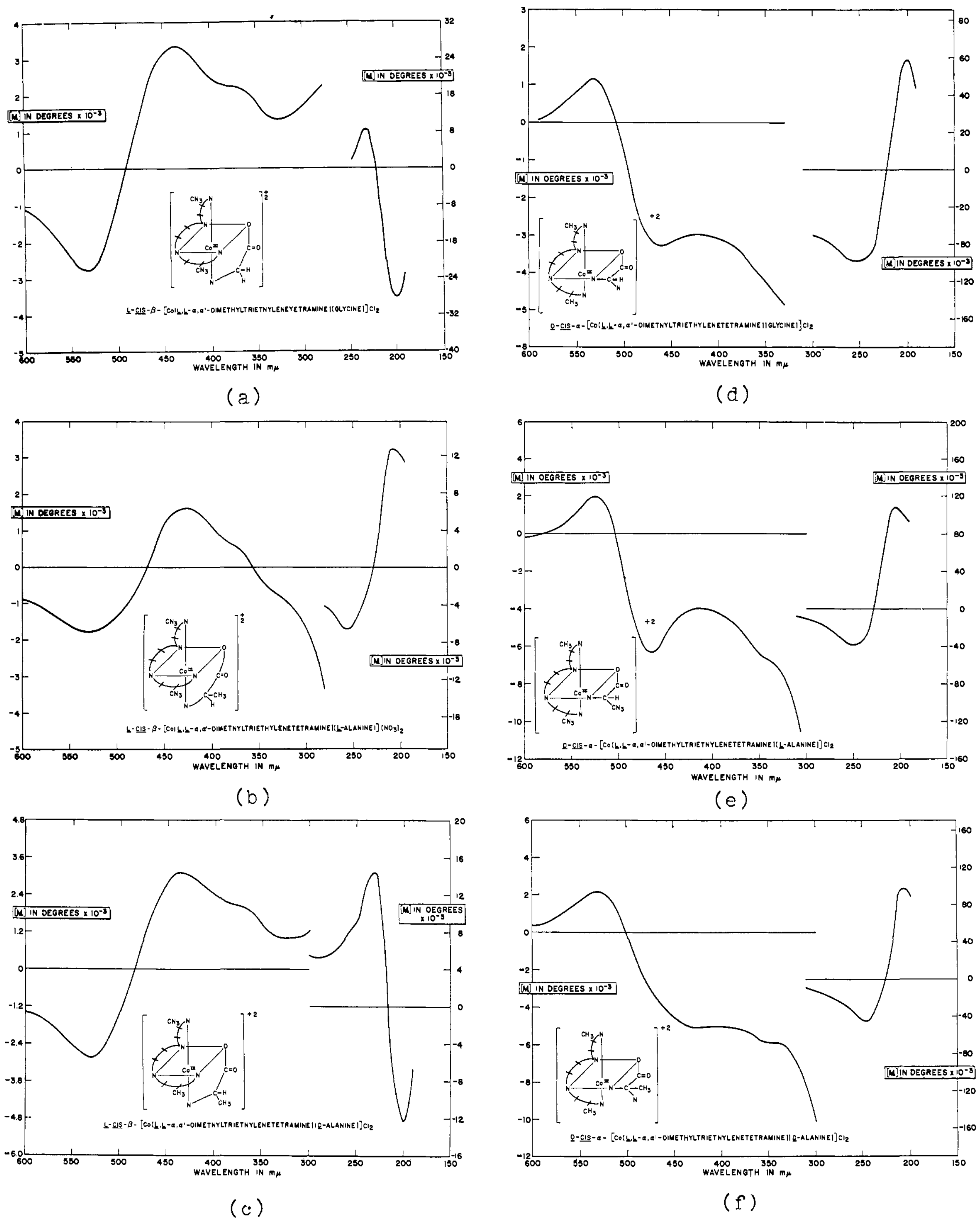

Figure 1. Optical rotatory dispersion.

ORD spectra are reported in Figures 1–3. Assignments of absolute configuration of the complex with respect to the central metal atom are based on the sign of the Cotton effect of the 550–450-mμ region as compared with the negative Cotton effect of $(-)_{546}$-$[Co(en)_2gly]^{2+}$.[8–10]

The complexes with positive Cotton effects in the 550–450-mμ region are assigned the absolute configuration D-*cis*-α and not D-*cis*-β because of large thermo-

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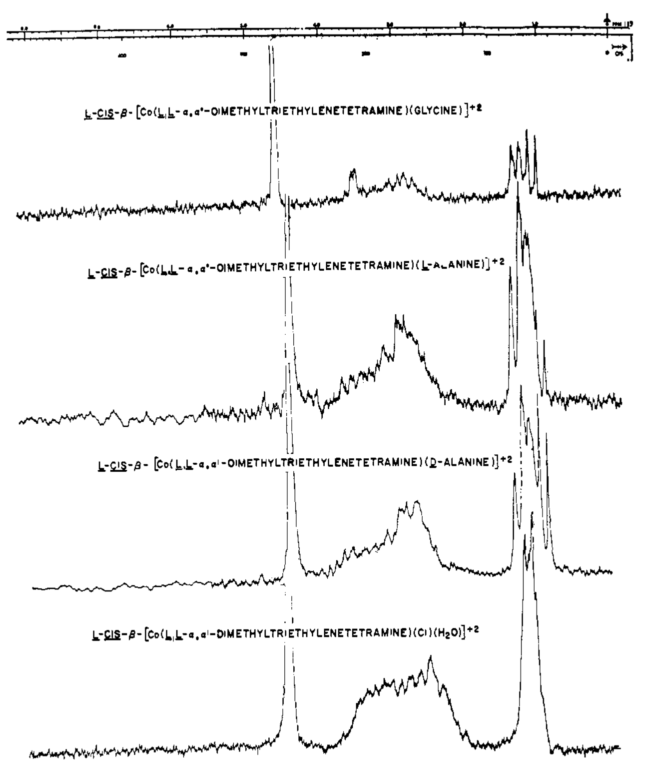

Figure 2. Nmr spectra.

dynamic instability expected for the D-*cis*-β[7] isomer. The L-*cis*-β absolute configurations are similarly assigned. The nmr spectra (Varian A-60;[11] ≈0.005 g/0.1 cc of D_2O; ambient temperatures of probe ≈33°; scans taken after samples stood at room temperature for 1-2 hr; all exchangeable protons were lost; external standard, NaTMS) are shown in Figures 2 and 3. It can be seen that every *cis*-β isomer has a characteristic methyl doublet, $J = 6.5$ cps, shifted upfield from the remaining methyl resonance peaks (Figure 2 and Table I). This doublet is absent in the *cis*-α isomers of Figure 1d-f as is shown in the nmr spectra of Figure 3. This difference permits the distinction between the α and β configurations whenever the L,L or D,D form of α,α'-dimethyltrien is used as a tetradentate ligand. Owing to the stereopreference of the optically active ligand,[7] the α and β isomers formed from one particular enantiomer of the ligand acquire opposite chirality with respect to the central metal atom. In the case of the L,L ligand the *cis*-β complexes exhibit a negative Cotton effect and are assigned the L absolute configuration [in analogy with $(-)_{546}$-$(Co(en)_2gly)^{2+}$],[8] whereas the *cis*-α complexes exhibit a positive Cotton effect and are assigned the D absolute configuration.

Table I

D-*cis*-α complex	Upfield methyl doublet, τ
D-Alanine	8.85
L-Alanine	8.89
Glycine	8.82

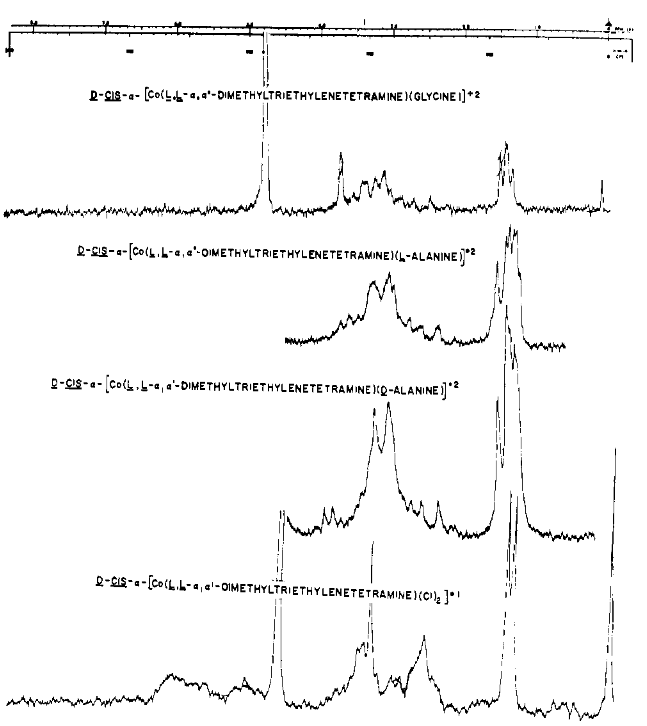

Figure 3. Nmr spectra.

Thus, the assignment of absolute configurations for these stereospecific complexes can be made quickly and easily by noting the pattern of the nmr methyl region. This ability is very important to the development of fundamental knowledge of inorganic reaction mechanism and ligand conformational effects.

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Robert G. Asperger
Edgar C. Britton Research Laboratory
The Dow Chemical Company, Midland, Michigan 48640

Chui Fan Liu
Department of Chemistry
University of Illinois at Chicago Circle, Chicago, Illinois 60680

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(11) The solutions were prepared in a microcell; scans were on the "Dog" mode of the time-averaging attachment by Dow Chemical Co., Midland, Mich.

A Correlation between the Triplet State Lifetime and Electronic Polarizability

Sir:

During recent years, lifetime measurements of triplet decay in aromatic compounds have received considerable attention.[1] Many of these triplet lifetimes have been obtained by phosphorescent emission studies carried out in rigid glass solutions at low temperatures. Under these experimental conditions the decay of the triplet molecules usually follows first-order kinetics.[2]

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(2) R. G. Bennett, R. P. Schwenker, and R. E. Kellogg, *J. Chem. Phys.*, **41**, 3040 (1964).