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.

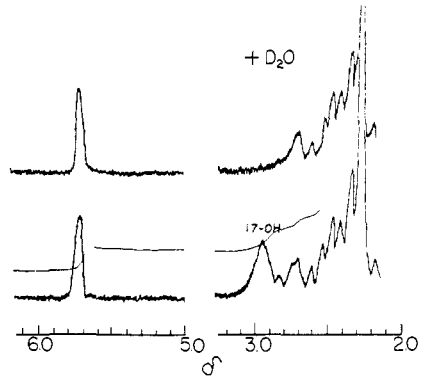

Figure 1.

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

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Received November 21, 1966

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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