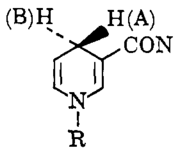
Comments on the Factors Controlling Product Stereospecificity in the Reduction of Carbonyl Compounds with Alcohol Dehydrogenase and Diphosphopyridine Nucleotide

Sir:

The classic experiments of Westheimer and coworkers[1] showed that the DPNH reduction of acetaldehyde with yeast alcohol dehydrogenase is stereospecific in both substrate and coenzyme. From the absolute configuration[2] at C-4 of the pyridine nucleus of DPND it is now known that yeast and liver alcohol dehydrogenases cause transfer of the A proton (I),

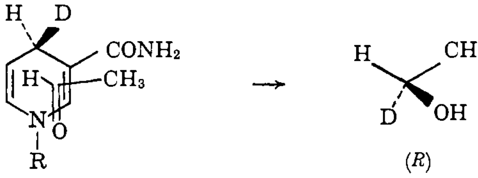


I

whereas a- and e-ketone reductases from *Curvularia falcata* cause transfer of the B proton.[3]

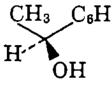
The high product stereospecificity of the DPNH carbonyl reduction has been rationalized in terms of repulsive interactions between carbamido and the groups attached to the carbonyl[3a] and in terms of hydrophilic and hydrophobic regions near the active site of the enzyme.[3,4] We wish to present evidence pertinent to this subject.

First, we call attention to II as a formal representa-

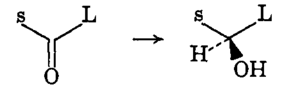


II

tion of the spatial relationship between DPNH and acetaldehyde[5] in the yeast and liver alcohol dehydrogenase reactions by correlating the absolute configuration of I with the following evidence: (a) DPNH and 1-deuterioacetaldehyde give (−)-ethanol-1-*d*.[6] The absolute configuration of (+)-ethanol-1-*d* is (*R*).[7] This, plus the finding that yeast alcohol dehydrogenase and DPN react with (*S*)-2-octanol (III)[8] but not (*R*)-2-octanol, indicate that Prelog's general scheme IV → V (L = large, s = small) is followed with enzymes associated with transfer not only of the B, but also of the A proton, and argue against the importance of the carbamido group in product stereospecificity control.

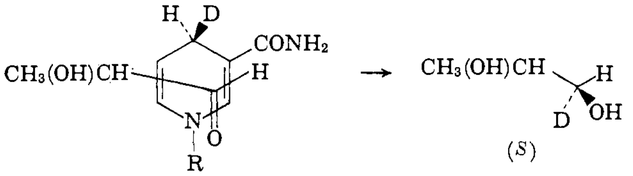


III

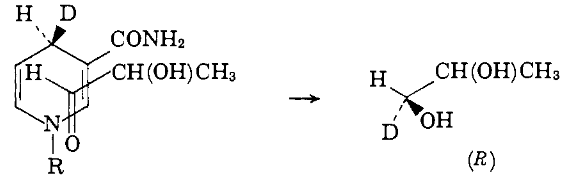


IV V

Second, we have determined the absolute configuration at C-1 of 1,2-propanediol-1-*d* obtained from the reduction of D- and L-lactaldehyde with DPND and horse liver alcohol dehydrogenase in order to evaluate the importance of hydrophilic and hydrophobic enzyme regions. The polar hydroxyl group that is capable of hydrogen bonding might conceivably force DPND and lactaldehyde in VI rather than VII.

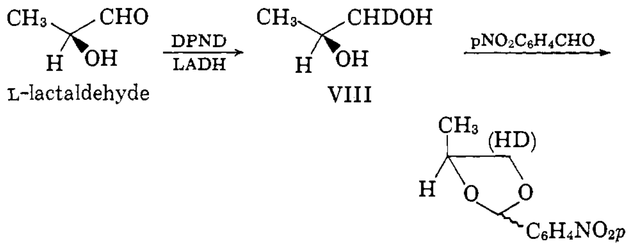


VI

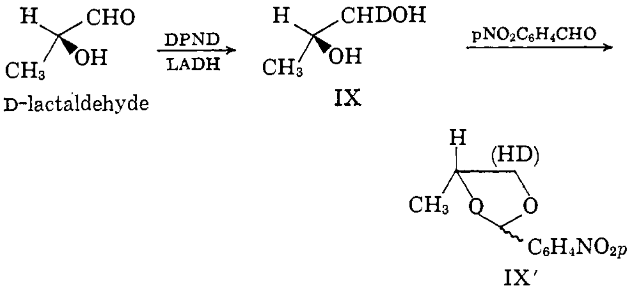


VII

By showing that the nmr spectra of VIII′ and IX′ are different, we established that the relative configura-



L-lactaldehyde VIII VIII′



D-lactaldehyde IX IX′

tions at C-1 of VIII and IX were the same.[9] *cis*- and *trans*-1-bromopropenes were converted to X and XI according to the sequence outlined below.[10] The pertinent regions of the nmr spectra for X and XI are shown in Figure 1. Since the spectrum of X is the

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[1] F. A. Loewus, F. H. Westheimer, and B. Vennesland, *J. Am. Chem. Soc.*, **75**, 5018 (1953).

[2] J. W. Cornforth, G. Ryback, G. Popjak, C. Donninger, and G. Schoepfer, Jr., *Biochem. Biophys. Res. Commun.*, **9**, 371 (1962).

[3] (a) V. Prelog, *Ind. Chim. Belge*, **27**, 1309 (1962), and papers cited therein; (b) *Colloq. Ges. Physiol. Chem.*, **14**, 288 (1964); *Pure Appl. Chem.*, **9** (1), 119 (1964).

[4] E. M. Kosower, *Biochim. Biophys. Acta*, **56**, 474 (1962).

[5] The oxygen is placed over the nitrogen as in ref 4. Although the same stereochemical result is obtained by any rotation of the aldehyde in its mirror plane, we will adapt this formulation throughout the paper for convenience, since it does not affect the subsequent arguments and conclusions.

[6] H. R. Levy, F. A. Loewus, and B. Vennesland, *J. Am. Chem. Soc.*, **79**, 2949 (1957).

[7] R. U. Lemieux and J. Howard, *Can. J. Chem.*, **41**, 308 (1963).

[8] J. van Eys and N. O. Kaplan, *J. Am. Chem. Soc.*, **79**, 2782 (1957)

[9] P. A. Frey, G. J. Karabatsos, and R. H. Abeles, *Biochim. Biophys. Res. Commun.*, **18**, 551 (1965).

[10] The bromopropenes were separated by fractional distillation and gas chromatography. Each isomer was contaminated by the other by about 5%. The 57–58° boiling isomer was assigned the *cis* configuration and the 62–63° the *trans*. See D. Y. Curtin and J. W. Crump, *J. Am. Chem. Soc.*, **80**, 1922 (1958); M. Farina and M. Perald, *Gazz. Chim. Ital.*, **90**, 973 (1960). We confirmed the assignments by carbonating the lithium salts and obtaining the *cis* ($J_{\mathrm{HH},\,vic}$ = 11.4 cps) and *trans* ($J_{\mathrm{HH},\,vic}$ = 15.5 cps) acids with better than 95% stereospecificity. The osmium tetroxide hydroxylation was done according to J. S. Baren, *J. Org. Chem.*, **25**, 257 (1960).

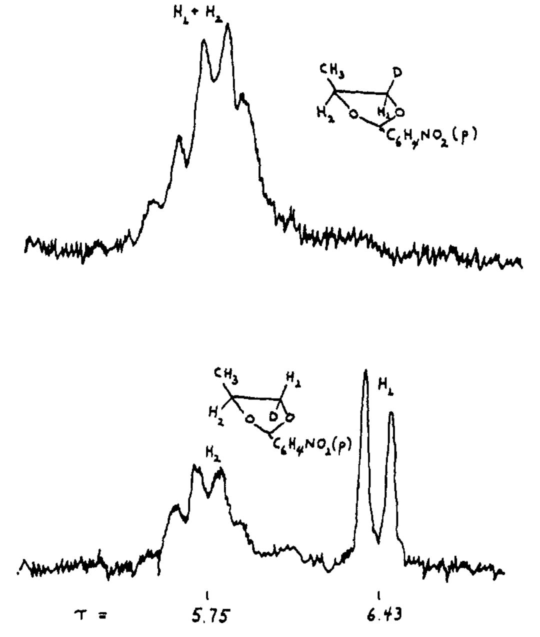
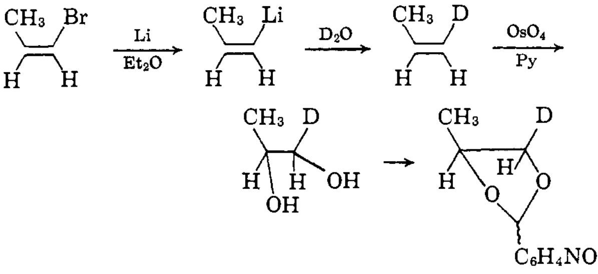
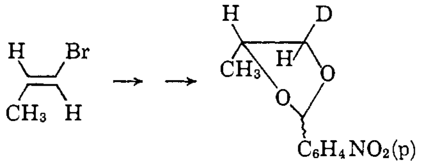


Figure 1.

same as that of VIII'[9] and that of XI as that of IX', it follows that the absolute configuration at C-1 of VIII and IX is (*R*). As far as product stereospecificity is therefore concerned, lactaldehyde, either D or L, and acetaldehyde have the same substrate–coenzyme relationship (VII and II).



X



XI

The above results point out the need for further testing the importance of hydrophilic and hydrophobic regions in product stereospecificity control.

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A Novel Amination Reaction of Carboxylic Acid Derivatives with Tetrakis(dimethylamino)titanium

Sir:

We wish to report a new reaction in which tetrakis(dimethylamino)titanium (I) converts carboxylic acids and their common derivatives (esters, anhydrides, amides) into orthoamides and ketene N,N-acetals, conveniently and in good yields.

N,N-Dimethylformamide, for example, is converted to the previously unknown[1] tris(dimethylamino)methane ($HC[N(CH_3)_2]_3$, bp 70° (50 mm), $n^{25}D$ 1.4348), in 83% yield by I at room temperature in ethyl ether in several hours. The structural assignment of the triamine is based on its molecular weight, nmr spectra, and elemental analysis. *Anal.* Calcd for $C_7H_{19}N_3$: C, 57.9; H, 13.2; N, 28.9; mol wt, 145. Found: C, 57.9; H, 13.3; N, 29.3; mol wt (cryoscopy in benzene), 144. The nmr spectrum (benzene solution, TMS internal standard) exhibited sharp singlets at τ 6.98 and 7.69 in the expected ratio of 1:18.

N,N-Dimethylacetamide is converted to 1,1-bis(dimethylamino)ethylene ($CH_2{=}C[N(CH_3)_2]_2$, bp 115° (744 mm), $n^{25}D$ 1.4500, lit.[2] $n^{20}D$ 1.4518) in 87% yield under essentially the same conditions as above. *Anal.* Calcd for $C_6H_{14}N_2$: C, 63.1; H, 12.4; N, 24.5; mol wt, 114. Found: C, 62.7; H, 12.1; N, 24.3; mol wt (mass spectroscopy), 114. The nmr spectrum (benzene solvent, TMS internal standard) exhibited sharp singlets at τ 6.60 and 7.53 in the expected ratio of 1:6.

The titanium is converted in both examples to insoluble oxide.

Experiments are in progress to determine the generality of the reaction as a synthetic tool, and a detailed description of this and further work will be reported shortly.

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(1) The first authentic member of this series, N,N',N''-triphenyl-N,N',N''-trimethyltriaminomethane, was reported by D. H. Clemens, E. Y. Shropshire, and W. D. Emmons, *J. Org. Chem.*, **27**, 3664 (1962).
(2) H. Bredereck, F. Effenberger, and H. P. Beyerlin, *Chem. Ber.*, **97**, 3081 (1964).

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The Oxidation of Water Coordinated to Cobalt(III)

Sir:

Until recently, there have been few systematic investigations of the oxidation of water by metal ion complexes. Some ideas on the mechanism of the oxidation taking account of existing kinetic and thermodynamic data were recently advanced,[1] but the data leave much latitude in the interpretations based on them. In this communication we report the results of some tracer experiments which prove that the water in the first coordination sphere of $(NH_3)_5CoOH_2^{3+}$ can be oxidized. The observations thus fix an important feature of the mechanism, at least in this case.

When, at 50°, a solution of $AgNO_3$ is added to an acidic solution of $K_2S_2O_8$ and $(NH_3)_5CoOH_2(ClO_4)_3$, a small percentage of the Co(III) complex is reduced to

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(1) H. Taube, *J. Gen. Physiol.*, **49**, 29 (1965).