Facilitation of Intramolecular 1,2-Shifts in Radicals by Protonation, and the Mechanism of Reactions Catalysed by 5′-Deoxyadenosylcobalamin

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Summary *Ab initio* molecular orbital calculations show that 1,2-intramolecular shifts in simple organic radicals may be facilitated by protonation of the migrating group; the relevance of this result to reactions catalysed by 5′-deoxyadenosylcobalamin is demonstrated.

ABUNDANT experimental and theoretical information is available which shows that intramolecular 1,2-shifts in carbocations often occur readily.[1] However, with simple organic radicals (not containing π-systems or hetero-atoms with low-lying *d*-levels) there are very few authenticated intramolecular 1,2-shifts since the transition state for such a process generally involves one-electron occupancy of an orbital of relatively high energy.[2] By applying *ab initio* molecular orbital theory[3] to a simple model system, we have examined whether protonation of a potential migratory group can facilitate its 1,2-shift to a radical centre.

Consider the hypothetical degenerate rearrangement of the hydroxyethyl radical, (**1**) $\rightleftharpoons$ (**1′**) *via* the bridged species (**2**) (Scheme 1). Our calculations fail to reveal any structure corresponding to (**2**) with energy lower than for the separated species ethylene and hydroxyl radical. Therefore, if the rearrangement (**1**) $\rightleftharpoons$ (**1′**) does occur, it proceeds through a dissociation–recombination mechanism.

If the above system is modified by protonation, the rearrangement can be formulated as (**3**) $\rightleftharpoons$ (**3′**) *via* (**4**)

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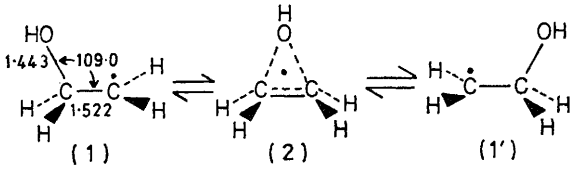
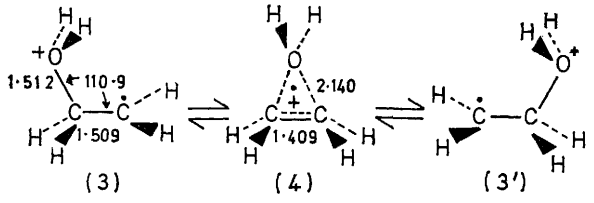
(Scheme 2). In this case, our calculations show that the bridged structure (**4**) is bound relative to the separated species H_2O and $C_2H_4^+$ by 17·4 kcal mol^{-1}. Furthermore, the transformation (**3**) ⇌ (**3′**) *via* (**4**) as putative transition state is calculated to require an activation energy of only 8·3 kcal mol^{-1}.



SCHEME 1. 1,2-Intramolecular shift in the hydroxyethyl radical showing important (calculated) bond lengths (Å) and bond angles (degrees).

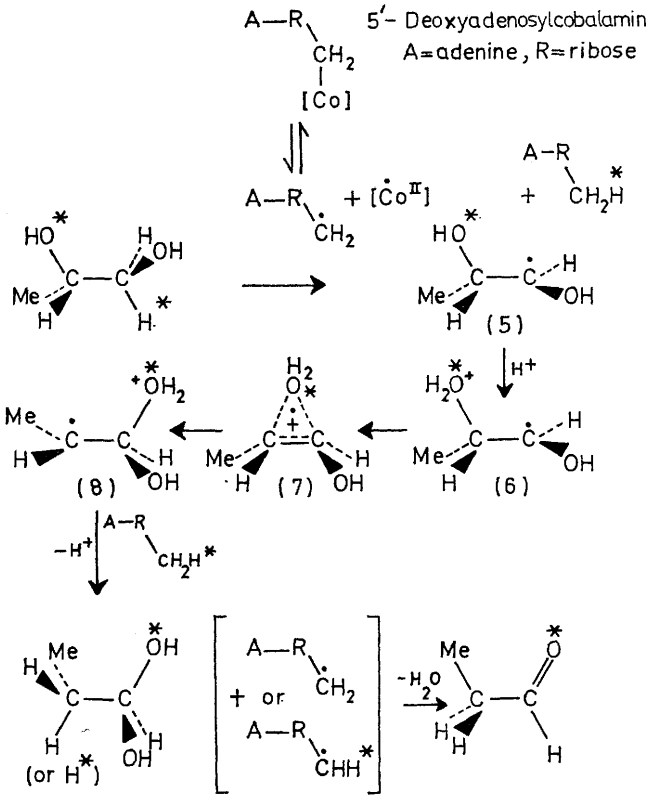
The lowering of the activation energy for (**3**) ⇌ (**3′**) compared with the unprotonated example (**1**) ⇌ (**1′**) may be due to inductive withdrawal of electron density from the radical centre following protonation of (**1**). This makes species (**3**) more like a carbocation and so the 1,2-shift occurs more easily. In addition, the bridged structure (**4**) may be stabilised by a charge–dipole interaction. An approximate assessment of this factor shows that it is likely to contribute significantly to the binding energy of 17·4 kcal mol^{-1}.



SCHEME 2. 1,2-Intramolecular shift in the protonated hydroxyethyl radical showing important (calculated) bond lengths (Å) and bond angles (degrees).

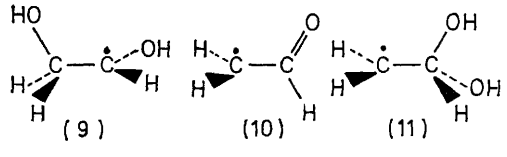
The simple idea that protonation of a group can promote its intramolecular 1,2-shift to a radical centre leads to the mechanism suggested below for a type of rearrangement catalysed by 5′-deoxyadenosylcobalamin.[4] In the conversion of (*R*)- or (*S*)-propane-1,2-diol into propanal induced by the enzyme dioldehydrase in the presence of 5′-deoxyadenosylcobalamin, the oxygen atom at C-2 of a molecule of substrate is transferred to C-1 of the probable intermediate 1,1-dihydroxypropane.[5a] Several mechanisms have been suggested for this reaction[5] (and the related conversion of ethane-1,2-diol into acetaldehyde). These suggestions include the intramolecular 1,2-shift of a hydroxy-group to a radical centre[5c] [analogous to (**1**) ⇌ (**1′**) *via* (**2**)] which we have shown to be unlikely. Nevertheless, there is good evidence for the involvement of substrate-derived and product derived radicals in the rearrangement.[6]

We suggest that the enzymatic rearrangement of propane-1,2-diols to propanal takes place as shown in Scheme 3. The crucial species (**6**)—(**8**) arise from the assumed ability[7]



SCHEME 3. Suggested mechanism for the conversion of (*S*)-propane-1,2-diol into propanal catalysed by dioldehydrase and 5′-deoxyadenosylcobalamin.

of dioldehydrase to protonate the radical (**5**). The retention of oxygen at C-2 of substrate by the product (despite an aqueous medium) is thus easily explained. Although the protonated radicals (**6**)—(**8**) differ from (**3**) and (**4**) by the presence of extra substituents in the former, our calculations suggest that the effect of these substituents (OH and Me) decreases the energy difference between the bridged and open species.



A model system for the above enzymatic reactions is provided[8] by the ready conversion at pH 2·5—4 of the

radical (**9**) (derived by attack of ·OH on ethane-1,2-diol) into (**10**). It is believed that radical (**11**) is also formed under these conditions. These results are consistent with a mechanism for the conversion of (**9**) into (**10**) proceeding *via* protonated (**9**) and (**11**), in a manner analogous to the steps (**6**) → (**8**) in Scheme 3.

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[1] See, *e.g.* 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963; V. Buss, P. v. R. Schleyer, and L. C. Allen, *Topics Stereochem.*, 1972, **7**, 253; L. Radom and J. A. Pople in M.T.P. Internat. Rev. Science (Theor. Chem.), ed. W. Byers Brown, Butterworths, London, 1972; P. C. Hariharan, W. A. Lathan, and J. A. Pople, *Chem. Phys. Letters*, 1972, **14**, 385.

[2] See, *e.g.* (a) C. Walling in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, ch. 7; (b) H. E. Zimmerman, *ibid.*, ch. 6; (c) W. J. Hehre, *J. Amer. Chem. Soc.*, 1973, **95**, 2643; (d) C. Walling and A. Cioffari, *ibid.*, 1972, **94**, 6064.

[3] Calculations were carried out using the Gaussian 70 system of programmes, W. J. Hehre, W. A. Latham, R. Ditchfield, M. D. Newton, and J. A. Pople, submitted to Q.C.P.E. Optimization of geometries was carried out with the minimal STO-3G basis set, W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, 1969, **51**, 2657, and relative energies then determined with the extended 4-31G basis, R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, 1971, **54**, 724.

[4] For a review see H. A. Barker, *Ann. Rev. Biochem.*, 1972, **41**, 55.

[5] (a) J. Rétey, A. Umani-Ronchi, J. Seibl, and D. Arigoni, *Experientia*, 1966, **22**, 502; (b) R. B. Silverman, D. Dolphin, and B. M. Babior, *J. Amer. Chem. Soc.*, 1972, **94**, 4028; (c) S. A. Cockle, H. A. O. Hill, R. J. P. Williams, S. P. Davies, and M. A. Foster, *ibid.*, p. 275.

[6] T. H. Finlay, J. Valinsky, A. S. Mildvan, and R. H. Abeles, *J. Biol. Chem.*, 1973, **248**, 1285.

[7] An analogous protonation may occur in catalysis by lysozyme (*cf.* B. M. Dunn and T. C. Bruice, *Adv. Enzymol.*, 1973, **37**, 1).

[8] B. C. Gilbert, J. P. Larkin, and R. O. C. Norman, *J.C.S. Perkin II*, 1972, 794.