

A MNDO SCF-MO Theoretical Study of the Mechanism of [1,2] Migrations in Free Radicals as a Model for Coenzyme B₁₂ Mediated Rearrangement Reactions

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MNDO SCF-MO calculations predict that [1,2] radical migrations that are thought to occur in coenzyme B₁₂ mediated rearrangements can proceed by three distinct mechanistic pathways: $-\text{CH}(\text{NH}_2)\text{CO}_2\text{H}$ by dissociation-recombination, in 1,2 diols by stepwise migration of a protonated OH group *via* an intermediate π -allyl complex, and acyl groups by either a concerted migration or dissociation-recombination; X = SiH₃, CHO, CN, and CS₂H are predicted to be good migrating groups in such reactions.

Among the reactions brought about by the coenzyme B₁₂ dependent enzymes, those which interchange a hydrogen atom with a vicinal functional group [X = (*inter alia*) OH, NH₂, COSCoA, CH(NH₂)CO₂H] (Scheme 1) are remarkable for their general lack of chemical analogy.¹ A widely accepted, generalised version of Abeles² mechanistic proposal for the diol dehydratase system is given in Scheme 2. This scheme, postulating hydrogen migration to occur *via* abstraction and addition steps, does not attempt to specify the crucial mechanism of substrate-product derived free radical interconversion. Mechanistic proposals¹ have varied from those involving intimate cobalt complexes to those involving [1,2] rearrangement of the isolated free radical S[•] (Scheme 2). This latter

option has been the subject of relatively few theoretical studies³ and none in which a wide range of substituents were investigated. We report here such a quantitative investigation into the mechanism of [1,2] rearrangements in free radicals.

The general reaction R'CH-CHXR to R'CHX-CHR was studied using the standard MNDO SCF-MO procedure⁴ with the unrestricted Hartree-Fock (UHF) option for open shell species and with optimisation of *all* geometrical variables. Transition states for the [1,2] migration of group X were located approximately (Figure 1) by carrying out a reaction path calculation using the reaction co-ordinate R₁, and located

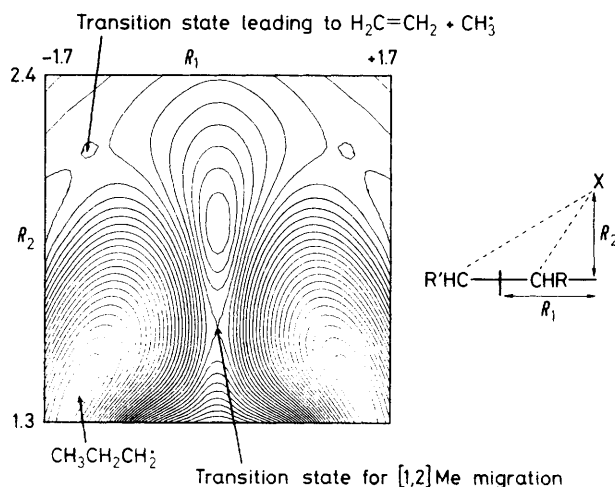
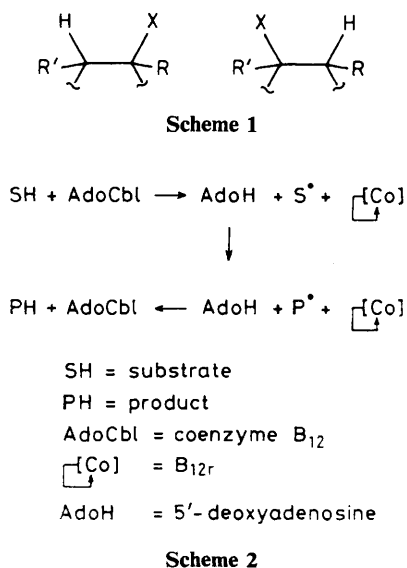


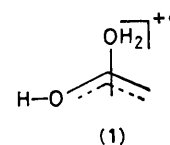
Figure 1. Calculated MNDO potential energy surface for [1,2] methyl migration in the n-propyl radical (X = Me), obtained by using the two reaction co-ordinates R₁ and R₂. The former is defined as the distance between the perpendicular from group X and the centre point of the C-C bond. Contour levels are separated by 2.21 kcal mol⁻¹.

Table 1. Calculated energies (in kcal mol⁻¹) for the radical rearrangement R'CH-CHXR to R'CHX-CHR.

Entry	R'HC-CHXR X	R	R'	ΔH_{298}^a	$\Delta H^{\ddagger b}$	ΔH_{diss}^c	$\Delta H_{\text{react}}^d$
1	H	H	H	10.5	52.3 ^e	57.0	0.0
2	Me	H	H	5.1	58.6 ^f	34.9	0.0
3	CH(NH ₂)CO ₂ H	H	H	-71.6	62.4 ^f	10.7	0.0
4	CH(NH ₃ ⁺)CO ₂ ⁻	H	H	-12.8	62.7 ^f	22.1	0.0
5	SiH ₃	H	H	4.8	21.2 ^f	48.0	0.0
6	NH ₂	H	H	18.1	44.2	33.8	0.0
7	NH ₃ ⁺	H	H	184.2	38.2 ^{g,t}	47.1 ^h	0.0
8	OH	H	H	-31.6	67.4	47.2	0.0
9	OH	H	OH	-88.2	74.2	53.5	10.3
10	OH ₂ ⁺	H	H	158.0	16.8 (10.5) ⁱ	18.8 ^j	0.0
11	OH ₂ ⁺	H	OH	97.4	14.5 (-1.4) ^k	6.4 ^l	9.3 ^m
12	SH	H	H	15.3	31.3	36.2	0.0
13	Cl	H	H	0.7	26.4	43.6	0.0
14	vinyl	H	H	30.1	17.1 ⁿ (3.5) ^o	44.2	0.0
15	CN	H	H	44.0	32.6 (29.5)	97.4	0.0
16	CHO	H	H	-18.1	30.8 (29.9)	31.9	0.0
17	CO ₂ H	H	H	-76.3	39.5	36.9	0.0
18	COSH	H	H	-18.4	34.4 (34.2)	27.7	0.0
19	CS ₂ H	H	H	-38.2	19.1 (10.3)	26.9	0.0
20	CO ₂ H	COSH	H	-99.0	34.3 ^p	25.5	-9.7
21	COSH	CO ₂ H	H	-99.0	31.6 ^p	16.7	-9.5
22	COSH	CO ₂ ⁻	H	-120.8	31.9 ^p	27.5	-3.2

^a Calculated (MNDO/UHF) heat of formation of the radical R'HC-CHXR. ^b Calculated activation enthalpy for the [1,2] migration of the group X. For stepwise reactions involving a cyclic intermediate, the value in parentheses represents the calculated energy of this intermediate relative to the reactant radical R'HC-CHXR. ^c [$\Delta H(\text{R'HC=CHR}) + \Delta H(\text{X}) - \Delta H(\text{R'HC-CHXR})$]. ^d [$\Delta H(\text{R'HXC-CHR}) + \Delta H(\text{R'HC-CHXR})$]. ^e Cf. 64.8 kcal mol⁻¹ calculated at the *ab initio* 4-31G level using MNDO optimised geometries (4-31G//MNDO). ^f Proceeds with retention of configuration at the migrating centre. ^g Cf. 33.3 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ^h Cf. 45.7 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ⁱ Cf. 8.3 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ^j Cf. 25.7 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ^k Cf. -3.1 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ^l Cf. 6.3 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ^m Cf. 0.3 kcal mol⁻¹ (calc. 4-31G//3G)^{3a}. ⁿ Cf. 17.3 (calc. 4-31G//3G)^{3c}, 9.1 kcal mol⁻¹ (exp.)^{3c}. ^o Cf. 8.6 (calc. 4-31G//3G)^{3c}, 5.1 kcal mol⁻¹ (exp.)^{3c}. ^p Due to the size of this system, the transition state located by the reaction path calculation was not characterised by a vibrational analysis.

exactly by minimising the sum of the squared scalar gradients.⁵ A vibrational analysis⁶ showed that each force constant matrix corresponding to these points had only one negative eigenvalue, whose vectors corresponded to the correct transformation of reactant to product.⁷ Inspection of the potential energy surface generated using *two* reaction co-ordinates (R_1 and R_2 , Figure 1, X = Me) shows that rearrangement can in fact occur by two distinct pathways, involving either direct (concerted or stepwise) [1,2] migration or dissociation to an alkene and the radical X followed by recombination. The energy of the latter route was in general estimated by calculating the total energy of the two fragments resulting from dissociation. Previous MNDO studies have shown⁸ that the transition states leading to such dissociation are from 3–10 kcal mol⁻¹ higher in energy, which agrees with experimental estimates.⁸ The activation energies for the direct [1,2] migration and the energies of the dissociated fragments relative to the reactant are shown in Table 1, together with the overall heat of reaction. Although these calculations relate to the gas phase, it has been shown experimentally that the kinetics of these reactions (*e.g.* for X = vinyl)^{9b,c} are similar in the gas phase and in solution.



Our calculations show that three mechanistic types can be distinguished; (i) those reactions that are predicted to proceed by dissociation-recombination, (ii) those that are predicted to proceed by direct concerted migration, and (iii) those that proceed by a stepwise migration involving an intermediate complex. Entries 12–14 in Table 1 (corresponding to migration of X = SR, Cl, and vinyl) are examples of groups well known⁹ to participate in [1,2] free radical rearrangements and in accordance with this the predicted activation energies are favourable. The MNDO method, however, does predict too high an activation energy for simple [1,2] hydrogen migrations in cations and carbenes¹⁰ and values for the [1,2] migrations shown in Table 1 are probably also too high. The fine balance between bridged and dissociative modes for SH migration^{9b} and the strong preference for the bridging mode for chloro and vinyl, concerted for the former^{9a} and stepwise and especially facile for the latter^{9c} is correctly reproduced by MNDO. The migration of a methyl group (entry 2), which has not been observed to occur, is correspondingly predicted to be a high energy process and belongs to mechanistic type (i) above (*cf.* Figure 1 and Table 1). The mechanistic distinction is more clear cut if the alkyl radical X is stabilised by substituents as in the glutamate mutase reaction [*cf.* X = CH(NH₂)CO₂H, entry 3]. The zwitterionic form of this system (entry 4) shows behaviour intermediate between entries 2 and 3. In contrast, the migration of X = SiH₃ (entry 5) belongs to mechanistic type (ii) and is predicted to be a relatively low energy process. Such a simple migration of a silyl group from carbon has apparently never been observed. Migration of X = NH₂ (entry 6) is calculated to have a relatively large activation energy, although the value may be too high (*vide supra*).¹⁰ Protonation (X = NH₃⁺, entry 7) does not lead to significant lowering of the activation energy, although mechanism (ii) is now more clearly favoured. These results for amino migration are to be contrasted with X = OH (entry 8), which in the neutral system is predicted to proceed by mechanism (i). Upon protonation (X = OH₂⁺, entry 10) the calculations indicate mechanism (iii), which involves an intermediate π complex between C₂H₄⁺ and H₂O and has a much lower activation energy. Golding and Radom in their *ab initio* study obtained a similar result,^{3a} although they did not identify the π complex as a distinct intermediate or locate the transition state leading to this complex. In the example of the diol dehydratase substrate¹, which is known to rearrange *in vivo* (*cf.* R' = OH, entries 9 and 11), protonation of the migrating group leads to an even more stable complex which can be best described as a loose π -allyl complex between water and the radical cation of vinyl alcohol (1).

Our calculations do not offer a clear distinction between the direct [1,2] migration [mechanisms (ii) or (iii)] and the dissociative mechanism (i) for the acyl series (entries 15–22). The calculations do predict that the direct mechanism would be effectively concerted (with the exception of CS₂H) and should be feasible.¹¹ The migratory aptitudes are predicted to be CHO > CN > COSH > CO₂H and in the malonyl series the preference for X = COSH over CO₂H (entries 20–22) is maintained. Although the migration of X = COSCoA in competition with X = CO₂H (or CO₂⁻) is observed in the methylmalonylCoA mutase system¹ little is known about the relative ease of migration of acyl groups in general.

† 1 kcal = 4.184 kJ.

These results demonstrate that in the radical mode of the B_{12} dependent types of [1,2] rearrangements, three distinct mechanisms may be possible. Further, we predict that groups such as $X = CHO, CN, SiH_3,$ and CS_2H should migrate relatively easily in [1,2] radical rearrangements. Experiments designed to test these predictions are in progress.¹²

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References

- 1 For a comprehensive account see 'B₁₂, Vol. 1: Chemistry,' ed. D. Dolphin, Wiley-Interscience, 1982.
 - 2 R. H. Abeles and D. Dolphin, *Acc. Chem. Res.*, 1976, **9**, 114.
 - 3 (a) B. T. Golding and L. Radom, *J. Am. Chem. Soc.*, 1976, **98**, 6331; (b) L. Salem, O. Eisenstein, N. T. Anh, H. B. Burgi, A. Devaquet, G. Segal, and A. Veillard, *Nouv. J. Chim.*, 1977, **1**, 335; (c) W. J. Hehre, *J. Am. Chem. Soc.*, 1973, **95**, 2643.
 - 4 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899, 4908; M. J. S. Dewar and M. L. McKee, *ibid.*, 5841; M. J. S. Dewar and H. S. Rzepa, *ibid.*, 1978, **100**, 58, 777; M. J. S. Dewar, M. L. McKee, and H. S. Rzepa, *ibid.*, p. 3607; L. P. Davis, R. M. Guidry, J. R. Williams, M. J. S. Dewar, and H. S. Rzepa, *J. Comput. Chem.*, 1981, **2**, 433; M. J. S. Dewar and M. L. McKee, *ibid.*, 1983, **4**, 84; M. J. S. Dewar and H. S. Rzepa, *ibid.*, 1983, **4**, in the press.
 - 5 P. K. Weiner, Ph.D. Dissertation, University of Texas, 1974.
 - 6 M. J. S. Dewar, G. P. Ford, M. L. McKee, H. S. Rzepa, W. Thiel, and Y. Yamaguchi, *J. Mol. Struct.*, 1978, **43**, 135.
 - 7 J. N. Murrell and J. K. Laidler, *Trans. Faraday Soc.*, 1968, **64**, 371.
 - 8 S. B. Brown, M. J. S. Dewar, G. P. Ford, D. J. Nelson, and H. S. Rzepa, *J. Am. Chem. Soc.*, 1978, **100**, 7832.
 - 9 (a) K. S. Chen, D. Y. H. Tang, L. K. Montgomery, and J. K. Kochi, *J. Am. Chem. Soc.*, 1974, **96**, 2201; (b) A. L. J. Beckwith and K. U. Ingold, 'Free Radical Rearrangements; Rearrangements on Ground and Excited States,' vol. 1, Organic Chemistry, A Series of Monographs, No. 42, ed. P. de Mayo, Academic Press, New York, 1980, p. 161; (c) A. Effio, D. Griller, K. U. Ingold, A. L. J. Beckwith, and A. K. Serelis, *J. Am. Chem. Soc.*, 1980, **102**, 1734.
 - 10 E. P. Kyba, *J. Am. Chem. Soc.*, 1977, **99**, 8830.
 - 11 M. Okabe, T. Osawa, and M. Tada, *Tetrahedron Lett.*, 1981, 1899.
 - 12 A. P. F. Cook, J. J. Russell, and D. A. Widdowson, to be published.
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