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Mechanism of action of coenzyme B₁₂. Quantum-chemical considerations

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Abstract. Quantum-chemical calculations are carried out on simplified models to obtain insight in the mechanistic aspects of coenzyme B₁₂.

Introduction

One of the fundamental functions of the title vitamin has been shown to be a cofactor in at least three rearrangement processes in which hydrogen atoms and other groups undergo [1,2]-migrations¹: dehydration of propanediol to propionaldehyde, isomerization of glutamic acid to β -methyl-

aspartic acid and isomerization of methylmalonyl coenzyme A to succinyl-coenzyme A. With respect to the latter isomerization, the stereochemistry can be described as follows:

¹ W. W. Miller and J. H. Richards, J. Am. Chem. Soc. **91**, 1498 (1969).

Scheme 1

the thio ester group migrates in an intramolecular [1,2]-shift, the hydrogen which is transferred does not exchange with the solvent and the migration occurs with retention of configuration at both termini. Under non-enzymatic conditions the simulation of the thio ester migration has been nicely demonstrated by Scott et al.²

The formation of the thio ester in accordance with path b is not observed. We now suggest that a cyclopropane intermediate accounts for the exclusive outcome of this reaction:

The absence of 4 means that apical electron transfer from the Co-methylene bond to COOEt or COSEt is in favour of the latter, since the mesomeric contribution of SET in COSEt is less than that of OEt in COOEt³. The trapping of a carbanoid or transient carbanoid species by a protic solvent was established by Scott et al.⁴ using EtOD, leading to

Fig. 1

No attempts however have been made to confirm the stereochemistry of the chiral centre. Thus no definite answer can be offered to ascertain the proposed cyclopropane intermediate for the [1,2] thio ester group migration. On the other hand the biochemical studies for the isomerization of methylmalonyl coenzyme A (*vide supra*) catalyzed by methylmalonyl coenzyme A isomerase revealed that the migration occurs with retention of configuration. Thus we conclude

Scheme 2

that going from 1 to 2 the chirality must be transferred with retention of configuration. This is in sharp contrast to the inversion of configuration established for the glutamate isomerization. The apparent contradiction in stereochemistry for these related hydrogen migrations can be discussed with the proposed cyclopropane intermediates.

Quantum-chemical considerations

The exclusive formation of 2 over 4 has been studied with CNDO-2 calculations based on the stability of the cyclopropane intermediates:

Scheme 3

² A. I. Scott and K. Kang, J. Am. Chem. Soc. **99**, 1997 (1977).

³ H. R. Mahler and E. H. Cordes, Biological Chemistry, Second Edition, Harper and Row Publishers, New York, Evanston, San Francisco, London, 1971, p. 387-391.

⁴ A. I. Scott, J. Kang and D. Dalton, J. Am. Chem. Soc. **100**, 3603 (1978).

Table I Bond lengths and angles.

Bond ^a	Length	Type of angle	Value in degrees
C4-C4	1.457		110.8
C4-C3	1.449		60 ^b
C4-H	1.119		
C4-O2	1.367		1 116 ^b
C3-O2	1.358		2 124 ^b
C3-O1	1.267		3 113 ^b
C4-S2	1.81 ^b		111 ^b
C3-S2	1.74 ^b		105 ^b
		1 125 ^b
			2 110 ^b
			3 125 ^b

^a The number beside the atom refers to the number of substituents attached to it. Bond lengths are given in Å and are taken from: H. M. Niemeijer, Tetrahedron 33, 1369 (1977), unless specified differently.

^b Tables of Interatomic Distances and Configurations in Molecules and Ions; L. E. Sutton, Ed.; The Chemical Society, London, 1965.

^c Estimated.

In the next Figure the total energy and electron densities are given for the most relevant positions:

Scheme 4

Fig. 2a

Fig. 2b

These results show unambiguously that I is the favoured intermediate which controls the exclusive formation of 2. The same is true for II although this intermediate, which is 0.06394 a.u. higher in energy than I, might be converted in the enantiomeric form of 2 if the same mechanism for the ring opening of both intermediates is involved. Furthermore, the electrondensities clearly show that the vital positions for ring-opening are indeed negatively charged, thus favouring corner protonation.

Discussion

As regards the isomerization of methylmalonyl coenzyme A to succinyl coenzyme A and *vice versa*, it was shown that the hydrogen which migrates from the methyl group to C-3 of succinyl coenzyme A occupies the same steric location as was previously occupied by the -CoSCoA group. Thus the hydrogen migration occurs with retention of configuration. A similar shift in glutamic acid to β -methylaspartic acid and *vice versa*, however, occurs with inversion of configuration. Our suggested cyclopropane intermediate as a mechanistic rational for the product formation in the [1,2]-shift of the thio ester in the dimethylmalonate com-

plex (see Scheme 2, compound I) can be used also as a model for discrimination between a hydrogen shift which results with retention or inversion of configuration for both termini. Generally speaking, there are two possibilities for ring opening: 1) the configuration of the (protonated) chiral carbon is retained when the edge electrons, necessary for corner protonation, are polarized in the front-side direction of the chiral carbon; 2) the configuration of the (protonated) chiral carbon is inverted when the edge electrons are polarized with inversion leading to back-side protonation of the chiral carbon. Retention of configuration occurs when the chiral carbon to be protonated, is substituted by electron-withdrawing groups. This is the situation in *Scott's* model compounds and in the isomerization of methylmalonyl coenzyme A to succinyl coenzyme A. In the latter case we propose the following cyclopropane intermediate, thereby following the results of the quantum-chemical calculations:

Fig. 3

The interaction between the donor O^- and the acceptor $COOH$ is favoured by a front-side polarization in the direction of the chiral carbon thus preserving retention of configuration after protonation. Inversion of configuration takes place in the absence of electron-withdrawing groups. More simply stated it means that polarization of the edge electrons to the chiral carbon must occur with inversion to prevent electron back-donation to the donor. This situation is present in the isomerization of glutamic acid to β -methylaspartic acid:

Fig. 4

Experimental and theoretical work is in progress to ascertain the differences in stereochemistry for the acid-catalyzed ring opening of the various cyclopropanes, in particular compounds derived from **1** in an optically pure form.

Oxidation of (–)-2-bromo-3-hydroxy-*N*-methyl-6-oxomorphinan with Fremy's salt. An unprecedented 2,4-shift of the bromo substituent. (Chemistry of opium alkaloids, Part XIII)*

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Abstract. (–)-3-Hydroxy-*N*-methyl-6-oxomorphinan (**6a**) and its (–)-2-bromo derivative (**6b**) were converted into (–)-2,3-dihydroxy-*N*-methyl-6-oxomorphinan (**8a**) and its (–)-4-bromo derivative (**8b**), respectively, by oxidation with Fremy's salt to the *ortho*-quinones, followed by reduction. Methylation of **8a** and **8b** gave the corresponding methyl ethers **9a** and **9b**. Catalytic hydrogenolysis of **8b** and **9b** gave **8a** and **9a**, respectively. The structure of (–)-2,3-dimethoxy-*N*-methyl-6-oxomorphinan (**9a**) was confirmed by total synthesis, and that of (–)-4-bromo-2,3-dimethoxy-*N*-methyl-6-oxomorphinan (**9b**) by single-crystal X-ray analysis. The model compound 2-bromo-4,5-dimethylphenol (**15**) gave, analogously, 3-bromo-4,5-dimethylpyrocatechol (**16**).

We have investigated the acid-catalysed ring closure, important in our synthesis of morphine and codeine^{1,2} (Fig. 1), of various 1-benzyl-1,2,3,4,5,8-hexahydroisoquinolines³. A strategy which was developed here¹, made use of a 1-benzylhexahydroisoquinoline, substituted symmetrically in the benzyl radical.

R = H, Morphine
R = CH₃, Codeine

Fig. 1

¹ H. C. Beyerman, J. van Berkel, T. S. Lie, L. Maat, J. C. M. Wessels, H. H. Bosman, E. Buurman, E. J. M. Bijsterveld and H. J. M. Sinnige, *Recl. Trav. Chim. Pays-Bas* **97**, 127 (1978).

² T. S. Lie, L. Maat and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas* **98**, 419 (1979).

³ H. C. Beyerman, E. Buurman, L. Maat and C. Olieman, *Recl. Trav. Chim. Pays-Bas* **95**, 184 (1976).

* Part XII: L. Maat, J. A. de Groot and H. C. Beyerman, *Synth. Commun.* **9**, 713 (1979).