

Letter

Biradical mechanism of the 1,2-bond shift reaction catalysed by vitamin B₁₂ coenzyme

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Abstract

The vast amount of research on the B₁₂ coenzyme catalysed 1,2-bond shift reactions now provides strong evidence for the conclusion that spin-spin coupled biradical intermediates (R[•]...[Co]) are responsible for the facile rearrangements involved via π -complexed (charge-transfer complexed) half-reaction states. The biradical intermediates are also likely to be involved in stereospecific [2+2] activation of the substrates. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: B₁₂ Coenzyme; Spin-spin coupled biradical intermediates; π -Complexed half-reaction states

1. Results and discussion

The cobalt-alkyl complex, which is the central feature of vitamin B₁₂ coenzyme, catalyses a remarkable series of reactions whereby, (i) a paraffinic H atom is abstracted from a substrate, i.e. an sp³ hybridised C-H bond is broken, (ii) a vicinal substituent X (OH, NH₂, alkyl, COSCoA, etc.) undergoes a 1,2-bond shift step, and (iii) an H atom is added back to the new unsaturated carbon atom. This series of steps is often attributed entirely to free radicals, the initial radical being formed by homolytic fission of the [Co]-CH₂Ad σ bond, as shown in Scheme 1.

However, Scheme 1, as applied to the methyl malonate-CoA mutase system, has been thoroughly tested by Dowd et al. [1,2] who have provided powerful evidence that it is seriously deficient. They synthesised cyclopropane models for the methyl

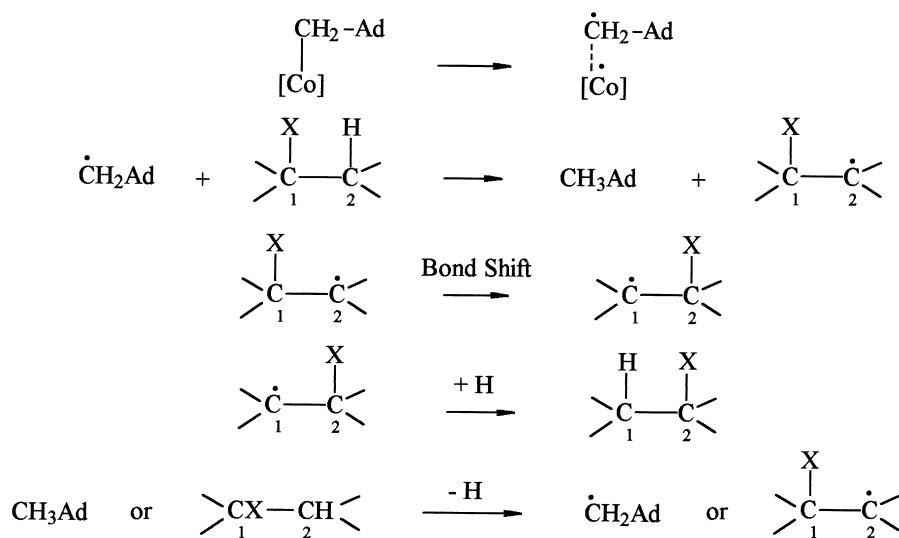
malonyl-CoA to succinyl-CoA carbon skeleton rearrangement and subjected these to reactions using cobalamin, B₁₂S, or tin hydride reagents. Remarkably, the C₃ ring remained intact during the transformation as shown in Scheme 2.

On the other hand, when the appropriate free radical is deliberately generated, an extremely fast opening of the C₃ ring occurs (Scheme 3).

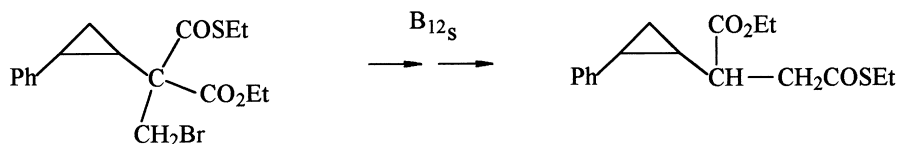
The authors conclude that free radicals per se are not responsible for the B₁₂ catalysed transformation shown in Scheme 2, but when they considered the other extreme, a covalently σ -bonded [Co]-alkyl intermediate, they were not very happy with it either.

Almost two decades ago, arising out of studies of the rearrangement of the 2,2,6,6-tetramethylcyclohexyl radical in the presence of B₁₂S, we suggested [3–6] that a biradical intermediate is the key to both the rearrangement step, and to that involving C-H activation in the substrate. This model radical probe was chosen because the flanking gem dimethyl centers frustrate the formation of a [Co]-cyclohexyl cova-

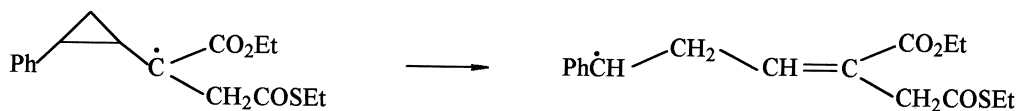
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Scheme 1.



Scheme 2.



Scheme 3.

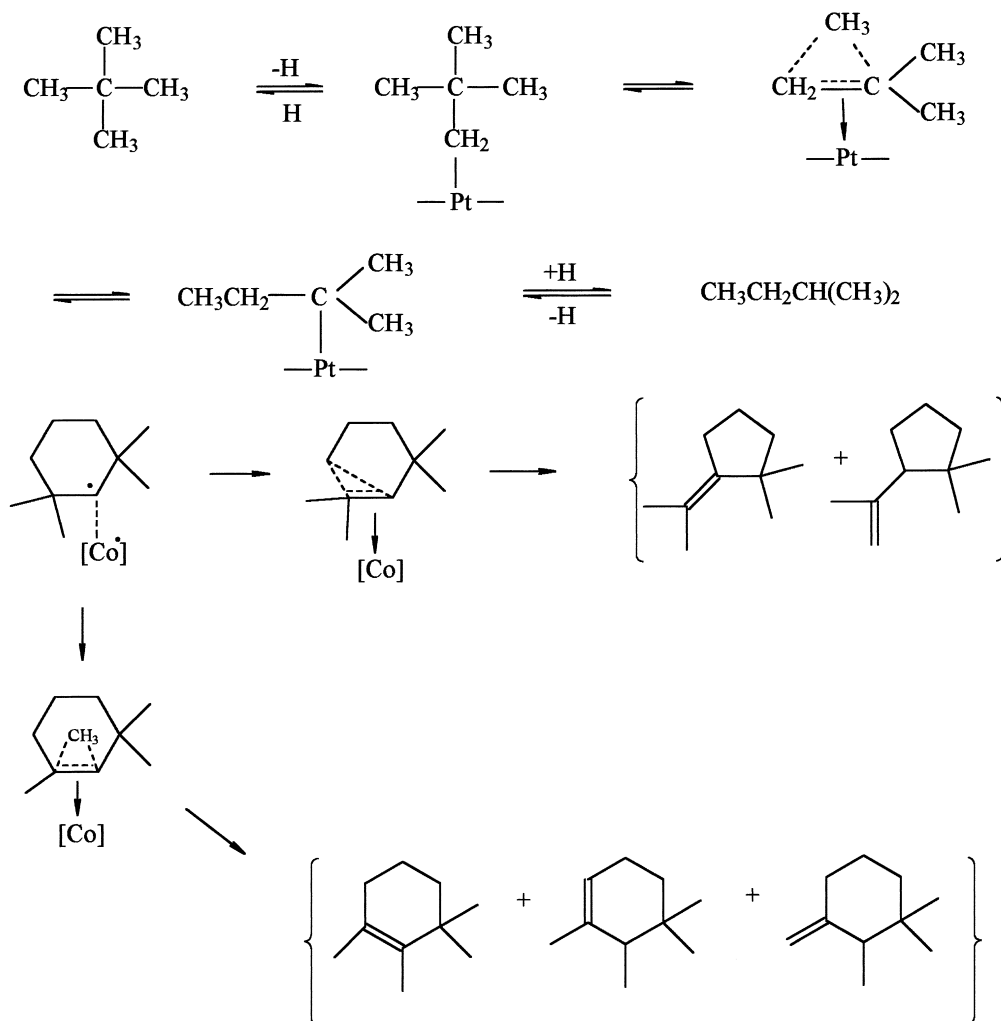
lent σ -bond. Furthermore, it allowed us to compare the behaviour of this saturated free radical in the presence of the Co ion with that of other hydrocarbyl radicals, neopentyl etc., which are known [7] to undergo 1,2-bond shift reactions in H_2 on the surfaces of noble metal catalysts, especially $Pt \geq 150^\circ C$, Scheme 4.

This potential correspondence between the heterogeneous and metallaenzyme fields of catalysis has been largely ignored, but recent work now greatly emphasises the importance of the biradical concept as a subtle distinction between two extremes, namely, the completely free radical and the covalently σ -bonded

[Co]-alkyl species. As we shall see, this resolves many of the paradoxes, found previously [1,2].

Excellent EPR investigations [8] have shown that the Co ion and the organic radical are weakly spin-spin coupled in the case of B_{12} ethanolamine deaminase cocatalysts, but strongly spin-spin coupled for the methylmalonyl-CoA mutase system [9,10].

When the biradical concept is applied to the model reactions shown in Schemes 2 and 3, it is obvious that spin-spin coupling will facilitate 1,2-bond shift but retard free radical mediated opening of the C_3 ring [1,2]. The molecular orbitals of the appropriate half-reaction state π -complex make this obvious, as



Scheme 4.

shown in Scheme 5, where $\text{X}=\text{COSEt}$, $\text{Y}=\text{CO}_2\text{Et}$, and $\text{Z}=(\text{CHCH}_2\text{CH})\text{-Ph}$.

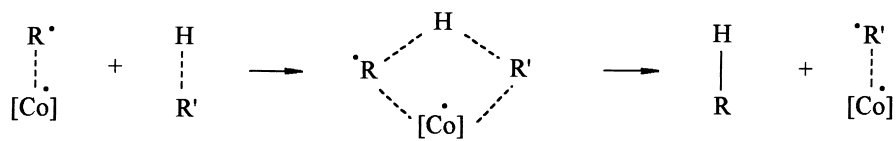
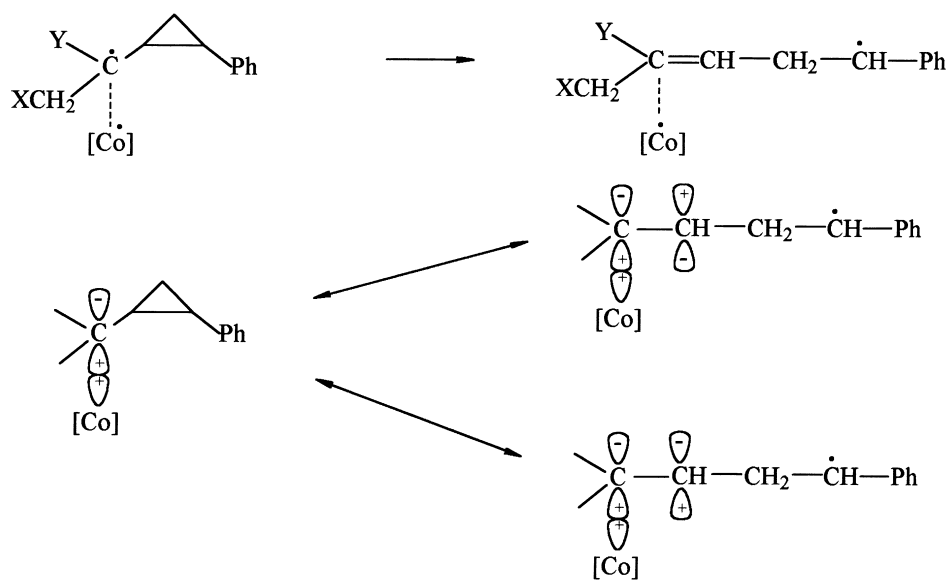
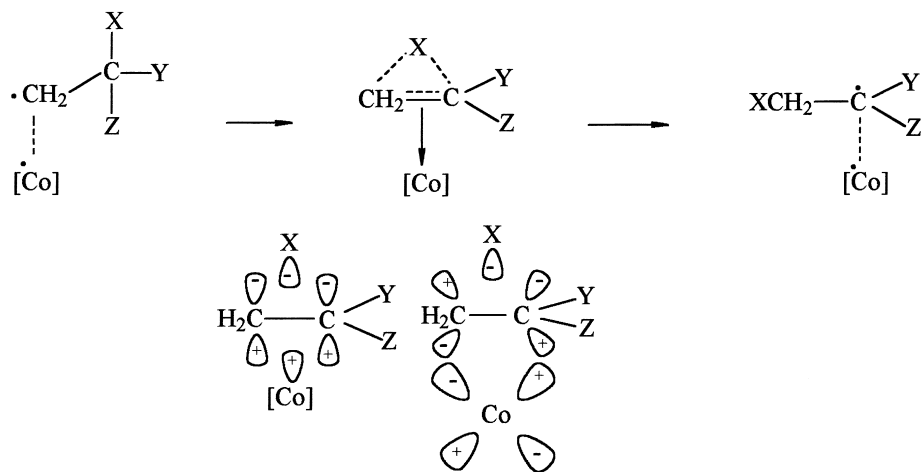
A very important feature of the overall M.O. description of the π -complex or charge transfer complex is the bonding interaction between the $\text{p}\pi^*$ anti-bonding orbital of the organic moiety and the $\text{d}\pi$ centered orbital of the Co-corrin complex. Similar interactions facilitate 1,2-bond shift in alkanes and cycloalkanes in H_2 on transition metal surfaces [7] (Scheme 4).

On the other hand, Scheme 6 shows that the spin coupled biradical is in the wrong mode for opening of

the C_3 ring (see Scheme 3). Now, the third electron has to move into an anti-bonding $\text{p}\pi^*$ -orbital as the C_3 ring is fissioned, so the initial spin coupling and biradical character are no longer conducive to very fast reaction as found for the corresponding free radical [1,2].

Another major advantage of the biradical character of the key intermediate [3–6] is that it should facilitate $[2\sigma+2\sigma]$ activation of the C–H bond in the substrate (Scheme 7).

Furthermore, [2+2] reactions of this type are often very stereospecific so the mechanism described in



Scheme 7 may be the source of the very stereospecific behaviour observed in B₁₂ coenzyme catalysis.

2. Conclusion

In conclusion, the spin-spin coupled biradical intermediate has the capacity to either move smoothly into the p π -bonded half-reaction state for 1,2-bond shift, or to engage in a [2+2] reaction with the substrate, thereby affording more efficient and stereospecific activation of the latter. In all of this, the Co ion is always central to the catalytic action, and is not merely a free radical generator. In any event, while the complete extremes, totally free radical, or covalent σ -bonded [Co]-alkyl, may sometimes be present in B₁₂ systems and their models, such species may not of themselves be conducive to efficient and selective catalysis.

The idea of a biradical, or metal coupled free radical intermediate, may also be very relevant for the recently developed area of atom transfer free radical

polymerization (ATRP) of olefins catalysed by metals in lower oxidation states.

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