The Importance of Peripheral Association for Vitamin B_{12} catalysed Methylmalonyl–Succinyl-Rearrangement

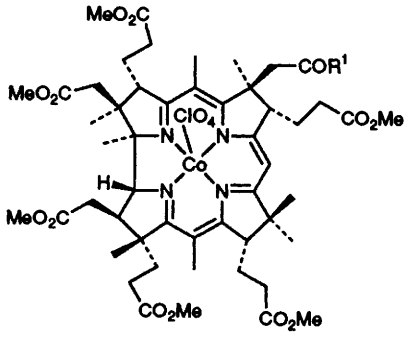
Annemarie Wolleb-Gygi, Tamis Darbre, Vuk Siljegovic and Reinhart Keese*

Institut für organische Chemie, Universität Bern, Freiestrasse 3, 3012 Bern, Switzerland

The rearrangement of methylmalonyl to succinyl radicals becomes an efficient process, when the reaction is performed in a protic solvent with both the vitamin B_{12}-derived catalyst and the substrate carrying a C_{18} instead of a C_2 alkyl chain.

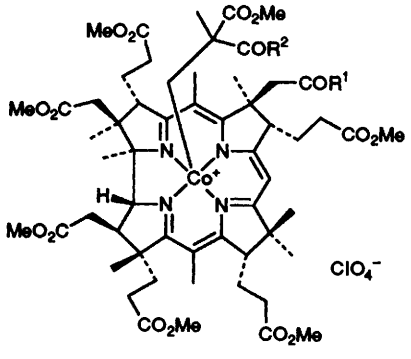
Most model studies of the B_{12} coenzyme catalysed rearrangements have been concerned with the mechanism and the electronic nature of the reorganization step.[1] Supramolecular features like preassociation of an appropriately modified substrate with the Co-complex bearing complementary functionalities at its periphery and the importance of the polarity of solvents, that assists or suppresses molecular recognition, have hardly obtained the deserved attention. Most noteworthy are the results by Rétey,[2] who provided clear evidence for hydrophobic interactions and concomitant enhancement of the methylmalonyl–succinyl-rearrangement and, more recently, the intriguing model studies of a holoenzyme by Murakami *et al.*[3]

As a mimic of the B_{12} coenzyme-apoenzyme complex, which provides the catalytic site and an anchor group with a substrate recognizing subunit, we have investigated the properties of vitamin B_{12} **1a**, modified by a C_{18}-alkyl side chain as catalyst for the rearrangement of a methyl–malonyl moiety bearing a complementary substitutent to succinate in both protic and polar-aprotic solvents (Scheme 1).



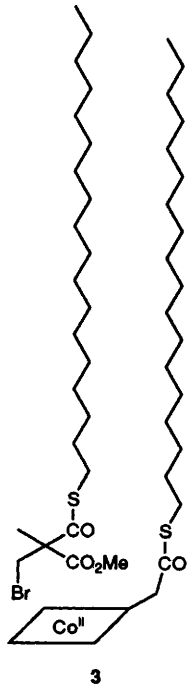
1

a; $R^1 = O(CH_2)_{17}Me$
b; $R^1 = OMe$



2

a; $R^1 = O(CH_2)_{17}Me$, $R^2 = S(CH_2)_{17}Me$
b; $R^1 = OMe$, $R^2 = SEt$



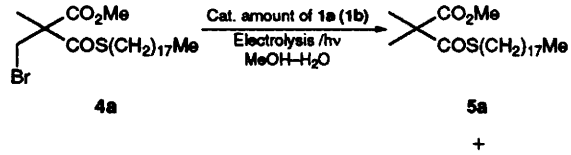
3

The Co-complexes **1a**[4,5,6] and **b**[5], used as catalyst, were readily prepared from vitamin B_{12}. The substrates **4a** and **b** were prepared according to Scheme 2. The reference compounds **5a** and **b** were prepared from methyl–thioalkyl–methylmalonate by alkylation with MeI, whereas the rearrangement products **6a** and **b** were accessible by alkylation of methyl propionate with *tert*-butylbromoacetate and subsequent transformation of the *tert*-butyl ester into the thioester group by literature procedures.

When **4a** was electrolysed with 5 mol% **1a** in MeOH–H_2O = 4:1 at −0.85 V (*vs.* SCE) and irradiated with a 150 W lamp for 20 h, **5a** and **6a** were obtained in a ratio of 1.3:1 in a total yield of 50% (42% of **4a** were recovered). In MeCN, the reaction proceeded more slowly, giving at 4.5:1 ratio of **5a** and **6a** in an overall yield of 15%. When **4a** was reacted with the heptaester **1b** in MeOH–H_2O = 4:1, the reaction was rather sluggish, giving **5a** and **6a** in a reduced yield (Table 1).

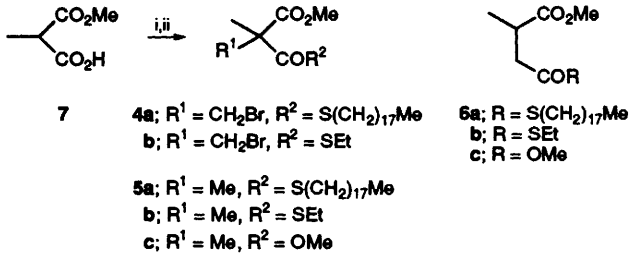
Under the same conditions, the substrate **4b** gave with **1a**, as catalyst, a mixture of **5b** and the dimethyl malonate **5c**. Surprisingly, the rearranged methyl succinate **6c**, but not **6b** could be detected.

According to CV, the B_{12} catalyst **1a** but not **1b** is adsorbed in MeOH–H_2O at the glassy carbon electrode, used as cathode. The potential of −0.85 V is sufficiently negative to reduce Co^{II} to Co^{I} (which forms Co–alkyl complexes with alkyl bromides) but much too positive to trigger reductive cleavage of the Co–C bond. In the case of **1b** and **4b**, the Co-



4a → **5a** + **6a**

Scheme 1



7 → **4a**; $R^1 = CH_2Br$, $R^2 = S(CH_2)_{17}Me$
b; $R^1 = CH_2Br$, $R^2 = SEt$
5a; $R^1 = Me$, $R^2 = S(CH_2)_{17}Me$
b; $R^1 = Me$, $R^2 = SEt$
c; $R^1 = Me$, $R^2 = OMe$

6a; $R = S(CH_2)_{17}Me$
b; $R = SEt$
c; $R = OMe$

Scheme 2 *Conditions:* **5a**: i DCC, DMAP, $Me(CH_2)_{17}SH$ (**5b**: EtSH); ii NaH, CH_2Br_2, Me_2SO[7]

Table 1[a]

Catalyst **1**	Amount /mol%	Solvent	Substrate **4**	Products (% recovered) **5a**	**6a**	**4a**
a	5.3	MeOH–H_2O 4:1	**a**	31	23	42
a	8.8	MeCN	**a**	14	3	16
b	5.5	MeOH–H_2O 4:1	**a**	3–11	2–6	50
a	5	MeOH–H_2O	**b**	8 (**4b**)	—(**4b**)[c]	—

[a] *Conditions*: a degassed solution of the catalyst in the solvent, containing 0.1 mol dm^{-3} $LiClO_4$ was reduced in an electrolysis cell with a cathode of carbon felt at −1.0 V (*vs.* SCE) for 0.5 h. After addition of the substrate, the potential was set at −0.85 V (*vs.* SCE) and the cell irradiated with a 150 W lamp for 20 h. The solution was extracted 3× with diethyl ether and the residue submitted to GC analysis under standardized conditions. [b] 6–7% of **5c** has been detected. [c] Only 14% of **6c** has been found.

complex **2b** has been isolated.[5] By analogy, **2a** may be formed as an intermediate in the catalytic cycle with **1a** as catalyst and **4a** as substrate. Upon irradiation methylmalonyl radicals are formed, which rearrange to succinate species with different yields. A blank experiment with **4a**, in the absence of **1a**, gave only trace amounts of the product **5a**.

The larger proportion of rearranged product, in the case where the catalyst and the substrate carry a long alkane chain, is interpreted in terms of a hydrophobic interaction between **1a** and **4a** in the protic solvent MeOH–H_2O to give **7**, providing a favourable microenvironment for reaction between Co^I and the CH_2–Br bond and eventual rearrangement of the radical formed.

With the readily available B_{12}-model catalyst preassociation phenomena, their impact on the selectivity of the rearrangements can be assessed. Since the peripheral alkyl chain can be replaced both in the B_{12} catalyst and in the substrate by an alkyl chain of variable length bearing a terminal anchoring group, the extent of the preassociation in a wider variety of solvents and the distance of the bromomethyl group from the Co-centre can be modulated.

We thank PD Dr L. Walder for his continuing interaction. This work has been supported by the Swiss National Science Foundation, the Helm-Vögtlin Fonds and a SCIENCE project.

Received, 8th November 1993; Com. 3/06690H

References

1 B. T. Golding and D. N. Rao, in *Enzyme Mechanisms*, ed. M. I. Page, A. Williams, RSC, London, 1987, p. 404; R. G. Finke, *Molecular Mechanisms in Bioorganic Processes*, in C. Bleasdale and B. T. Golding, RSC, 1990, p. 244.
2 J. Rétey, in *Vitamin B_{12}*, ed. B. Zagalak and W. Friedrich, W. de Gruyter, Berlin, 1979, p. 439.
3 Y. Murakami, Y. Hisaeda, J. Kikuchi, T. Ohno, M. Suzuki, Y. Matsuda and T. Matsuura, *J. Chem. Soc., Perkin Trans.* 2, 1988, 1237; Y. Murakami, Y. Hisaeda and T. Ohno, *Bioorg. Chem.*, 1990, **18**, 49; Y. Murakami, Y. Hisaeda and T. Ozaki, *J. Coord. Chem.*, 1991, **23**, 77; Y. Murakami, Y. Hisaeda, H. Kohno, T. Ohno and T. Nishioka, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 3094.
4 P. Schulthess, D. Ammann, W. Simon, C. Caderas, R. Stepanek and B. Kräutler, *Helv. Chim. Acta*, 1984, **67**, 1026.
5 S. Müller, A. Wolleb, L. Walder and R. Keese, *Helv. Chim. Acta.*, 1990, **73**, 1659.
6 R. Stepanek, Dissertation, ETH Zürich, 1987, No. 8069.
7 W. M. Best, P. F. Cook, J. J. Russell and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1139.