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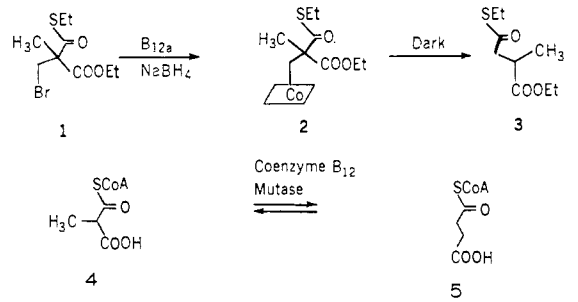
Mechanism of Action of Coenzyme B_{12}. An Overall Anionic Mechanism for Carbon-Skeleton Rearrangement in a Model Reaction

Sir:

It was recently shown that the dimethyl malonate–cobalamin complex **2** undergoes exclusive rearrangement of the



thioester group during the dark reaction **1** → **3** as an analogy for the methylmalonyl CoA → succinyl CoA (**4** → **5**) interconversion mediated by methylmalonyl CoA mutase which contains coenzyme B_{12} as a cofactor.[2,3]

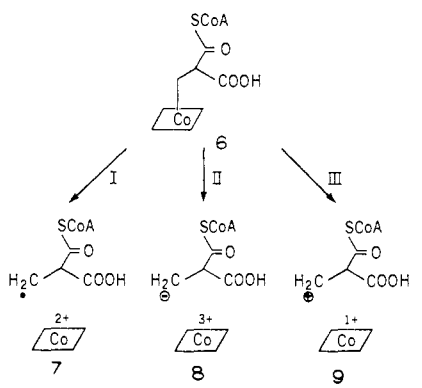
In spite of the accumulation of evidence pointing towards a homolytic cobalt–carbon bond cleavage[4] of coenzyme B_{12} and of the subsequently formed hypothetical intermediate such as **7** as part of the catalytic cycle (Scheme I, route I), there is abundant in vitro analogy for ionic mechanisms in the chemistry of alkyl cobalamins portrayed by routes II (carbanion **8**)[5] and III (carbocation **9**).[6] Most of the enzyme-catalyzed reactions involving coenzyme B_{12} are without precedent in terms of known organic reactions,[7] whilst mechanisms involving a reactive free radical[4] in a vicinal migration have little parallel with chemical experience. Thus, although the first (and last) committed steps in the enzymatic reaction of coenzyme B_{12} probably involve homolysis of the cobalt–carbon bond at C-5′ of the adenosyl moiety, the rearrangement of the substrate might stem from an ionic or radical mechanism operating on a covalently attached intermediate such as **6** (Scheme I).

We now wish to report some of our observations which suggest an overall anionic mechanistic feature for carbon-skeleton rearrangement in the model reaction. We have examined the mechanism of the facile thioester migration,[1] **1** → **3**, which requires abstraction of hydrogen from the reaction milieu, using deuterium label as a probe for possible differentiation among the various mechanisms depicted in Scheme I as a first step toward understanding the methylmalonyl CoA mutase conversion, at least in terms of a viable chemical model. Experiments designed to trap analogs of the various possible intermediates, namely radical, carbanion, and carbonium ion, were performed as follows (Scheme II). (1) The use of CD_3CD_2OH as a solvent constitutes a probe for the involvement of possible radical intermediates and should lead to incorporation of deuterium from ethanol-d_5[8] into the rearranged product. No deuterium incorporation was observed in the conversion of **1** to **3**. (2) Generation of an anionic species could be readily demonstrated by employing CH_3CH_2OD as solvent. Thus, the reaction of bromo ester **1** with hydroxycobalamin (B_{12a}), CH_3CH_2OD, and $NaBH_4$ in the dark under N_2 over 1–5 h gave 33–44%[9] of the completely deuterium-incorporated rearranged product **3**-*d*, whose NMR and mass spectra[10] locates the deuterium label exclusively at C-3. In comparing the ^1H NMR of **3**-*d* with that of **3**, the methyl singlet at δ 1.21 becomes a sharp doublet (J = 6.6 Hz) and the well-resolved AB pattern of the $-CH_2-$ protons has additional multiplicity due to spin–spin coupling with the methine proton. Integration of the ^1H NMR of **3** shows one additional proton than in **3**-*d* at δ 2.98 with complex coupling superimposed on the other resonances. (3) The presence of a cationic species would result in incorporation of the deuterium label from $NaBD_4$ in the rearranged product **3**-*d*. When a competition experiment was run in CH_3CH_2OH in the presence of $NaBD_4$, the rearranged ester was not deuterated, thus making the intervention of a cationic species unlikely.

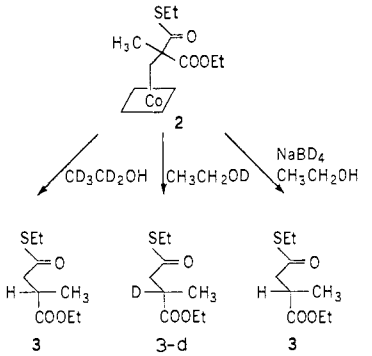
It should be pointed out that the overall carbanionic deuteration does not necessarily support the notion that the skeletal rearrangement is taking place at the stage of the carbanionic intermediate. In fact, the bromo ester **1** was found to rearrange, although in much poorer yields and under different conditions, to the product **3** upon reductive treatment with $NaBH_4$ or zinc in aprotic solvent at elevated temperature. From these results we conclude that the overall mechanism for the present model reaction is anionic, and that possibly the skeletal rearrangement may take place at the radical (or radical anion) stage, followed by a rapid second electron reduction to give the carbanionic intermediate which is then protonated by the reaction medium. It is also to be noted that, in the *enzymatic* rearrangement, no hydrogen exchange between the substrate and the medium takes place, perhaps because of an intimate association between 5′-deoxyadenosine and the reaction site of the enzyme.

Further model studies on the development of the catalytic action by coenzyme B_{12} and on the nature of the rearrangement reactions involving cobalamin, both as reagent and catalyst, are in progress.

Scheme I



Scheme II



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(9) The product yields are calculated on the basis of the amount of bromo thioester I used in the reaction and isolated weight of **3**-*d*. A minor product, *O,S*-diethyl dimethylmalonate-*1*-*d*, was also isolated.

(10) NMR ($CDCl_3$, 270 MHz) δ 1.21 (s, 3 H), 1.26 (m, 6 H), 2.63 (d, 1 H, J = 16 Hz), 2.89 (q, 2 H, J = 8 Hz), 2.98 (d, 1 H, J = 16 Hz), 4.15 (q, 2 H, J = 8 Hz); mass spectrum *m/e* (rel intensity, assigned ion) 160 (31.87%, $M^+ - 45$, OEt), 159 (10.08), 144 (100, base ion, $M^+ - 61$, SEt), 143 (20.73), 116 (83.10, $M^+ - 89$, COSEt), 115 (22.14). We thank Professor P. Dowd for the mass spectral data.

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Binuclear Copper(II) "Face to Face" Inclusion Complex of a Macrotricyclic Ligand

Sir:

The synthesis of macropolycyclic ligands allows the preparation of complexes containing several transition metal ions located *inside* the intramolecular cavity. The case of *binuclear "face to face"* [1] complexes where the metal ions are not bridged by a ligand and are separated by a distance of the order of 4 to 6 Å is particularly interesting: (i) there should be no direct interaction between the two metal cations, (ii) an external substrate should be able to interact by *inclusion* simultaneously with the two metal ions. Such compounds may be able to act as *catalysts*, as dioxygen or dinitrogen *carriers*, and as attractive *models* for some metalloproteins.[2,3]

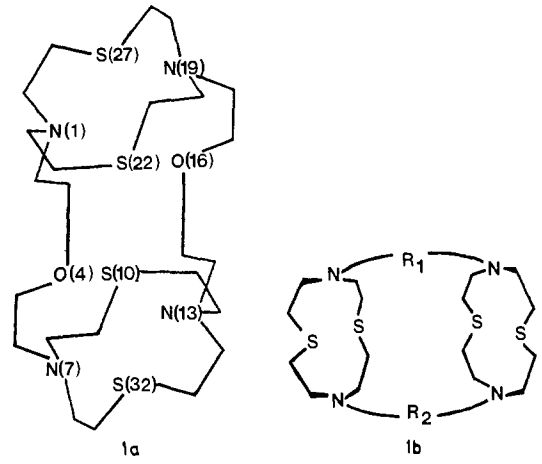

Figure 1. The ligand (L) tricyclo[17.5.5.5^{7,13}]tetraaza-1,7,13,19-dioxa-4,16-tetrathia-10,22,27,32-tetratriacontane, $C_{24}H_{48}N_4O_2S_4$, and atomic leading.

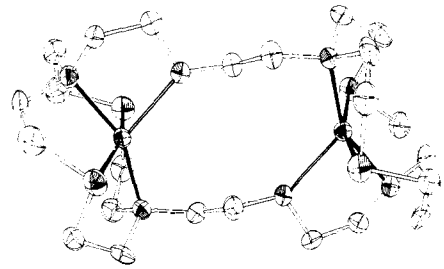

Figure 2. Structure of $[Cu_2\subset(L)]^{4+}$ cation. All atoms are represented by 50% probability thermal ellipsoids. Selected bond distances (in Ångstroms) follow: Cu(1)–N(1), 2.020 (5); Cu(1)–N(19), 2.024 (6); Cu(1)–O(4), 2.291 (5); Cu(1)–S(22), 2.313 (1); Cu(1)–S(27), 2.323 (1); Cu(2)–N(7), 2.047 (6); Cu(2)–N(13), 2.058 (5); Cu(2)–O(16), 2.283 (4); Cu(2)–S(10), 2.306 (1); Cu(2)–S(32), 2.332 (1). Selected bond angles (in degrees) follow: N(1)–Cu(1)–S(22), 88.9 (1); N(1)–Cu(1)–S(27), 88.2 (1); N(19)–Cu(1)–S(22), 87.3 (1); N(19)–Cu(1)–S(27), 88.0 (1); O(4)–Cu(1)–N(1), 80.7 (1); O(4)–Cu(1)–N(19), 126.6 (2); O(4)–Cu(1)–S(22), 103.4 (1); O(4)–Cu(1)–S(27), 91.7 (1); N(7)–Cu(2)–S(10), 88.0 (1); N(7)–Cu(2)–S(32), 87.8 (1); N(13)–Cu(2)–S(10), 88.4 (1); N(13)–Cu(2)–S(32), 87.9 (1); O(16)–Cu(2)–N(7), 126.4 (2); O(16)–Cu(2)–N(13), 79.9 (1); O(16)–Cu(2)–S(10), 103.7 (1); O(16)–Cu(2)–S(32), 92.5 (1). The most attractive interatomic distances follow: Cu(1)···Cu(2), 5.621 (1); O(4)···O(16), 4.211 (6) Å.

Ligand (L) shown in Figure 1a is tetraaza-1,7,13,19-dioxa-4,16-tetrathia-10,22,27,32-tricyclo-[17.5.5.5^{7,13}]tetratriacontane, $C_{24}H_{48}N_4O_2S_4$.[4] It contains two twelve-membered macrocyclic subunits with four hetero donor atoms, N_2S_2. The two subunits are joined together by two lateral five-membered chains, each carrying an ether group.

Addition of copper(II) perchlorate to a chloroform solution of L gives a violet solution for a 2:1 ratio of metal to ligand.[4] Crystals of $[Cu^{II}_2\subset(C_{24}H_{48}N_4O_2S_4)](ClO_4)_4(H_2O)$ **1** obtained by slow evaporation produce, when redissolved in nitromethane, intense absorptions near 400 and 600 nm (380 nm ($\epsilon \simeq 4000$ M^{-1} cm^{-1}) and 550 nm ($\epsilon = 1200$ M^{-1} cm^{-1})). The very strong absorption near 400 nm can be assigned to π(s) → Cu charge transfer. The band at 550 nm could be assigned also to a charge-transfer transition (σ(s) → Cu); however, in view of the somewhat distorted geometry around the copper(II) cations (see below) and the presence of two thioethers in the ligand donor set, this transition could also arise from a ligand field absorption of enhanced intensity.[5-7]

1 crystallizes in the monoclinic space group $P2_1/n$ (an alternate setting of $P2_1/c$) with a = 15.736 (4), b = 27.491 (7),

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