A New Model for Coenzyme B_{12} with an Intramolecular Cobalt–Carbon Bridge

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The synthesis and structure of the first H_2salen {2,2′-[1,2-ethanediylbis(nitrilomethylidyne)]diphenol} derived model for coenzyme B_{12} with an intramolecular carbon bridge between the ligand and cobalt are reported.

Although it is generally accepted that homolysis of the cobalt–carbon bond of coenzyme B_{12} (5′-deoxyadenosylcobalamin) generating a 5′-deoxyadenosyl radical and cob(II)alamin is an essential step in enzymatic 1,2-rearrangements catalysed by coenzyme B_{12},[1] factors that promote this process are far from fully understood. Enzyme-caused conformational distortion of the corrin ring of B_{12} and angular distortion of the Co–C bond are supposed to play an important role.[2] Furthermore, it is controversial whether a substrate radical, formed by H-abstraction by the adenosyl radical, undergoes 1,2-rearrangement as a free radical[3] (protein-protected)[4,5] or cobalt corrinoids interact with the substrate and product radicals,[6] or even organocobalt intermediates are the rearranging species.[7]

To contribute to the solution of these questions we have synthesized intramolecularly alkylated coenzyme B_{12} model compounds which permit, on the one hand, a study of the reactivity of the cobalt–carbon bond and its dependence on the distortions imposed by the carbon bridge and, on the other hand, an investigation of the properties of carbon-centred radicals forced to stay in the proximity of a Co^{II} complex. In this communication we describe the synthesis and structural details of the first intramolecularly alkylated Co(salen) complex **1**.

The required salen ligand **5** was synthesized by condensation of salicylaldehyde with diamine **4**, which itself was prepared from hexenol **2** (Fig. 1). Protection of **2** as THP–ether (DHP, PPTS, CH_2Cl_2)† and addition of IN_3 to the double bond (ICl, NaN_3, MeCN)[8] followed by substitution of

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† THP = tetrahydropyran-2-yl; DHP = dihydropyran; PPTS = pyridinium toluene-*p*-sulphonate; DMSO = dimethyl sulphoxide; DMF = dimethylformamide.

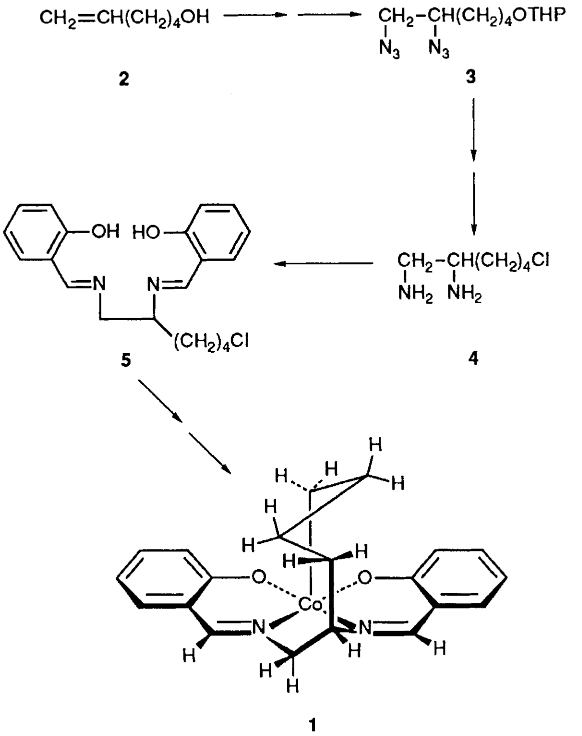

Fig. 1 Synthesis of (*SPY*-5-54)-[2,2′-[{[1-(tetramethylene-κC^4)-ethanediyl]bis(nitrilomethylidyne)}diphenolato](3−)-κ$^2N,N'$; κ$^2O,O'$]cobalt **1**

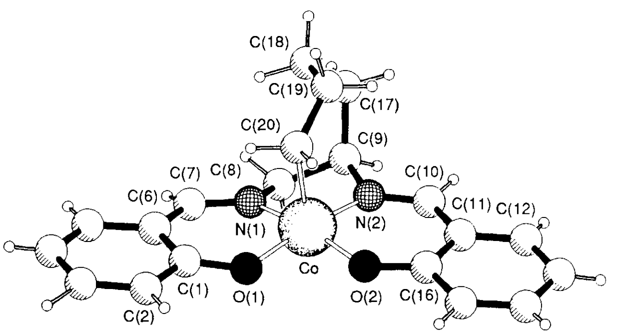

Fig. 2 Crystal structure and atom numbering scheme of cobalt complex **1**. Selected bond lengths (Å) and angles (°): Co–C(20) 1.975(3), Co–O(1) 1.879(2), Co–O(2) 1.873(2), Co–N(1) 1.861(2), Co–N(2) 1.857(3), N(1)–C(7) 1.286(4), N(2)–C(10) 1.291(4), C(19)–C(20) 1.512(5), C(20)–H(201) 0.99(4), C(20)–H(202) 0.98(4); Co–C(20)–C(19) 119.3(2), C(18)–C(19)–C(20) 117.0(3), C(17)–C(18)–C(19) 115.1(3), H(201)–C(20)–H(202) 103(3), C(20)–Co–O(1) 91.29(11), C(20)–Co–O(2) 96.64(11), C(20)–Co–N(1) 93.34(12), C(20)–Co–N(2) 95.99(12).

I by N_3 (NaN_3, DMSO)[†] gave diazide **3**. Removal of the protecting group (Dowex 50, MeOH),[9] replacement of OH by Cl ($SOCl_2$, CH_2Cl_2, DMF)[10][†] and reduction of N_3 to NH_2 (Ph_3P, THF, H_2O, HCl)[11] furnished diamine **4** as its dihydrochloride in *ca.* 50% overall yield based on **2**.

Condensation with salicylaldehyde to give ligand **5** was effected by rapid mixing of an ethanol–water solution of **4** with an ice-cold solution of 3 mol. equiv. of sodium acetate in ethanol–water and immediate addition (to prevent cyclization of **4**) to a rapidly stirred warm (60 °C) solution of salicylaldehyde in ethanol (*ca.* 80% yield after chromatographic purification). Finally, complexation with Co^{II} and intramolecular alkylation was effected in a one-pot reaction by a modified (15-fold dilution) procedure of Schrauzer[12] ($CoCl_2$, NaOH, $NaBH_4$, $PdCl_2$). After purification by fractional precipitation from methanol by water, crystallization from wet acetone gave a brown-red microcrystalline solid (*ca.* 50% yield), which most probably is **1** with its sixth coordination site occupied by water. On drying *in vacuo* or dissolution in non-coordinating solvents like chloroform or toluene, a colour change to dark green indicates loss of the sixth ligand[13] and formation of **1**.

Pentacoordination in chloroform and the presence of a Co–C bond is corroborated by the UV–VIS spectrum which shows, besides bands at 342, 406 (sh) and 460 (sh) nm, a band at 647 nm ($\varepsilon = 1.25 \times 10^3$) indicative of the Co–C bond in pentacoordinate alkylcobalt(III) salen complexes such as butylCo(salen).[13] Vaporimetric molecular weight determination ($CHCl_3$, 18 mmol dm^{-3}) gives a value of 430 (calcd. 380) indicating the presence of partly associated monomer in solution. Mass spectrometry (FAB) convincingly demonstrates **1** to be a monomer (most abundant signal at *m/z* 380; no fragments corresponding to dimers or oligomers).

Further proof of the structure of **1** in solution is provided by ^1H NMR ($CDCl_3$, 250 MHz), which clearly shows the non-equivalence of both the α- and β-protons of the bridge owing to the very different positions they occupy with respect to the electron-rich equatorial ligand and its diamagnetic shielding cone. Whereas in butylCo(salen) the α-protons are found at δ 3.55 and the β-protons at δ 0.65, the corresponding four protons of **1** resonate at δ 5.06 and 3.16, and at 0.81 and −0.63, respectively. Molecular models of **1** show that structures in which the four-carbon bridge has a zigzag conformation over the equatorial ligand are energetically favoured. In such conformations, one of the β-protons is positioned above a C=N bond, which causes the high field shift.

Crystals of **1** suitable for X-ray structural analysis were obtained by slow evaporation of a $CDCl_3$ solution. The crystal structure is shown in Fig. 2 together with some pertinent bond lengths and angles.[‡] In the solid state, **1** is a pentacoordinate monomer and has a nearly planar ligand conformation [the angle between the planes formed by O(1)–N(1)–C(1)–C(6)–C(7) and O(2)–N(2)–C(10)–C(11)–C(16) is only 3.47°]. For each molecule of **1**, two molecules of deuteriochloroform are present (not depicted in Fig. 2), of which one is weakly bonded *via* deuterium to both oxygens of the equatorial ligand [D–O(1) 2.55(4) Å; D–O(2) 2.32(4) Å]. In contrast, crystalline ethylCo(salen) is a stepped-shape dimer in which an oxygen atom of one salen unit coordinates to the cobalt atom in a second one (Co–O′ 2.342 Å).[14,15] As molecular models had indicated, the four-carbon bridge is positioned zigzag over the salen ligand with one of the β-protons [H(19)] being held above a C=N bond. The length of the Co–C bond [1.975(3) Å] is comparable with that of related organocobalt Schiff base complexes[15] [*e.g.* 1.990 Å in ethylCo(salen)] as is the angle of Co–C(20)–C(19) [119.3(2)°; 119.5° in ethylCo(salen)]. The atoms of the coordination plane [O(1), O(2), N(1) and N(2)] are coplanar within 0.020 Å, whereas the cobalt atom is displaced 0.142 Å from this plane towards the coordinated carbon atom C(20) [0.058 Å in ethylCo(salen)]. The angle

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[‡] *Crystal data* for **1**: $C_{20}H_{21}N_2O_2Co{\cdot}2CDCl_3$, $M = 621.1$, monoclinic, space group $P2_1/n$, $a = 14.308(2)$, $b = 10.352(1)$, $c = 17.108(3)$ Å, $\beta = 93.09(1)°$, $U = 2530.3(6)$ Å^3, $Z = 4$, $D_m = 1.58(4)$ g cm^{-3}, $D_c = 1.630$ g cm^{-3}, μ(Mo-Kα) = 13.4 cm^{-1}, $F(000) = 1256$. Data were collected on an Enraf-Nonius CAD4-diffractometer using Mo-Kα-radiation (0.71073 Å), $T = 100$ K, 6366 independent reflections ($\theta < 28.5°$), of which 4906 unique reflections with $I > 2.5\,\sigma(I)$ were used to solve (direct methods, SHELXS-86) and refine (full-matrix, SHELX-76) the structure. H atom positions from difference map and refined with one U(iso). Final $R = 0.045$ and $R_w = 0.065$, $w^{-1} = \sigma^2(F) + 0.002\,F^2$, $S = 1.76$. Number of refined parameters 368, maximum residual electron density 1.18 e Å^{-3} (indicating some $CDCl_3$ disorder). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

between Co–C(20) and the coordination plane deviates from perpendicularity (acute angle: 87.03°). Whether the monomeric and nearly planar conformation of **1** and other crystal structure data differing from what is usually found in alkylCo(salen) complexes are due to steric factors imposed by the carbon bridge or to co-crystallization of chloroform remains to be elucidated.

Preliminary results of homolysis experiments show the intramolecularly alkylated salen complex **1** to be more stable than butylCo(salen) and give indications for essentially differing reaction pathways.

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