Synthesis, structure and Co–C bond homolysis of an intramolecularly bridged (tetrahydrofurfuryl)cobalt(salen) complex: a simple model of enzyme-bound coenzyme B_{12}

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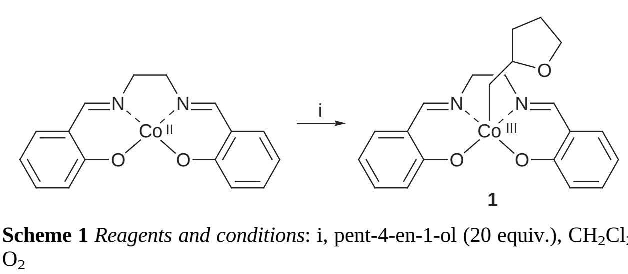
Air oxidation of a Co^{II}(salen) derivative, whose ethanediyl moiety carries a methylene-linked 4-hydroxypent-1-en-3-yl substituent, yields an intramolecularly bridged (tetrahydrofurfuryl)Co^{III}(salen) complex of which the crystal structure has been determined; this B_{12} model is very resistant to Co–C bond homolysis, even in the presence of a large excess of the radical trap TEMPO.

The bond dissociation energy of the Co–C bond of coenzyme B_{12} (5′-deoxyadenosylcobalamin) is estimated to be 31 kcal mol^{-1}. Despite the weakness of the Co–C bond, there is a high efficiency of radical recombination following Co–C bond homolysis,[1] a key step in coenzyme B_{12}-dependent enzymatic rearrangements. It has been suggested that one of the factors responsible for this apparent contradiction is the β-oxygen of the 5′-deoxyadenosyl ligand, which can stabilise the initial pyramidal geometry at the 5′-C of the adenosyl radical and/or impose a rotational barrier to the $C_{4'}$–$C_{5'}$-bond.[2] Radical pair recombination efficiency is expected to be even higher when the cofactor is bound to the active site of the enzyme, where the cobalamin and 5′-deoxyadenosyl moieties are kept close to each other until the substrate enters. Recently, we found that (organo)Co(salen) complexes containing a cobalt-to-salen polymethylene bridge show a much stronger resistance to thermal and photochemical decomposition than the non-bridged complex (*n*-butyl)Co(salen).[3] In order to study whether this resistance would be further enhanced by the introduction of a β-oxygen substituent, we have synthesised a (tetrahydrofurfuryl)Co(salen) complex in which the tetrahydrofurfuryl ligand (as a deoxyadenosyl mimic) is attached to the equatorial salen ligand by a methylene link. Here, we report on the synthesis and structure of this compound and present some preliminary results concerning the photolytic homolysis of its Co–C bond.

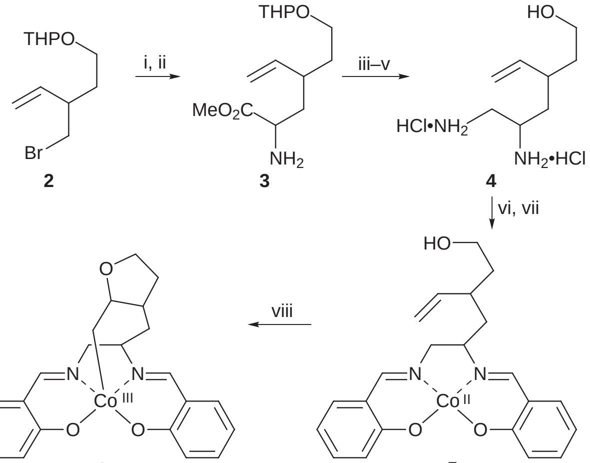
Our synthetic approach was based on our finding that (tetrahydrofurfuryl)Co^{III}(salen) **1** is formed in 78% yield when a *ca*. 3×10^{-2} M solution of Co^{II}(salen) in CH_2Cl_2 containing 20 equiv. of pent-4-en-1-ol is exposed to air for 20 h (Scheme 1).§ The formation of **1** may proceed by intramolecular nucleophilic attack by the hydroxy group on an intermediate cobalt(III)–alkene π-complex.[4,5] The reaction is regiospecific: (tetrahydropyran-3-yl)Co(salen) is not formed.

In order to prepare an intramolecularly bridged tetrahydrofurfurylcobalt complex in a way analogous to **1**, we synthesised Co^{II}(salen) derivative **5** according to Scheme 2. Bromide **2** (prepared from but-3-yn-1-ol *via* *C*-alkylation with $THPOCH_2CH_2Br$, reduction to *trans*-alkenol with LAH, *O*-alkylation with Bu_3SnCH_2I followed by Wittig–Still rearrangement, and bromination with Ph_3PBr_2) was reacted with methyl *N*-benzylideneglycinate to give a monoalkylation product which was then treated with tartaric acid in THF–H_2O at 0 °C to selectively deprotect the amino ester moiety while leaving the THP ether intact. Subsequent conversion of amino ester **3** to 1,2-diamine **4** (isolated as its dihydrochloride) was straightforward and analogous to our previously published procedure.[5] Addition of NaOAc to a solution of **4** and 2 equiv. salicylaldehyde in hot EtOH, followed by reaction of the resulting H_2salen ligand with $Co(OAc)_2$ in THF at 60 °C gave cobalt(II) complex **5** as an orange microcrystalline product. From the ^1H and ^{13}C NMR spectra of compounds **2–5** [paramagnetic **5** was characterised after oxidation with iodine to the corresponding iodocobalt(III) complex] it is evident that the alkylation step leading to glycine derivative **3** is diastereoselective, **4** being obtained as a mixture of two diastereomers in a ratio of *ca*. 3 : 1.

Upon exposure to air, a red solution of **5** in CH_2Cl_2 turned green in one day, indicating oxidation to a pentacoordinate organocobalt(III) complex. Concentration *in vacuo* and precipitation with Et_2O furnished a green solid, which was subjected to flash column chromatography (aluminium oxide, 10% MeOH in CH_2Cl_2) to remove traces of cobalt(II) material. The green product (80% yield) was shown by ^1H and ^{13}C NMR spectroscopy to consist of a 3 : 1 mixture of two diastereomers of **6**.¶ Thus, a reaction similar to that of Co^{II}(salen) with pent-4-en-1-ol had occurred, but now in an intramolecular fashion



Scheme 1 *Reagents and conditions*: i, pent-4-en-1-ol (20 equiv.), CH_2Cl_2, O_2



Scheme 2 *Reagents and conditions*: i, $MeO_2CCH_2N{=}CHPh$, LDA, DMPU,‡ THF; ii, tartaric acid, THF–H_2O, 0 °C; iii, NH_3, MeOH; iv, $LiAlH_4$, THF; v, 1 M HCl; vi, salicylaldehyde, NaOAc·$3H_2O$, EtOH, 60 °C; vii, $Co(OAc)_2$, THF, 60 °C; viii, CH_2Cl_2 or MeOH, O_2

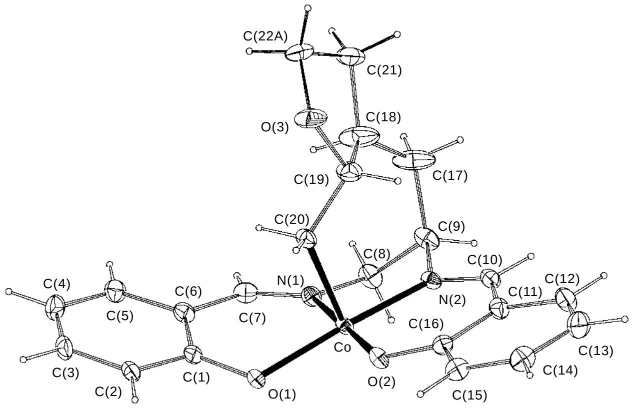


Fig. 1 ORTEP diagram drawn at the 30% probability level and atom numbering scheme of half a dimer of **6a**. The minor disorder component and solvent molecules have been omitted for clarity. Suffix A denotes the major disorder component. Selected distances (Å) and angles (°): Co–C(20) 1.960(6), Co–O(1) 1.932(3), Co–O(2) 1.882(4), Co–N(1) 1.864(5), Co–N(2) 1.886(4), C(19)–C(20) 1.476(9), C(18)–C(19) 1.534(10), C(17)–C(18) 1.422(10), N(1)–C(7) 1.276(8), N(2)–C(10) 1.287(8), C(19)–O(3) 1.456(8); Co–C(20)–C(19) 119.3(4), C(18)–C(19)–C(20) 115.5(6), C(17)–C(18)–C(19) 122.0(8), C(20)–Co–O(1) 91.8(2), C(20)–Co–O(2) 90.0(2), C(20)–Co–N(1) 91.5(2), C(20)–Co–N(2) 92.7(2).

(Scheme 2). The reaction was found to be much faster in MeOH (reaction time *ca*. 1 h), yet gave the two diastereomers of **6** in the same yield and ratio as in CH_2Cl_2.

The major diastereomer of **6** was selectively crystallised from CH_2Cl_2 and gave crystals suitable for X-ray structure analysis, establishing its structure as **6a** (Fig. 1).‖ The solid-state structure of **6a** is a centrosymmetric dimer. Hexacoordination of cobalt is established by the bonding of the cobalt atom of one molecule to a salen oxygen atom of its enantiomeric partner [Co–O = 2.259(3) Å]. Half of the dimeric structure is shown in Fig. 1, together with selected bond lengths and angles.** The Co–C bond length of 1.960(6) Å is comparable with the values found in related organocobalt Schiff base complexes.[6,7] In the crystal structure, the THF moiety is described with a disorder model consisting of two alternative positions for atom C(22). The bond lengths around C(18), the anisotropicity of C(17) and C(18) as well as the distribution of residual electron density around the furan moiety indicate the presence of additional, unresolved disorder, which is most probably conformational in nature. The twist-chair conformation of the carbon bridge and the anti-periplanar orientation of cobalt and oxygen in the *trans*-annulated THF ring are almost identical with those found in the crystal structures of other bridged organocobalt(salen) complexes.[5,6]

Preliminary laser photolysis experiments in toluene show that **6** is very resistant to Co–C bond homolysis. Even in the presence of a large excess of the radical trap TEMPO, the quantum yield Φ is only 0.03 ± 0.005.†† This value is much lower than the quantum yield determined under similar conditions for the (alkyl)Co(salen) complex with a cobalt-to-ligand four-methylene bridge (Φ = 0.25).[3] The quantum yield as a function of trap concentration has also been determined for non-bridged complex **1** and compared to that of (*n*-butyl)Co(salen).[3] The difference in Φ-values at high trap concentration is less pronounced than for the bridged complexes, but nevertheless significant; Φ-values are 0.19 and 0.28 for **1** and (*n*-butyl)Co(salen), respectively. These results support the suggestion that the β-oxygen substituent in (β-alkoxyalkyl)cobalt(III) complexes facilitates radical recombination of cobalt(II) and C· following Co–C bond homolysis.[2] Recombination efficiency is dramatically enhanced in complexes like **6**, whose β-alkoxy substituent is part of an intramolecular bridge which, like B_{12}-dependent enzymes, enforces a close proximity of the alkyl radical to cobalt(II). A detailed study of the homolysis of the Co–C bond of **6** and comparable complexes is in progress.

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Notes and References

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‡ DMPU = *N,N′*-dimethylpropyleneurea.

§ *Selected data* for **1**: δ_H($CDCl_3$, 200 MHz) 7.81, 7.77 (2s, 2 H), 7.28 (m, 4 H), 6.92 (dd, 2 H), 6.50 (dd, 2 H), 4.1–3.7 (m, 5 H), 3.60 (m, 1 H), 3.33 (m, 1 H), 2.95–2.7 (m, 2 H), 1.95–1.5 (m, 4 H); δ_C($CDCl_3$, 400 MHz) 165.6 (qC), 165.5 (qC), 164.3 (CH), 163.9 (CH), 133.0 (CH), 132.9 (CH), 132.5 (CH), 123.8 (CH), 123.5 (CH), 119.7 (qC), 119.6 (qC), 115.0 (CH), 82.1 (CH), 67.4 (CH_2), 59.2 (CH_2), 58.9 (CH_2), 30.2 (CH_2), 25.7 (CH_2) (Calc. for $C_{21}H_{23}N_2O_3Co.CHCl_3$: C, 49.88; H, 4.57; N, 5.29; O, 9.06. Found: C, 49.90; H, 4.51; N, 5.75; O, 9.79%).

¶ *Analytical data* for **6**: (Calc. for $C_{22}H_{23}N_2O_3Co{\cdot}0.25H_2O$: C, 61.90; H, 5.55; O, 12.18. Found: C, 61.48; H, 5.48; O, 12.05%).

‖ *Selected data* for **6a**: δ_H(CD_3OD, 200 MHz) 8.11, 7.95 (2s, 2 H), 7.18 (m, 4 H), 7.02 (m, 2 H), 6.50 (2dd, 2 H), 4.20–3.95 (m, 3 H), 3.75–3.5 (m, 3 H), 3.40 (m, 1 H), 2.63 (dd, 1 H), 2.25–2.0 (m, 2 H), 1.65 (m, 2 H), 1.51 (m, 1 H); δ_C (CD_3OD, 200 MHz) 166.9 (C-7), 165.5 (C-10), 134.8, 134.5, 134.4, 134.2 (C-3/5/12/14), 123.7, 123.1 (C-2/5), 115.4, 115.0 (C-4/13), 88.5 (C-19), 67.5 (C-9), 66.5 (C-8), 64.5 (C-22), 43.2 (C-17), 42.4 (C-18), 37.0 (C-21). Quaternary carbons and C-20 not observed.

** *Crystal data* for **6a**: $C_{44}H_{46}Co_2N_4O_6{\cdot}4CH_2Cl_2$, M_r = 1184.47, red–brown, block-shaped crystal (0.1 × 0.2 × 0.2 mm), monoclinic, space group $P2_1/c$ (no. 14) with a = 11.0406(19), b = 11.0095(19), c = 20.838(4) Å, β = 103.209(14)°, V = 2465.9(8) Å^3, Z = 2, D_c = 1.595 g cm^{-3}, $F(000)$ = 1216, μ(Mo-Kα) = 11.6 cm^{-1}, 15 569 reflections measured, 4341 independent, R_{int} = 0.1097, (1.0 < θ° < 27.5, ω scan, T = 150 K, Mo-Kα radiation, graphite monochromator, λ = 0.71073 Å) on an Enraf–Nonius CAD4 Turbo diffractometer on rotating anode. Data were corrected for Lp effects and for a linear instability of 3% of the reference reflections, but not for absorption. The structure was solved by automated direct methods (SHELXS96). Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL96) for 311 parameters; no observance criterion was applied during refinement. A disorder model was introduced to describe the conformational disorder of the tetrahydrofuran moiety. Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. Refinement converged at a final $wR2$ value of 0.1796, $R1$ = 0.0655 [for 2936 reflections with $F_o > 4\sigma(F_o)$], S = 1.047. A final difference Fourier showed no residual density outside −1.00 and 1.28 e Å^{-3} (near CH_2Cl_2, indicating a slight disorder). CCDC 182/849.

†† Samples of **6** (1.0 × 10^{-4} M) and TEMPO (0–1.0 M) in toluene were irradiated with a 337 nm nitrogen laser at 295 ± 0.5 K. Decomposition was followed at the maximum absorbance of the Co^{III}–C band at 668 nm. Detailed experimental set-up and conditions are described in ref. 3.

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