Intramolecular Alkoxycobaltation: a Novel Route to the Cobalt–Carbon Bond in a Coenzyme B_{12} Model

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Co^{II}(salen)† derivatives whose ethanediyl moiety carries an ω-alkenyl side chain react with oxygen and methanol or ethanol to give, via interaction between intermediate Co^{III} species and the pendant olefin, alkylated products with a β-alkoxy substituted carbon bridge between cobalt and the equatorial ligand; the corresponding intermolecular reaction between Co^{II}(salen) and hex-1-ene does not take place.

Since the discovery of the importance of the cobalt–carbon σ-bond in coenzyme B_{12} (5′-deoxyadenosylcobalamin) with respect to the mechanism of B_{12} dependent isomerization reactions, there has been great interest in this bond and its reactivity, both in B_{12} and in model compounds.[1] We are interested in the formation and breaking of the Co–C bond in model systems of B_{12} in which cobalt and functional groups are forced to stay in close proximity, i.e. a mimic of the situation that exists in the holoenzyme.[2] In this context, we have now investigated whether under this condition a bonding interaction can occur between cobalt(III) and an unactivated carbon–carbon double bond, a type of reaction that normally does not take place with simple alkenes.[3,4] For that purpose, we have prepared Co(salen)† derivatives 1a and b with an ω-unsaturated side chain attached to the ethanediyl moiety of the equatorial ligand. Here, we describe the synthesis and characterization of 1a and b, and the discovery of ring closure of these compounds resulting in the formation of a Co–C bond and, thereby, a carbon bridge between the ligand and cobalt.

The H_2salen derived ligands 2a,b required for the synthesis of 1a and b, respectively, were prepared from methyl glycinate in a six-step procedure as shown in Scheme 1. Reaction of 2a,b with cobalt(II) acetate in DMF† gave,[5] after evaporation of DMF in vacuo, thorough washing with deaerated water to

remove residual DMF and drying in vacuo, complexes 1a and 1b as bright red, microcrystalline products. The UV–VIS spectra of these paramagnetic products in deaerated dichloromethane showed typical Co^{II}(salen) bands [λ_{max}/nm (ε/ dm^3 mol^{-1} cm^{-1}) 1a = 350 (ε = 1.1 × 10^4), 408 (ε = 1.1 × 10^4), 490sh (ε = 2.5 × 10^3); λ_{max} 1b = 350 (ε = 9.4 × 10^3), 406 (ε = 8.7 × 10^3), 485sh (ε = 1.9 × 10^3)]. Oxidation of 1a,b by iodine (large excess of I_2, pyridine) gave diamagnetic iodocobalt(III) complexes, which were characterized by ¹H NMR {C_5D_5N, 200 MHz, [1a: δ 8.72 and 8.67 (2s, 2H, N=CH), 5.8

Scheme 1 Reagents: i, benzaldehyde, TEA, $MgSO_4$, CH_2Cl_2;[6] ii, (a) allyl ethyl carbonate, $Pd(PPh_3)_4$, THF;[7] (b) LDA, 4-bromobutene, THF;[8] iii, (1) HCl, H_2O; (2) NH_3, MeOH;[8] iv, $LiAlH_4$, THF;[9] v, salicylaldehyde, EtOH:[10] vi, $Co(OAc)_2$, DMF^5†
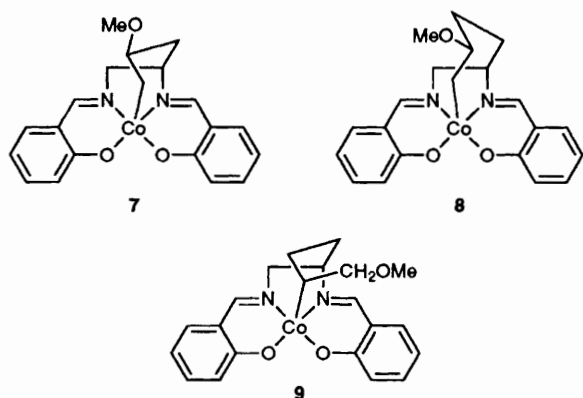

Scheme 2 Possible mechanism of formation of **7**, **8** and **9** from **1a,b** *via* cobalt(III)-olefin π-complex **B**

(m, 1H, CH=), 5.1 (m, 2H, =CH₂); **1b**: δ 8.64 and 8.60 (2s, 2H, N=CH), 5.8 (m, 1H, CH=), 5.1 (m, 2H, =CH₂)]}. Additional signals at δ 2.59, 2.67 and 8.07 revealed slight contamination by DMF, as also indicated by the cobalt analysis (**1a**: $C_{19}H_{18}N_2O_2Co·0.25$ DMF; **1b**: $C_{20}H_{20}N_2O_2Co·0.20$ DMF).

Like Co^{II}(salen),[11] **1a** and **b** are stable compounds under anaerobic conditions at room temperature but are, analogously, very rapidly oxidized in methanol by dissolved oxygen. The UV–VIS spectral changes that accompany this oxidation are quite similar in shape and extinction for **1a**, **1b** and Co^{II}(salen), which is known to give a mixture of methoxo- and hydroxo-cobalt(III) complexes under exactly the same conditions.[11] However, where these complexes are end-products in the case of Co^{II}(salen), the corresponding Co^{III} complexes derived from **1a** and **b** exhibit a further slower reaction showing UV–VIS spectral changes that, finally, lead to the spectrum of alkylCo^{III}(salen) compounds.[2] Spectroscopic analysis (¹H and ¹³C NMR, UV–VIS, MS) of the reaction products revealed that the olefinic bond had disappeared and that intramolecularly alkylated cobalt(III) complexes had been formed containing a methoxy substituent at the β-carbon atom. Starting from compound **1a**, a bridged compound **7** with three carbon atoms between cobalt and the salen ligand was obtained in 76% yield after concentration *in vacuo* and chromatographic purification. Compound **1b** gave a mixture of two isomers (ratio 2:1) of which the major component **8** has a four-carbon atom bridge with a β-methoxy group and the minor constituent **9** has a three-carbon atom bridge with an α-methoxymethyl substituent. Sofar, we have been unable to detect diastereoisomers of **7**, **8** and **9** in the reaction mixtures.

The corresponding reaction of **1a** and **b** in ethanol gives ethoxy analogues of **7**, **8** and **9**. However, similar intermolecular addition of hex-1-ene to Co^{II}(salen) in oxygen-containing methanol or ethanol could not be accomplished, the only products detected being alkoxo- and hydroxo-Co^{III}-(salen). This is in line with reported[3] behaviour of cob(III)-alamines and cob(III)aloximes, and demonstrates that close proximity is required for this unprecedented bond formation between Co^{III} and an unactivated olefin to occur.

¹H NMR and ¹³C NMR data (CDCl₃, 200 and 400 MHz, respectively) of **7**, **8** and **9** strongly resemble those of intramolecularly bridged compounds without the methoxy function.[2] Compound **9** was easily characterized by the specific high-field shift of one of the β-protons of the bridge,

resonating at δ −0.46, and the presence of a MeOCH₂CH group giving resonances at δ 3.18 (s, 3H), 3.23 (d, 2H) and 3.77 (m, 1H). Selected spectroscopic data of **7** are both characteristic and representative: δ(¹H) 3.33 (s, 3H, CH_3OCH) and 3.25 (m, 1H, CH₃OCH); δ(¹³C) 56.2 (q, CH₃OCH) and 77.9 (d, CH₃OCH); mass: 396.088 ± 0.001 (calc.: 396.0884 for $C_{20}H_{21}N_2O_3Co$), UV–VIS (CH₂Cl₂): λ$_{max}$ = 650 nm (ε = 1.6 × 10³ dm³ mol^{-1} cm^{-1}), typical for (pentacoordinate) alkylCo(III)(salen) complexes in non-coordinating solvents.[2]

Crystals of **8** suitable for X-ray structure analysis were obtained by slow evaporation of a CDCl₃ solution. In the unit cell two monomers, one dimer and four deuteriochloroform molecules are found. One of the solvent molecules is bonded *via* deuterium to both oxygen atoms of the equatorial ligand of the monomer unit [D–O(1) = 2.50(3), D–O(2) = 2.29(3) Å]. In the dimer, hexacoordination is established by bonding of an oxygen atom of the equatorial ligand of one molecule to the cobalt atom in the other molecule [Co–O = 2.29(1) Å]. The crystal structure of a monomeric species is shown in Fig. 1, together with selected bond lengths and angles.‡ A striking feature is the short C(19)–C(20) bond [1.41(4) Å], possibly even shorter than the corresponding bond in coenzyme B₁₂ (1.45 Å). It is also noted that C(19)–O(3) [1.48(4) Å] is longer than normally found for such bonds.[12]

The formation of alkylcobalt compounds **7**, **8** and **9** seems related to several other reactions in the B₁₂ field, *e.g* the addition of vinyl ethers to cob(III)alamine and cob(III)aloximes in ethanol,[3] and the formal reversal of the acid-induced decomposition of coenzyme B₁₂,[13] of β-hydroxy- and β-alkoxyethyl-cobalamines and -cobinamides,[14] and of β-hydroxy-and β-alkoxyethyl-cobaloximes.[15] Mechanisms involving cobalt(III)-olefin π-complexes,[3] β-cobaltethyl cations stabilized by cobalt–carbon hyperconjugation,[15] and concerted elimination[14] of water or alcohol and dealkylated cobalt(III)(ligand) species have been proposed for these reactions and may be extremes in a structure dependent mechanistic continuum. The interaction of Co^{III} with a carbon–carbon double bond in the present reaction leading to β-alkoxyalkylcobalt compounds might proceed *via* similar mechanisms and intermediates as seems to be evinced by the shortening of the C(19)–C(20) bond, lengthening of the C(19)–O(3) bond, and attack of methanol *trans* to the incipient Co–O bond of **8** (Fig. 1). In either case, reaction of methanol at the former
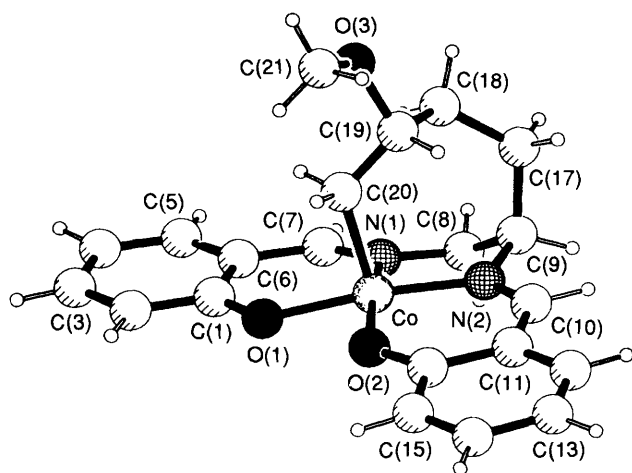
Fig. 1 Crystal structure and atom numbering scheme of cobalt complex **8** (monomer). Selected bond lengths (Å) and angles (°): Co–C(20) 1.98(3), Co–O(1) 1.886(17), Co–O(2) 1.860(15), Co–N(1) 1.859(18), Co–N(2) 1.876(18), C(19)–C(20) 1.41(4), C(18)–C(19) 1.49(4), C(7)–N(1) 1.30(3), C(10)–N(2) 1.30(3), C(19)–O(3) 1.48(4); Co–C(20)–C(19) 122(2), C(18)–C(19)–C(20) 114(2), C(17)–C(18)–C(19) 120(2), C(20)–Co–O(1) 88.5(11), C(20)–Co–O(2) 96.7(9), C(20)–Co–N(1) 93.6(10), C(20)–Co–N(2) 99.0(11), C(19)–O(3)–C(21) 117(2).

olefinic carbon atoms would in principle give a mixture of two isomeric products. Starting with **1b**, indeed both **8** and **9** are formed, in accordance with our finding that analogous Co(salen) complexes with three- as well as four-membered carbon bridges between cobalt and the equatorial ligand are stable compounds.[2] After reaction of **1a**, only **7** is found, probably because a Co(salen) complex with a two-membered carbon bridge is not stable under the reaction conditions.[2] In Scheme 2, a possible mechanism for the formation of **7–9** from **1a,b** *via* a cobalt(III)-olefin π-complex **B** is shown.

The rate of formation of **7** from **1a** is *ca.* 10^2 times faster at pH 4 than at pH 7 suggesting that species such as **A** or **C** (Scheme 2) are involved in the rate-determining step.§

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§ In 90% (v/v) methanol-water the pH-rate profile, as measured with a glass electrode calibrated for this solvent mixture,[16] follows a titration curve and gives a pK_a value of 7.6.

Detailed mechanistic aspects and synthetic applications of the reaction, as well as the significance of the results with regard to B_{12}-related chemistry are presently under investigation.

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