A Catalytic Model for the Dioldehydratase Reaction

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The diastereoisomeric 6,7-dihydroxycycloundecyl iodides (**3a**), (**3b**), and (**3c**) have been synthesised; their conversion into cycloundecanone (**12**) in the presence of sodium borohydride and traces of cobalt complexes provides the first catalytic model for the coenzyme B$_{12}$ catalysed dioldehydratase reaction.

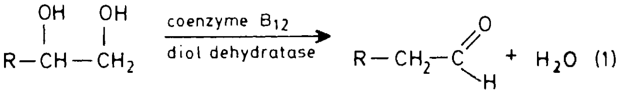
Among the many models of the coenzyme B$_{12}$-dependent dioldehydratase[1] (equation 1) the one presented by Golding *et al.*[2] mimics not only the conversion of a vicinal diol into a carbonyl function but also the abstraction of a hydrogen atom by an intermediate radical. Their apparently stable 4,5-dihydroxycyclo-octylcobaloxime (**1**) upon irradiation in acidic solution gave cyclo-octanone (**2**) with concomitant transannular migration of a hydrogen atom.

With a similar goal in mind we prepared the diastereoisomeric 6,7-dihydroxycycloundecyl iodides (**3a**), (**3b**), and (**3c**) as precursors for cobalt derivatives like (**1**). The key synthetic step was the acyloin condensation of the substituted unde-

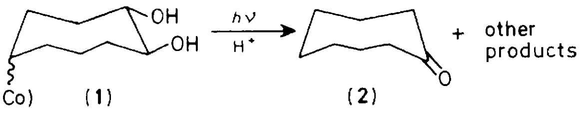
Table 1. Products, yields, and reaction conditions in the conversion of the diastereoisomeric 6,7-dihydroxycycloundecyl iodides with cobalt(I) complexes.[a]

Expt.	Yields (%) (12)	(13)	(11)	Equiv. of $NaBH_4$ reducing agent	Reaction conditions Catalyst[b] (equiv.)	pH	Configuration of substrate
1	10	—	4.5	4	A (0.5)	11—12	Diastereoisomeric mixture
2	—	—	7.0	"	"	9—9.5	" "
3	—	—	2.5	"	"	8	" "
4	6	13	—	120	"	11—12	" "
5	27	—	n.d.[c]	4	A (0.5)	11—12	(±)-(*R*,*S*)-(**3a**)
6	28	—	*ca.* 9	"	"	"	(1*r*,6*R*,7*S*)-(**3b**)
7	27	—	16	"	"	"	(1*s*,6*R*,7*S*)-(**3c**)
8	44	—	—	4	A (0.1)	11—12	Diastereoisomeric mixture
9	54	—	—	"	A (0.05)	"	" "
10	75	—	—	"	A (0.01)	"	" "
11	—	—	—	"	None	"	" "
12	24	—	25	4	B (0.2)	11—12	" "
13	9	—	—	"	C (0.1)	"	" "
14	—	31	—	200	D (0.05)	"	" "

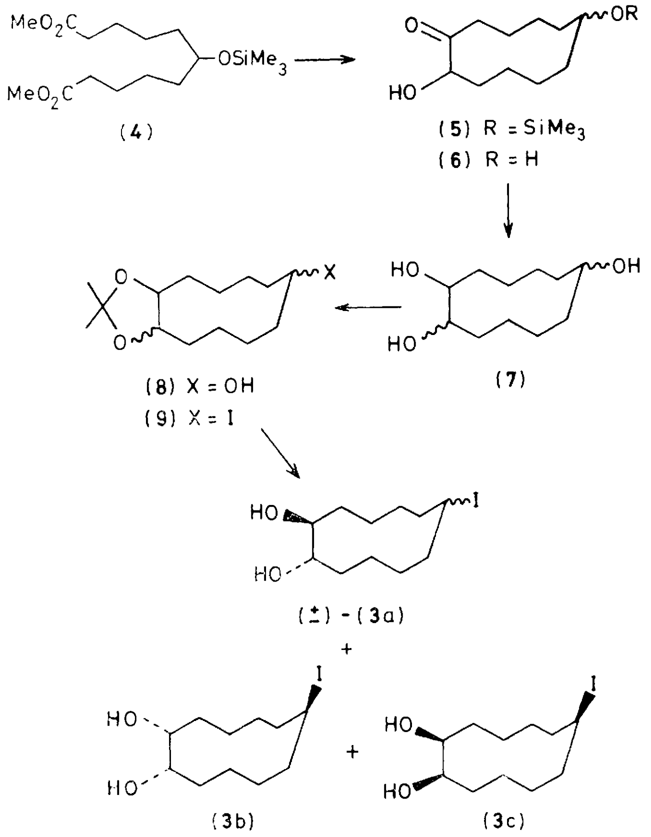
[a] The cobalt(I) complexes were prepared in methanol (150 ml) in the presence of sodium borohydride at 0 °C. After the addition of (**3**) (1 mmol) in ethanol (10 ml) the temperature was raised to 22 °C for 2 h. All yields were determined on isolated products. In expt. 1 the yield is low since the isolation procedure had not yet been optimised. [b] A = Costa complex; B = $CoCl_2$; C = cobaloxime; D = cobalamin. [c] Not determined.



$$\mathrm{R{-}\overset{\overset{OH}{|}}{C}H{-}\overset{\overset{OH}{|}}{C}H_2} \xrightarrow[\text{diol dehydratase}]{\text{coenzyme } B_{12}} \mathrm{R{-}CH_2{-}C(=O)H} + H_2O \quad (1)$$



(Co) = cobaloxime



canedioic acid dimethyl ester (**4**) to give the α-hydroxyketone (**5**) (80%). Removal of the trimethylsilyl protecting group afforded (**6**) (90%), reduction of which with sodium borohydride furnished a mixture of the diastereoisomeric 1,2,7-trihydroxycycloundecanes (**7a**), (**7b**), and (**7c**) (75%). The acetonides (**8a**), (**8b**), and (**8c**), separated or as a mixture of three diastereoisomers, could be converted by two methods (triphenylphosphine–diethyl azodicarboxylate–methyl iodide at −10 °C[3] or triphenylphosphine–tri-iodoimidazole at 120 °C[4]) into the iodides (**9a**), (**9b**), and (**9c**) (40—45%). Removal of the isopropylidene protecting group led to (**3a**), (**3b**), and (**3c**) (m.p.s 80, 125, and 135 °C, respectively). The configurations were assigned by ^{1}H and ^{13}C n.m.r. spectroscopy of the precursors (**7**) and (**8**).†

Reaction of (**3a**), (**3b**), or (**3c**) with di-iodo(2,3,9,10-tetramethyl-1,4,8,11-tetra-azaundeca-1,3,8,10-tetraen-11-ol-1-olato)cobalt(III) (Costa complex[5]) or with other cobalt complexes in the presence of sodium borohydride and alkali in the dark did not lead to stable alkylated cobalt complexes but yielded, depending on the reaction conditions, cycloundecene-6,7-diol (**10**) [mixture of (*E*) and (*Z*)], 2-hydroxycycloundecanone (**11**), cycloundecanone (**12**), and cycloundecanol (**13**). The results from selected experiments are listed in Table 1. The diol (**10**) was formed only in the absence of a strong base and its quantity was therefore usually not estimated. The following conclusions may be drawn. (i) Cycloundecanone (**12**), the analogous dioldehydratase product, is formed only at or above pH 11 and will be reduced to (**13**) by a large excess of sodium borohydride. (ii) The yield of (**12**) is hardly dependent

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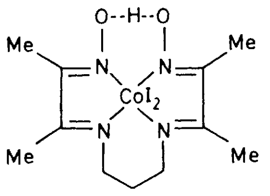
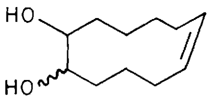
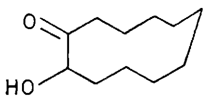
† All new compounds were characterised fully by analytical and spectroscopic methods.



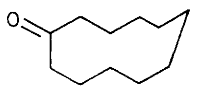
Costa complex



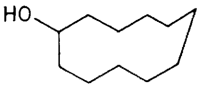
(10)



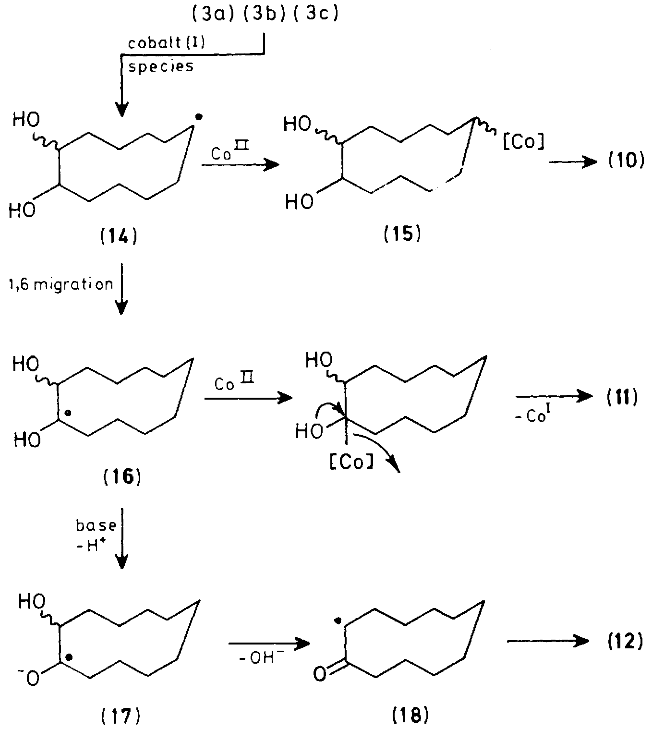
(11)



(12)



(13)



Scheme 1. Hypothetical mechanism for the model reaction.

on the configuration of the substrate. (iii) The Costa complex is catalytically active and its decreasing concentration increases the yield of (**12**). (iv) Though the Costa complex is the best catalyst tried [up to 75% yield of (**12**) corresponding to 75 catalytic cycles], cobaloxime, cobalamin, and cobalt(II) chloride are also active.

On the basis of these results the mechanism of the model reaction can be envisaged as follows (Scheme 1). One-electron transfer from the cobalt(I) species followed by the elimination of iodide yields the radical (**14**). Combination of the latter with a cobalt(II) species leads to the unstable alkylated cobalt complex (**15**), whose elimination product is the observed olefin (**10**). On the other hand, (**14**) can rearrange by transannular 1,6-migration[2,6] to the more stable radical (**16**), whose combination with a cobalt(II) species followed by cobalt(I) elimination[7] yields the observed 2-hydroxycycloundecanone (**11**). Finally, in basic solution, (**16**) could lose a proton yielding the radical anion (**17**) which, in turn, will eliminate OH[8] and furnish, *via* the stabilised radical (**18**), cycloundecanone (**12**). Consistent with this mechanism is the fact that (**11**) is only observed at higher concentrations of the Costa complex.

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