Journal of Organometallic Chemistry, 133 (1977) 87—92

STABILITIES AND ENTHALPIES OF FORMATION OF BASE ADDUCTS OF VITAMIN B_{12} MODEL COMPLEXES

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(Received December 7th, 1976)

Summary

Thermodynamic data, obtained by calorimetric titration, are reported for the addition of bases to alkylcobalt disalicylidene-1,2-diaminoethane complexes in acetonitrile and methylcobaloxime in benzene. The complexes RCo(salen) form 1 : 1 adducts of moderate stability with N-donors; adduct stabilities are greater when R = Me than when R = Et, Pr or Bu and are also affected by base structure: heterocyclic bases form less stable adducts than amines and in the latter chain branching lowers adduct stability and ring formation raises it; some of the most stable adducts are formed by pyrollidine and imidazole; enthalpies of adduct formation for all bases are about —30 kJ mol^{-1} and variations are apparently entropy controlled. Methylcobaloxime is a much stronger Lewis acid and forms 1 : 1 adducts of very high stability ($K > 10^5$ l mol^{-1}) with N-, O-, S- and P-donors; enthalpies of adduct formation are mostly about —50 kJ (g-at. Co)$^{-1}$ with the dimeric form of the cobaloxime.

Introduction

In recent years there has been increasing interest in organocobalt complexes as models for the naturally occurring cobalt-corrins in the cobalamins and vitamin B_{12}. Typically the models are of the type $RCoL_2B$, where R = an alkyl or aryl group, B is a Lewis base and LH is an organic acid, the anion of which is capable of chelation. The most extensively studied systems are those in which LH = dimethylglyoxime, of which the cobalt complexes are known as cobaloximes. and those in which L_2H_2 = a Schiff base, the dianion of which can behave as a quadridentate ligand. There have been several reviews of these systems [1—4].

The cobaloximes have been particularly intensively studied since they were first proposed as appropriate models by Schrauzer [5]. Studies have been made of the hard/soft or A/B character of the cobalt centre [6] and there have been several structure determinations [7]. The base-free complex, $RCoL_2$, has been shown to be dimeric, both in the solid state and in solution [8]. Studies have also

been made of various Schiff base complexes, including that of disalicylidene-1,2-diaminoethane (salenH_2), and these studies include the effects of varying in-plane ligands on the rates of exchange of the base L [9]. There have however been few reports of thermodynamic data for the addition of B to $RCoL_2$ in these systems.

We now report thermodynamic data, obtained by calorimetric titration in benzene or acetonitrile solution, for the addition of a variety of Lewis bases to methyl cobaloxime (R = CH_3, LH = dimethylglyoxime) and to the Schiff base complexes RCo(salen) (R = CH_3, C_2H_5, C_3H_7, C_4H_9).

Base adducts of RCo(salen)

In most of these systems adduct stabilities were such that both the adduct formation constants and enthalpies of formation could be conveniently determined by the calorimetric titration method. Acetonitrile was used as solvent in these systems because of the low solubility of the cobalt complexes in benzene. The calorimetric titration data in all cases were fitted very well by the equations for the formation of 1 : 1 base adducts. Complete thermodynamic data are recorded in Tables 1—4 for the addition of an extensive range of N-donor bases to all four cobalt compounds.

In addition to the data in the tables studies were also made of the reaction of these cobalt compounds with various other bases: the typical colour change from green to red, which accompanies adduct formation, was also observed with 2-methyl-2-aminopropane, 2-aminobutane, *N,N,N',N'*-tetramethyl-1,2-diaminoethane and pyridine-*N*-oxide, but the adduct formation constants were too low for evaluation of K or ΔH^0 to be possible; tributylamine and several tertiary phosphines gave no evidence for adduct formation.

Comparison of the results in Tables 1—4 shows a distinct difference between MeCo(salen) and the higher homologues: invariably the methyl compound forms

TABLE 1

THERMODYNAMIC DATA FOR ADDITION OF BASES TO MeCo(salen) IN ACETONITRILE SOLUTION AT 30°C

Base	[MeCo(salen)] (mmol l^{-1})	K ($l\ mol^{-1}$)	$-\Delta H^0$ (kJ mol^{-1})	$-\Delta G^0$ (kJ mol^{-1})	$-\Delta S^0$ (J K^{-1} mol^{-1})
Pyridine	1.0—3.0	83 ± 9	26.8 ± 2.7	11.1 ± 0.3	52 ± 10
3-Mepy	1.5—3.0	84 ± 9	20.5 ± 1.0	11.2 ± 0.3	31 ± 4
4-Mepy	1.0—3.0	79 ± 6	26.1 ± 1.0	11.0 ± 0.2	50 ± 3
Isoquinoline	1.5—3.0	111 ± 21	26.8 ± 2.1	11.9 ± 0.5	49 ± 9
Piperidine	1.5—3.0	185 ± 15	28.6 ± 0.9	13.2 ± 0.2	51 ± 4
Pyrollidine	1.5—2.5	769 ± 123	32.0 ± 0.4	16.7 ± 0.4	50 ± 3
Imidazole	1.0—2.5	445 ± 41	27.1 ± 3.2	15.4 ± 0.3	39 ± 11
Benzylamine	1.5—3.0	153 ± 13	27.5 ± 2.5	12.7 ± 0.3	49 ± 9
Ethylamine	1.0—2.0	203 ± 20	33.3 ± 2.7	13.4 ± 0.3	66 ± 10
Propylamine	1.0—3.0	162 ± 18	32.8 ± 1.2	12.8 ± 0.3	66 ± 5
Butylamine	1.0—2.0	544 ± 68	24.9 ± 0.5	15.9 ± 0.3	30 ± 3
Amylamine	1.0—2.0	266 ± 21	36.8 ± 1.7	14.1 ± 0.2	75 ± 6
Isobutylamine	1.0—2.0	284 ± 19	24.0 ± 1.3	14.2 ± 0.2	32 ± 5
Isopropylamine	1.5—2.5	56 ± 9	25.7 ± 2.6	10.1 ± 0.5	51 ± 10
Cyclohexylamine	1.0—2.0	62 ± 6	23.4 ± 1.5	10.4 ± 0.2	43 ± 6

TABLE 2

THERMODYNAMIC DATA FOR ADDITION OF BASES TO EtCo(salen) IN ACETONITRILE SOLUTION AT 30°C

Base	[EtCo(salen)] (mmol l^{-1})	K ($l\ mol^{-1}$)	$-\Delta H^0$ (kJ mol^{-1})	$-\Delta G^0$ (kJ mol^{-1})	$-\Delta S^0$ J K^{-1} mol^{-1})
Pyridine	2.0—3.0	18 ±1	32.0 ± 2.2	7.3 ± 0.2	82 ± 8
3-Mepy	1.5—3.0	18 ± 1	28.7 ± 1.6	7.3 ± 0.2	71 ± 6
4-Mepy	1.5—3.0	24 ± 3	31.7 ± 2.7	8.0 ± 0.3	78 ± 9
Isoquinoline	2.0—3.0	28 ± 4	19.0 ± 2.0	8.4 ± 0.4	35 ± 8
Piperidine	1.0—3.0	74 ± 14	28.6 ± 3.1	10.8 ± 0.5	59 ± 12
Pyrollidine	1.5—3.0	136 ± 20	32.2 ± 1.4	12.4 ± 0.4	65 ± 6
Imidazole	1.5—2.5	59 ± 6	28.9 ± 2.7	10.2 ± 0.3	62 ± 10
Benzylamine	1.0—3.0	55 ± 5	23.7 ± 1.1	10.1 ± 0.2	45 ± 4
Ethylamine	1.5—2.5	97 ± 18	21.7 ± 0.8	11.5 ± 0.5	34 ± 4
Propylamine	1.5—3.0	87 ± 17	27.6 ± 3.7	11.2 ± 0.6	54 ± 13
Butylamine	1.0—3.0	85 ± 5	27.4 ± 0.4	11.2 ± 0.2	54 ± 2
Amylamine	1.5—3.0	49 ± 9	26.6 ± 1.0	9.8 ± 0.5	56 ± 5
Isobutylamine	1.0—3.0	50 ± 5	22.1 ± 1.2	9.9 ± 0.3	40 ± 5
Isopropylamine	1.5—3.0	20 ± 5	19.7 ± 2.0	7.5 ± 0.7	40 ± 9
Cyclohexylamine	1.5—3.0	35 ± 5	20.3 ± 1.0	8.9 ± 0.4	38 ± 4

more stable adducts. Apparently however this greater acidity of the methyl compound is not a simple inductive effect, as there is no general increase in the enthalpy of adduct formation; the increased adduct stability appears to be entropic in origin. A possible explanation might be more extensive solvation in the vacant sixth site of MeCo(salen), so that more solvent molecules are displaced.

Heterocyclic bases, such as pyridine, generally form less stable adducts than aliphatic amines; this also is not an enthalpy effect and cannot be adduced as evidence for "hard" or A-character in the cobalt atom. Adduct stabilities are considerably affected by amine structure: secondary and tertiary amines are relatively poor bases in these systems and chain branching at the α-carbon atom of primary amines also leads to reduced adduct stability, as shown by the data for isopropylamine and cyclohexylamine.

TABLE 3

THERMODYNAMIC DATA FOR ADDITION OF BASES TO PrCo(salen) IN ACETONITRILE SOLUTION AT 30°C [a]

Base	[PrCo(salen)] (mmol l^{-1})	K ($l\ mol^{-1}$)	$-\Delta H^0$ (kJ mol^{-1})	$-\Delta G^0$ (kJ mol^{-1})	$-\Delta S^0$ (J K^{-1} mol^{-1})
Pyridine	1.0—2.5	17 ± 2	34.0 ± 1.7	7.1 ± 0.3	89 ± 7
4-Mepy	1.5—2.5	23 ± 3	35.7 ± 0.9	7.8 ± 0.4	92 ± 4
Piperidine	2.0—2.5	96 ± 7	29.2 ± 1.1	11.5 ± 0.2	59 ± 5
Pyrollidine	1.5—2.5	220 ± 20	30.3 ± 0.7	13.6 ± 0.2	55 ± 4
Benzylamine	1.5—2.5	111 ± 19	20.8 ± 0.5	11.8 ± 0.5	29 ± 3
Butylamine	1.5—2.5	72 ± 8	36.5 ± 1.0	10.8 ± 0.3	85 ± 4
Amylamine	1.0—2.5	83 ± 8	37.0 ± 3.7	11.1 ± 0.3	85 ± 13
Isobutylamine	1.5—2.5	38 ± 4	30.0 ± 2.0	9.1 ± 0.3	69 ± 8
Cyclohexylamine	2.0—2.5	56 ± 5	27.7 ± 0.6	10.1 ± 0.3	58 ± 3

[a] Imidazole gave an insoluble adduct. With isoquinoline and isopropylamine a small amount of heat was liberated, but K and ΔH^0 could not be determined.

TABLE 4

THERMODYNAMIC DATA FOR ADDITION OF BASES TO BuCo(salen) IN ACETONITRILE SOLUTION AT 30°C [a]

Base	[BuCo(salen)] (mmol l^{-1})	K ($l\ mol^{-1}$)	$-\Delta H^0$ (kJ mol^{-1})	$-\Delta G^0$ (kJ mol^{-1})	$-\Delta S^0$ (J K^{-1} mol^{-1})
Pyridine	1.5—2.5	22 ± 4	27.8 ± 0.8	7.8 ± 0.6	66 ± 5
3-Mepy	1.5—2.5	16 ± 1	31.0 ± 1.0	7.0 ± 0.2	79 ± 4
4-Mepy	1.5—2.5	44 ± 5	28.0 ± 1.7	9.5 ± 0.3	61 ± 7
Piperidine	1.0—2.0	74 ± 9	37.6 ± 0.7	10.8 ± 0.4	88 ± 4
Pyrollidine	1.0—2.0	338 ± 28	31.4 ± 1.2	14.7 ± 0.2	55 ± 5
Benzylamine	1.0—1.5	100 ± 13	34.1 ± 2.7	11.6 ± 0.4	74 ± 10
Ethylamine	1.0—2.0	162 ± 22	33.3 ± 2.1	12.8 ± 0.4	67 ± 8
Butylamine	1.0—2.0	277 ± 38	33.8 ± 1.4	14.2 ± 0.4	65 ± 6
Amylamine	1.0—2.0	166 ± 21	39.6 ± 1.8	12.9 ± 0.4	88 ± 7
Isobutylamine	1.0—2.0	100 ± 9	36.5 ± 3.5	11.6 ± 0.3	82 ± 12
Isopropylamine	1.0—2.0	41 ± 5	23.5 ± 1.7	9.4 ± 0.4	47 ± 7
Cyclohexylamine	1.0—2.0	82 ± 12	25.4 ± 0.9	11.1 ± 0.4	47 ± 4

[a] Imidazole gave an insoluble adduct.

Ring formation greatly increases the stability of adducts with aliphatic amines, particularly if the ring is small; the most stable of all adducts are those with bases which have the donor N-atom in a five-membered ring: pyrollidine and imidazole. This is particularly interesting in view of the preference in natural cobalamin type systems for bases of the imidazole type.

Base adducts of methylcobaloxime

Methylcobaloxime, which is known to be dimeric in solution [8], was found to form much more stable adducts than RCo(salen); indeed adduct stabilities were too large to be measured by the calorimetric technique and all the base addition reactions were effectively quantitative. The enthalpies of addition of eight bases (four N-donors, two phosphines, one S-donor and one O-donor) in benzene solution are summarized in Table 5, which also includes enthalpies for addition to the monomeric form of the cobaloxime, calculated using Drago's value [6] of —28 kJ (g-at. Co)$^{-1}$ for the enthalpy of dimerisation.

The enthalpy observed for addition of pyridine to the dimer in benzene solution is close to Drago's value for the same reaction in 1,2-dichloroethane (—49 kJ (g-at. Co)$^{-1}$), but that for addition of tetrahydrothiophene in benzene is rather smaller than his values obtained in $C_2H_4Cl_2$ or CH_2Cl_2 (both about —33 kJ (g-at. Co)$^{-1}$). The enthalpies of addition of the four N-bases are closely similar, comparison of piperidine and the heterocyclic bases suggesting that π-bonding is not of much significance. Enthalpies of addition of the two phosphines are similar to those of the N-bases, as has been observed with "soft" or B-class acids, such as mercury(II) halides [10]. The enthalpies of addition of tetrahydrothiophene and pyridine-*N*-oxide are much smaller, but their similarity to one another suggests that the cobaloxime exhibits less "softness" than mercury halides; a similar conclusion was reached by Drago [6].

Comparison of the data for methylcobaloxime and RCo(salen) shows that the former forms much more stable base adducts with more negative enthalpies

TABLE 5

ENTHALPIES OF FORMATION OF ADDUCTS OF BASES WITH DIMERIC AND MONOMERIC FORMS OF METHYLCOBALOXIME kJ (g-at. Co)$^{-1}$, IN BENZENE AT 30°C [a]

Base	[cobaloxime] (mmol l^{-1})	Dimer $-\Delta H^0$	Monomer $-\Delta H^0$
Pyridine	1.0—2.0	47.4 ± 1.0	75.4
3-Mepy	0.5—1.0	46.5 ± 0.3	74.5
4-Mepy	1.0—2.0	50.7 ± 1.3	78.7
Piperidine [b]	0.5	52.0	80.0
Pyridine-*N*-oxide	0.5—0.8	22.6 ± 0.6	50.6
Tetrahydrothiophene	0.5—1.0	21.9 ± 0.5	49.9
Tributylphosphine	0.5—1.0	56.9 ± 0.7	84.9
Triphenylphosphine	0.5—0.8	38.5 ± 0.2	66.5

[a] Imidazole gave an insoluble adduct. [b] The adduct with piperidine was of so low a solubility that higher concentrations could not be used.

of formation. The reactions of all these compounds with bases provide typical examples of entropy dominated systems: with little variation of enthalpy there is a wide range of adduct stabilities. The small enthalpies of reaction make such systems particularly appropriate for biological conditions, where control of the equilibria could be managed through solvation effects.

Experimental

Materials

Alkyl derivatives RCo(salen) (R = Me, Et, Pr, Bu) were prepared from the complex bromide $[Co(salen)py_2]Br \cdot H_2O$ by the Grignard method described by Costa, Mestroni and Stefani [11]. Aquamethylcobaloxime was prepared according to the method described by Schrauzer and Windgassen [12], with minor modification: In an atmosphere of nitrogen 23.8 g of $CoCl_2 \cdot 6H_2O$ and 23.2 g of dimethylglyoxime were stirred for 5 min with 100 ml of methanol and a solution of 8 g of NaOH in 150 ml of water then added. After stirring for 15 min, during which the temperature was lowered to —20°C, 7 g of CH_3I and 8 g of 50% aqueous NaOH were added, followed 5 min later by 2 g of 50% NaOH and 12 g of CH_3I. Next a solution of 4 g of NaOH and 0.6 g of $NaBH_4$ in 12 ml of water was added during about 5 min, the solution stirred for a further 15 min, then filtered. A stream of nitrogen was passed to free the filtrate from excess CH_3I; the solution was then concentrated under vacuum and cooled to —20°C, when dark orange crystals of the aquamethylcobaloxime separated. These were dried in vacuo over phosphorus pentoxide. Methylcobaloxime was obtained by dehydration by heating at 100°C for 12 h in vacuo over phosphorus pentoxide [6]. The dark red crystals were stored in a desiccator in the dark. The purity of all cobalt complexes was checked by C, H and N analysis.

Solid bases were purified by crystallisation, liquid bases by distillation and dried over anhydrous potassium carbonate. Benzene for use as solvent was purified by freezing and distillation and dried over calcium hydride; acetonitrile was redistilled and dried over anhydrous sodium sulphate.

Calorimetry

Calorimetric titrations were carried out in a LKB 8700 titration calorimeter using previously described techniques [13]. Briefly, a solution of base was titrated into 100 ml of a solution of the cobalt compound in the same solvent and the heat change measured after addition of each increment. The enthalpy of reaction was calculated from the extrapolated, integrated heat of reaction, after correcting for dilution effects. For adduct formation constants in the range $1 < K < 10^5$, the formation constant was calculated at each point in the titration and the enthalpy refined iteratively to give constant values of K throughout the titration. In Table 1—5 enthalpies are the average of at least three determinations over the range of concentrations stated; uncertainties in ΔH^0 are mean deviations. In Tables 1—4 the values of K are the average of at least three determinations; uncertainties in K are the sum of the mean deviation from different titrations and the average standard deviation from individual titrations. Values and uncertainties of ΔG^0 and ΔS^0 are derived.

Acknowledgments

We are grateful to the Australian Research Grants Committee for supporting this work. One of us (I.A.S.) acknowledges a Colombo Plan fellowship.

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