

## Effects of Solvent and Ionic Medium on the Kinetics of Axial Ligand Substitution in Vitamin B<sub>12</sub>.

### Part VII. The Reaction between Aquanitrocobaloxime and Thiourea in Dioxane–Water Mixtures

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#### Abstract

Rate constants for the reaction of aquanitrocobaloxime with thiourea were measured as a function of pH, solvent composition, pressure and temperature, in dioxane–water mixtures. With the aid of solubility measurements a complete quantitative analysis of solvent effects on the initial state and transition state transfer parameters could be made. It was found that the activation enthalpy and entropy vary strongly with solvent composition. This is in contrast to the variations found for vitamin B<sub>12</sub>, for which this cobaloxime is a model compound. The rate constants increase strongly after 50 vol.% dioxane in the dioxane–water mixtures, another difference with vitamin B<sub>12</sub>. The volumes of activation are small and positive, in accordance with a dissociative mode of activation.

#### Introduction

In a series of articles [1–6] it was shown that the influence of solvent composition on the axial ligand substitution reactions of vitamin B<sub>12</sub> is rather small. For the reactions with thiourea and the thiocyanate ion in dioxane–water and acetonitrile–water mixtures [1–6], an analysis was performed in terms of a dissection of solvent effects on the initial state and the transition state by combining kinetic data with solubilities of the reactants. The solubilities provided interesting information on solvational effects. From this study it was concluded that vitamin B<sub>12</sub> essentially creates a fairly constant chemical micro-environment resulting in small solvent effects on activation parameters, whereas the ground state parameters vary much more. Also in the isomerization reactions of thiocyanatocobalamin in dioxane–

water and acetonitrile–water mixtures the capability of vitamin B<sub>12</sub> to screen environmental changes was detected [4].

To compare these effects to the properties of model compounds like the cobaloximes a study was performed on the reactivity of vitamin B<sub>12</sub> and aquamethylcobaloxime towards several sulfur-coordinating ligands [3]. From this study it was concluded that the solvent effects on this model compound were comparable to those on vitamin B<sub>12</sub>. Differences occur because of the fact that the model compound cannot mimic the effects that the acetamide side-chains exert in vitamin B<sub>12</sub>.

In this paper solvent effects on the axial ligand substitution reaction of the model compound aquanitrocobaloxime with thiourea are studied more extensively in terms of transfer Gibbs energies, enthalpies, entropies and volumes of activation.

#### Experimental

##### Materials

Aquanitrocobaloxime ([Co(dmg)<sub>2</sub>NO<sub>2</sub>H<sub>2</sub>O]) was prepared according to Tschugaeff [7]. *Anal.*, found (calc.): Co 16.5% (16.69); C 27.05% (27.20); H 4.49% (4.57); N 19.78% (19.83); O 31.95% (31.71). Thiourea (abbreviated as tu, Merck) was used as purchased. Dioxane was purified as described before [1].

##### Methods

Solubilities of thiourea and aquanitrocobaloxime were determined with the aid of a specially designed solubility tube described before [3].

pH measurements were carried out with a Metrohm Herisau E603 pH meter, equipped with a Metrohm EA120 combination glass electrode.

Conductometric measurements were performed with a Metrohm 644 conductometer equipped with a glass titration vessel with internal conductivity plates.

Kinetic measurements at atmospheric pressure were conducted on a Beckman Acta CIII spectro-

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photometer equipped with a kinetic set. The kinetic measurements under high pressure were performed with a high pressure cell which can be placed in a conventional spectrophotometer and can be used with liquid pressures up to 1500 bar. This apparatus has been described elsewhere [8, 9].

## Results and Discussion

The reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with thiourea was studied in dioxane–water mixtures. From UV–Vis spectra it was shown that dioxane does not coordinate to  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  up to 90 vol.% dioxane. From IR spectra it was shown that the  $\text{NO}_2$  group is coordinated through nitrogen; an absorption at  $1330\text{ cm}^{-1}$  is present, characteristic of nitro complexes [10]. No signal appears in the region from  $1050$  to  $1100\text{ cm}^{-1}$ , characteristic of nitrito complexes [10]. The reactions were followed at a wavelength of  $375\text{ nm}$ . When the observed first-order rate constant was plotted against the thiourea concentration (large excess over  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$ ) a straight line was obtained, indicating first-order kinetics in thiourea. The intercept was always zero within experimental error, so no values for  $k_{-1}$  were obtained. Values for  $k_1$  were obtained from observed rate constants at at least three thiourea concentrations. Furthermore, the rate constants were found to be independent of the wavelength at which the reaction was followed in the range investigated ( $350$ – $400\text{ nm}$ ). A consecutive reaction was observed spectrophotometrically, which was accompanied by a change in the conductivity of the solution. This consecutive reaction is the dissociation of the nitro group (eqn. 1).

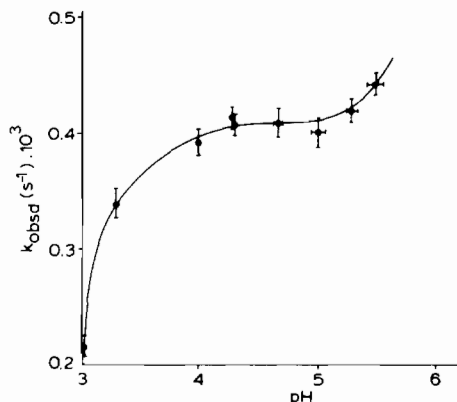
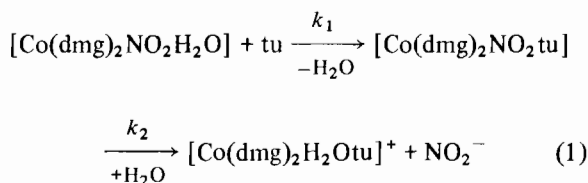


Fig. 1. pH dependence of the observed rate constant for the reaction between  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  and tu (0.4 M).

This consecutive reaction did not interfere with the first step at high thiourea concentrations. In water at  $0.1\text{ M NaClO}_4$  ( $35\text{ }^\circ\text{C}$ ,  $0.2\text{ M tu}$ ) the first-order reaction rate constant for the second reaction ( $k_2$ ) was found to be  $2 \times 10^{-5}\text{ s}^{-1}$  (measured conductometrically). In  $40\text{ vol.}\%$  dioxane–water it was found to be  $5 \times 10^{-6}\text{ s}^{-1}$  ( $35\text{ }^\circ\text{C}$ ,  $0.2\text{ M tu}$ ).

$[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  is known to be involved in several acid–base equilibria. At pH values above 6 a proton is abstracted, while at pH values below 4 the nitro group is protonated [11, 12]. For this reason the rate constant at  $0.4\text{ M tu}$  and  $0.1\text{ M NaClO}_4$  in water at  $35\text{ }^\circ\text{C}$  was determined as a function of pH (Fig. 1). From this figure it can be seen that protonation retards the reaction and deprotonation accelerates the reaction. A plateau is present between  $\text{pH} = 4$  and  $\text{pH} = 5$ . This rather narrow plateau is widened when an organic cosolvent is added, because in both the acid–base equilibria charge is created, which is more difficult in solvents with a lower dielectric constant. The reactions were measured in the presence of  $5 \times 10^{-5}\text{ M HClO}_4$ . Under these conditions it can be concluded that the reaction followed in all cases is the first reaction in eqn. 1. The rate constants at four temperatures in dioxane–water mixtures are given in Table I.

TABLE I. Ligation Rate Constants for the Reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with Thiourea ( $\text{s}^{-1}\text{ M}^{-1}$ )

Vol.% dioxane	15 °C	25 °C	35 °C	40 °C
0	$8.6 \times 10^{-5}$	$3.0 \times 10^{-4}$	$1.0 \times 10^{-3}$	$1.8 \times 10^{-3}$
10	$7.0 \times 10^{-5}$	$2.6 \times 10^{-4}$	$8.4 \times 10^{-4}$	$1.6 \times 10^{-3}$
20	$5.4 \times 10^{-5}$	$2.2 \times 10^{-4}$	$7.7 \times 10^{-4}$	$1.4 \times 10^{-3}$
30	$5.4 \times 10^{-5}$	$2.0 \times 10^{-4}$	$7.7 \times 10^{-4}$	$1.4 \times 10^{-3}$
40	$4.9 \times 10^{-5}$	$2.1 \times 10^{-4}$	$7.5 \times 10^{-4}$	$1.4 \times 10^{-3}$
50	$4.9 \times 10^{-5}$	$2.0 \times 10^{-4}$	$8.3 \times 10^{-4}$	$1.6 \times 10^{-3}$
60	$5.4 \times 10^{-5}$	$2.2 \times 10^{-4}$	$9.4 \times 10^{-4}$	$1.9 \times 10^{-3}$
70	$6.8 \times 10^{-5}$	$3.1 \times 10^{-4}$	$1.3 \times 10^{-3}$	$2.8 \times 10^{-3}$
80	$1.2 \times 10^{-4}$	$5.2 \times 10^{-4}$	$2.3 \times 10^{-3}$	$4.7 \times 10^{-3}$

The addition of dioxane to mixtures containing more than 50 vol.% dioxane–water increased the rate constant considerably, resulting in an almost two-fold increase at 80 vol.% dioxane–water relative to water. For a complete analysis of solvent effects on the initial state and transition state, the solubility data of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  (from ref. 5) and the solubilities of thiourea at four temperatures (data available on request) were combined with the kinetic data. In Table II the activation parameters are shown.

TABLE II. Activation Parameters for the Reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with Thiourea

Vol.% dioxane	$\Delta G_1^\ddagger$ <sup>a</sup>	$\Delta H_1^\ddagger$ <sup>b</sup>	$\Delta S_1^\ddagger$ <sup>c</sup>
0	93.1	89	-15
10	93.5	91	-10
20	93.9	95	4
30	94.1	96	6
40	94.0	98	12
50	94.1	102	26
60	93.9	105	36
70	93.0	108	52
80	91.8	108	54

<sup>a</sup>At 298.15 K, units  $\text{kJ mol}^{-1}$ , estimated standard deviation (e.s.d.):  $1 \text{ kJ mol}^{-1}$ . <sup>b</sup>Units  $\text{kJ mol}^{-1}$ , e.s.d.:  $2 \text{ kJ mol}^{-1}$ . <sup>c</sup>Units  $\text{J K}^{-1} \text{ mol}^{-1}$ , e.s.d.:  $6 \text{ J K}^{-1} \text{ mol}^{-1}$ .

For  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  the activation parameters change rather dramatically with solvent composition (Table II). The increase of  $k_1$  in dioxane-rich mixtures can be explained by a more strongly decreasing activation entropy contribution ( $-T\Delta S$ ). Apparently in dioxane-rich mixtures the transition state is more ordered in comparison to the initial state (the amount of bond-formation in the transition state is larger). This behaviour is different from the behaviour of vitamin  $\text{B}_{12}$  in its reactions with thiourea and thiocyanate in dioxane–water and acetonitrile–water mixtures. An explanation for this different behaviour could be that the mechanism of the reaction gradually changes from **Ia** to **Id** when the medium becomes more apolar. The latter assumption is in accordance with the gradual change of the activation entropy from negative to positive (Table II).

In comparison, for the reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  in water with the thiocyanate ion an enthalpy of activation of  $80 \text{ kJ mol}^{-1}$  and an entropy of activation of  $38 \text{ J K}^{-1} \text{ mol}^{-1}$  were found [11]. For the azide ion values of  $68 \text{ kJ mol}^{-1}$  and  $-80 \text{ J K}^{-1} \text{ mol}^{-1}$  were found, respectively [11].

In Fig. 2 the transfer Gibbs energy for the initial state and the transition state is shown. The transfer parameters were calculated as before [2]. In Fig. 3 the transfer enthalpy and entropy are shown for the initial state and the transition state. As can be seen, the transfer Gibbs energies of the initial state and the

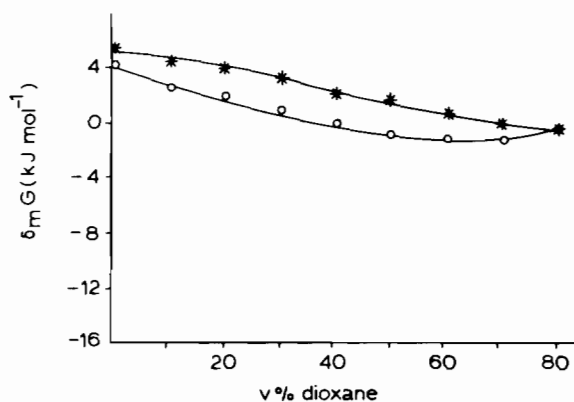


Fig. 2. Transfer Gibbs energy for the initial state (O) and transition state (\*) for the reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with tu in dioxane–water mixtures at 298.15 K. e.s.d. =  $0.5 \text{ kJ mol}^{-1}$ .

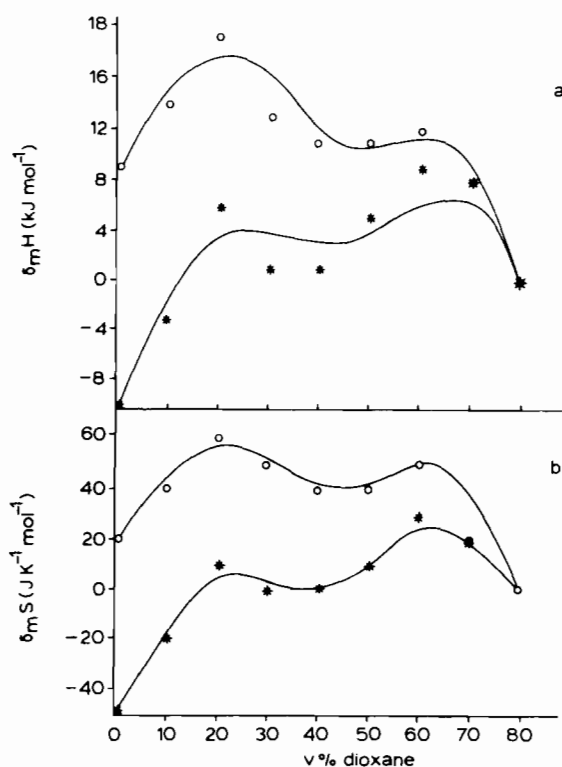


Fig. 3. Transfer enthalpy (a) and transfer entropy (b) for the initial state (O) and transition state (\*) for the reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with tu in dioxane–water mixtures. e.s.d.  $\delta_m H$ :  $3 \text{ kJ mol}^{-1}$  (i.s.),  $4 \text{ kJ mol}^{-1}$  (t.s.),  $\delta_m S$ :  $9 \text{ J K}^{-1} \text{ mol}^{-1}$  (i.s.) and  $11 \text{ J K}^{-1} \text{ mol}^{-1}$  (t.s.).

transition state are a result of large compensating contributions of the transfer enthalpy and entropy. The changes in transfer enthalpy and entropy of the initial state and the transition state are smaller than in the case of the reactions of vitamin  $\text{B}_{12}$  [2]. In the case of the reaction of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with tu the differences between the initial state and the

transition state are larger than the overall changes in the initial state and the transition state. Therefore in this case, clear differences between a model compound and vitamin B<sub>12</sub> are found, both in the change in reactivity when the solvent composition is changed and also in the changes of the activation parameters.

#### Activation Volumes

By measuring the influence of pressure on the rate constant of a reaction, it is possible to obtain the activation volume ( $\Delta V^\ddagger$ ), the difference between the molar volume of the initial state and the transition state. From  $\Delta V^\ddagger$ , inferences can be made about the reaction mechanism more directly than from  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ . The experimental volume of activation ( $\Delta V_{\text{exp}}^\ddagger$ ) can be thought to consist of two components [13]: the intrinsic volume contribution from the nuclear displacements at the reaction centre ( $\Delta V_{\text{intr}}^\ddagger$ ) and the volume contributions associated with rearrangement of solvent molecules ( $\Delta V_{\text{solvent}}^\ddagger$ ). For complexes with anionic leaving groups, the electrostriction of the solvent molecules usually dominates  $\Delta V_{\text{exp}}^\ddagger$ . In some cases the activation volume itself is also pressure dependent, resulting in a quadratic dependence of  $\ln k_{\text{obs}}$  versus pressure.

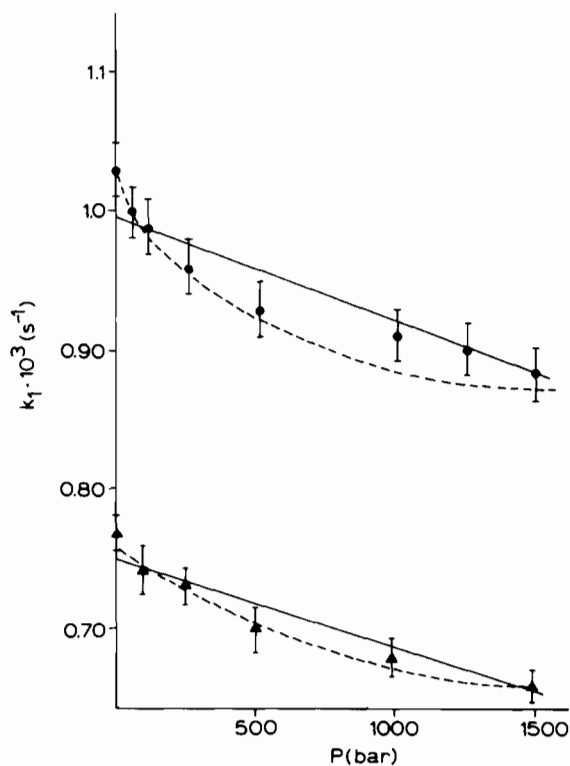


Fig. 4. Ligation rate constants for the reactions of  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  with tu as a function of pressure in water (●) and 20 vol.% dioxane–water (▲). Least-squares fitting curves for a linear (—) and a quadratic relationship (-----) are also displayed.

For a dissociative reaction a positive activation volume is expected [13], when  $\Delta V_{\text{solvent}}^\ddagger$  is small. For the reaction of  $[\text{B}_{12}-\text{H}_2\text{O}]^+$  with  $\text{I}^-$  at 25 °C, activation volumes were measured by Hasinoff [14]:  $\Delta V_1^\ddagger = 5.5 \text{ cm}^3 \text{ mol}^{-1}$ ,  $\Delta V_{-1}^\ddagger = 11.5 \text{ cm}^3 \text{ mol}^{-1}$ . The positive volumes of activation are consistent with a dissociative mode of activation. The negative reaction volume ( $\Delta V = -5.8 \text{ cm}^3 \text{ mol}^{-1}$ ) cannot be explained in terms of electrostriction. Generally, charge neutralization is accompanied by an increase in volume due to the release of electrostricted water. For the aquation of  $[\text{Co}(\text{dmg})_2\text{Cl}(\text{urea})]$  an activation volume of  $3.5 \text{ cm}^3 \text{ mol}^{-1}$  was found [15].

For the model compound  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$ , the activation volume for the reaction with tu was determined at 35 °C. The pressure effects are small and therefore it was not possible to distinguish statistically between a linear or a quadratic pressure dependence (Fig. 4). A similar problem occurred for the system studied by Hasinoff [14]. Both in water and in 20 vol.% dioxane–water a small positive activation volume was found, both for the linear ( $2.3 \text{ cm}^3 \text{ mol}^{-1}$ ) and quadratic ( $4.4 \text{ cm}^3 \text{ mol}^{-1}$ ) relationship. In the latter case a change in compressibility of the transition state of  $3 \times 10^{-3} \text{ cm}^3 \text{ mol}^{-1} \text{ bar}^{-1}$  was found. This is in accordance with a dissociative or dissociative interchange mechanism. In other mixtures of dioxane–water the same kind of pressure dependences were found, but activation volumes were not calculated because of the poor accuracy of the data in these mixtures.

It can be concluded that the activation volumes indicate a similar mode of activation for both vitamin B<sub>12</sub> and the model compound  $[\text{Co}(\text{dmg})_2\text{NO}_2\text{H}_2\text{O}]$  in their axial ligand substitution reactions, at least in water. This is contrary to the negative entropy of activation found for the reaction of the model compound. It must be noted, however, that the sign of the entropy of activation is reversed already when 20 vol.% dioxane is added.

#### Supplementary Material

Tables of solubility combined with kinetic data are available from the authors on request.

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