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Mechanism of the Reactions of Dichloromethionineplatinum(II) with L-Methionine

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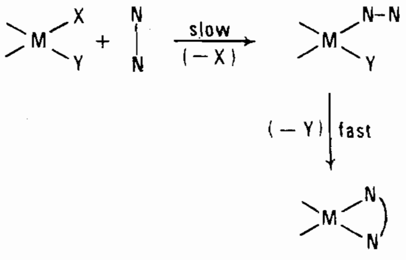
L-Methionine reacts with [Pt(L-methionine)Cl₂] to give [Pt(L-methionine)₂]Cl₂. A kinetic study under pseudo-first-order conditions in aqueous solution shows that this reaction takes place in two consecutive steps. The rate of the first step depends on the concentration of the entering aminoacid and on the concentration of chloride ion. The rate of the second step is a linear function of inverse hydrogen ion concenteration and the step is interpreted as involving closure of the methionine ring. The rate constant for ring closure is 25.1±0.9 sec⁻¹ at 35°C. The results are discussed in terms of trans- *and* chelate-effect.

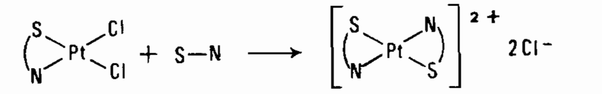
Introduction

The few kinetic data available concerning the substitution of 4-coordinate planar d^8-complexes with poly-dentate entering groups are related to ligands having the same donor atom at each "tooth" (*i.e.*, nitrogen), such as ethylendiamine, diethylenetriamine, bipyridyl, and 1,10-phenanthroline.[1,11] In these cases the reaction takes place through attack by one of the teeth on the complex, followed by rapid entrance of the second tooth,[7] accounting for a kinetic *chelate-effect*:



It is possible experimentally to discriminate between the rate of entrance of the two reacting ends of the chelate ligand by a retardation of the ring closure, as occurs for example, on protonation of one of the ends of the chelating agent.[2,11]

In order to check this possibility when the bidentate ligand has two different donor atoms, we have carried out a kinetic study of the reaction:



where S—N = L-methionine.

This system is related to the general topics of the resolution of racemates *via* complexation of multidentate ligands[12,13] and to the more general problem of the preparation of isomorphous heavy-atom derivatives for protein structure analysis.[14]

To the best of our knowledge, the only example of kinetic study on substitutions on Pt^{II} complexes by aminoacids is concerned with the ring closure in *trans*-$[Pt(Gl)_2Cl_2]^{2-}$ (Gl = glycinate ion) giving *trans*-$[Pt(Gl)_2]$.[15] The results we have obtained in the ring closure of methionine can be compared with those for glycine, and other chelating ligands.

Experimental Section

Materials. Doubly-distilled water was used as the solvent for the kinetics. Anhydrous lithium perchlorate and L-methionine were recrystallized before use. All other materials were of analytical reagent grade.

Dichloro L-methionine platinum(II) was prepared by the reaction of $K_2[PtCl_4]$ with L-methionine in aqueous solution. The i.r. spectrum of the product is identical to that repored in the literature.[16,17] *Anal.* Calcd for $C_5H_{11}Cl_2NSO_2Pt$: C, 14.47; H, 2.67; N, 3.37; Cl, 17.09. Found: C, 14.60; H, 2.60; N, 3.40; Cl, 16.80.

Bis(L-methionine)platinum(II) dichloride dihydrate, $[Pt(S-N)_2]^{2+}$ $2Cl^-$. $2H_2O$, was prepared by the reac-

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(1) For a survey see: U. Belluco, «Organometallic and Coordination Chemistry of Platinum», Academic Press, Inc., London 1973, Chapter II.

(2) W.J. Louw and W. Robb, *Inorg. Chim. Acta*, *3*, 29 (1969).

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(15) L.M. Volshtein and T.R. Lastushkina, *Russ. J. Inorg. Chem.*, *15*, 1267 (1970).

(16) L.M. Volshtein and M.F. Mogilevkina, *Dokl. Akad. Nauk. SSSR*, *142*, 1305 (1962); *163*, 1385 (1965).

tion of $[Pt(S\text{–}N)Cl_2]$ with an equimolar amount of L-methionine in aqueous solution:[18] *Anal.* Calcd for $C_{10}H_{26}Cl_2N_2S_2O_6Pt$: C, 20.02; H, 3.69; N, 4.67; Cl, 11.82. Found: C, 20.40; H, 3.70; N, 4.80; Cl, 12.00.

Kinetic Experiments. The kinetics were followed by measuring the absorbance changes in the spectral region 360-230 mμ with a Beckman DK2A or an Optica CF_4 recording spectrophotometer equipped with a thermostatted cell compartment. The $[Pt(S\text{–}N)Cl_2]$ and L-methionine solutions were thermostated in a water bath were temperatures were controlled within ±0.1°C. The reaction mixtures were prepared by adding a known volume of stock L-methionine solutions to the aqueous solutions of $[Pt(S\text{–}N)Cl_2]$. All the kinetic runs were carried out under pseudo-first-order conditions by the use of an excess of the entering aminoacid. The ionic strength was kept constant by addition of lithium perchlorate. Some sets of runs were carried out at various pH values, the pH being held constant within each set. The desired pH values were obtained with the appropriate conventional buffer systems (acetic acid/sodium acetate; total buffer concentration $5\times10^{-2}\,M$) and checked with a glass electrode.

Results

During the reaction the spectrum of the mixture rapidly changes from I to III and then very slowly to II (Figure 1). Spectrum I refers to a solution of the starting compound, $[Pt(S\text{–}N)Cl_2]$, without any lythium chloride added; it depends on the concentration of added chloride. The initial reaction solution may therefore contain $[Pt(S\text{–}N)Cl_2]$ and other species.

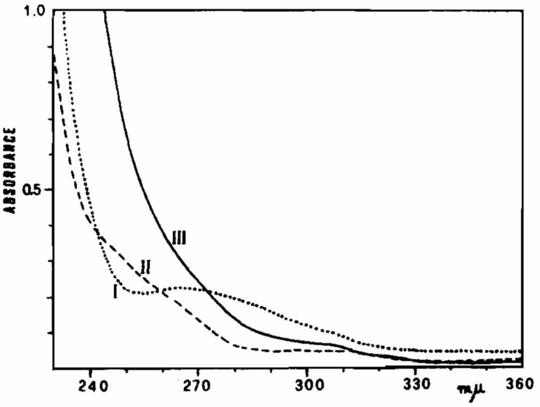
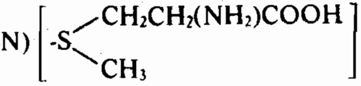


Figure 1. Spectral changes for the reaction of $[Pt(N\text{–}S)Cl_2]$ with N–S. Initial complex concentration = 2×10^{-4}, *M*.

Spectrum II refers to the final complex $[Pt(S\text{–}N)_2]^{2+}2Cl^-$, (**2**) which has a *trans*-disulfur configuration;[18] III is the approximate spectrum of the proposed S-bonded intermediate



$$\{Pt(S\text{-}N)\left[\text{-}S\begin{matrix}\diagup CH_2CH_2(NH_2)COOH\\ \diagdown CH_3\end{matrix}\right]Cl\}^+Cl^-,\ (\mathbf{3})$$

This was scanned by allowing the reaction to proceed under kinetic conditions for 1 minute, a time which is sufficient for the first stage of the reaction to reach completion. This spectrum is indipendent of the chloride ion added.

Therefore, the reaction proceeds according to the following scheme

$$\begin{tikzcd} \textit{Starting species} \arrow[r, "k'_{obs}(+S\text{–}N)"] & \text{Intermediate } \mathbf{3} \arrow[d, "k''_{obs}"] \\ & {[Pt(S\text{–}N)_2]^{2+}2Cl^-}\ \mathbf{2} \end{tikzcd} \qquad (1)$$

The pseudo-first-order rate constant (k'_{obs}, sec^{-1}) for the first stage were obtained from conventional plots of $\log(A_t\text{-}A_\infty)$ *vs.* time, where A_t is the absorbance of the reacting mixture at a given time t and A_∞ is the absorbance of the intermediate, at the same wavelength (*i.e.*, at 250 mμ), at pH 5.30. The values of the pseudo-first-order rate constants are independent of the wavelength used. In some experiments the two steps of the overall reaction were also resolved by Guggenheim's method,[19] the two sets of constants being in satisfactory agreement with each other.

The k'_{obs} values at 25°C depend linearly on the concentration of chloride ion and of L-methionine (Table I). However, the linear plots of k'_{obs} *vs.* the concentration of entering aminoacid display a non-zero intercept (Figure 2). This plot has a slope of 21.7 ± 1.1, $sec^{-1}\,M^{-1}$ and an intercept of $5.3\pm1.0\times10^{-2}$, sec^{-1}.

As for the dependence on the chloride ion, on plotting the inverse k'_{obs} at a constant entering methionine concentration *vs.* the inverse chloride ion concentration, the diagram reported in Figure 3 was obtained with a slope of $8.9\pm0.7\times10^{-2}$, *M* sec and an intercept of 5.2 ± 0.2, sec. This is consistent

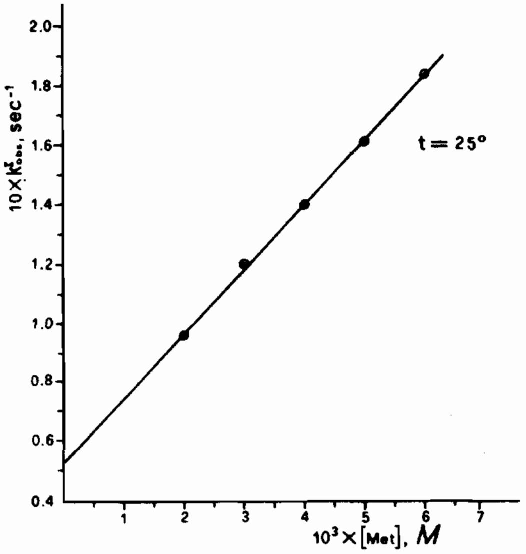


Figure 2. Plot of k'_{obs} *vs.*[Methionine] at constant[Cl] = 5×10^{-2}, *M*.

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(17) C.A. McAuliffe, *J. Chem. Soc. (A)*, 641 (1967).

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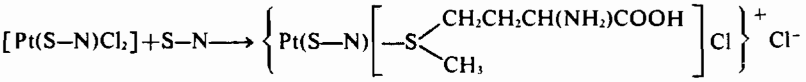
Table I. Pseudo-first-order Rate Constants, k'_{obs}, sec^{-1}, for the Reaction:

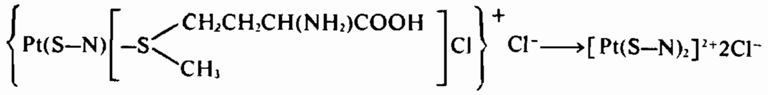


$$[\mathrm{Pt(S{-}N)Cl_2}]+\mathrm{S{-}N}\longrightarrow\left\{\mathrm{Pt(S{-}N)}\left[-\mathrm{S}\begin{array}{l}\diagup\mathrm{CH_2CH_2CH(NH_2)COOH}\\ \diagdown\mathrm{CH_3}\end{array}\right]\mathrm{Cl}\right\}^{+}\mathrm{Cl^-}$$

in Aqueous Solution (Initial Complex concn = $2\times10^{-4}, M$; t = 25°C; μ = 0.4, M)

Entering L-methionine concn, $10^3 M$	k'_{obs}, sec^{-1}	pH	Chloride concn, 10^2 M
2	0.096	5.30	5.0
3	0.120	5.30	5.0
4	0.140	5.30	5.0
5	0.161	5.30	5.0
6	0.184	5.30	5.0
4	0.090	5.30	1.5
4	0.106	5.30	2.0
4	0.111	5.30	2.5
4	0.161	5.30	7.5
4	0.162	5.30	10.0
4	0.177	5.30	20.0
4	0.186	5.30	30.0

Table II. Pseudo-first-order Rate Constants, k''_{obs}, sec^{-1}, for the Ring Closure Reaction:



$$\left\{\mathrm{Pt(S{-}N)}\left[-\mathrm{S}\begin{array}{l}\diagup\mathrm{CH_2CH_2CH(NH_2)COOH}\\ \diagdown\mathrm{CH_3}\end{array}\right]\mathrm{Cl}\right\}^{+}\mathrm{Cl^-}\longrightarrow[\mathrm{Pt(S{-}N)_2}]^{2+}2\mathrm{Cl^-}$$

(pH = 4.20, Initial complex concn = $2\times10^{-4}, M$; μ = 0.1)

L-methionine concn, $10^3 M$	$10^4\times k''_{obs}$, sec^{-1}	temperature °C
2	2.52	26.0
3	2.53	26.0
4	2.52	26.0
6	2.56	26.0
15	2.57	26.0
2	5.32	35.0
4	5.43	35.0
3	5.45	35.0
6	5.46	35.0
3	5.40	35.0
2	12.70	45.0
3	12.80	45.0
4	12.64	45.0
6	12.85	45.0

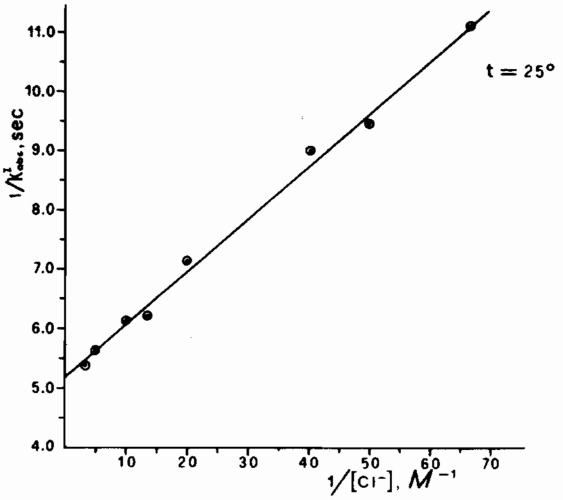


Figure 3. Dependence of $1/k'_{obs}$ from $1/[\mathrm{Cl^-}]$ at constant [Methionine] = $4\times10^{-3}, M$.

with the rate law,

$$1/k'_{obs}=\left\{1+\frac{K}{[\mathrm{Cl^-}]}\right\}\times\left\{\frac{1}{k_1+k_2[\mathrm{Met}]}\right\} \qquad (2)$$

Least-squares analysis of plots in Figures 2 and 3 gave the following values at 25°C and pH 5.30: k_1 = $(7.1\pm1.4)\times10^{-2}$, sec^{-1}; k_2 = 29.1 ± 1.8, sec^{-1} M^{-1}; K = $(17.1\pm0.7)\times10^{-3}$, M.

The pseudo-first-order rate constants for the second step (k^{II}_{obs}, sec^{-1}) were similarly obtained from absorbance changes in the range 240-310 mμ which were associated with the conversion of the intermediate (**3**) to the final product (**2**), at a constant pH of 4.20. The rate constants, k^{II}_{obs}, are independent of the concentration of L-methionine (Table II). This second step is also independent of chloride concentration and involves a quantitative reaction. Thus, the kinetic rate law for this step of reaction (1) is:

$$k^{II}_{obs}=constant \qquad (3)$$

The average value of k^{II}_{obs} at pH = 4.20 is 5.4×10^{-4},

Table III. Dependence of the Pseudo-first-order Rate Constants, k''_{obs}(sec^{-1}), on the pH of the Reaction Mixture.

pH	$10^3 \times k''_{obs}$, sec^{-1} [a]
4.10	0.51
4.50	1.20
4.85	1.34
5.00	2.08
5.23	3.36
5.50	5.20
5.57	6.60
5.70	8.10

[a] Values obtained at 35°C; $[Pt(S{-}N)Cl_2] = 2.10^{-4}$, M; $[S{-}N] = 4 \times 10^{-3}$, M; $\mu = 0.2$.

sec^{-1} at 35°C. The k''_{obs}'s are also dependent on proton concentration and the values obtained at different pH values are set out in Table III.

In both the starting complex and the reaction product the coordinated L-methionine molecule has two assymmetric centres, the sulfur and the carbon atom. As for the sulfur atom, there are two equally probable bonding modes to the platinum, corresponding to opposite chiralities about the sulfur.

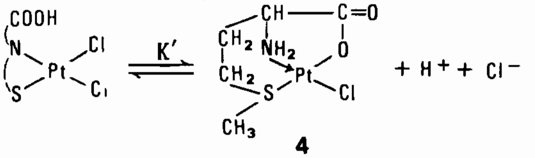
Relating to the assymmetry associated with the carbon atom, no racemization occurs in the starting complex, which is shown by crystal structure determination to be [Pt(L-methionine)Cl_2].[20] We recall that in the case of H_2[Pt(L-Glutamate)$_2$] the racemization of the coordinated ligand was found to be slow even at high pH values.[21]

Thus, the rates as measured under the above experimental conditions (relatively low pH and ambient temperature), refer to the entrance of L-methionine on the starting complex [Pt(L-methionine)Cl_2], the racemization of either free or coordinated aminoacid being prevented.

No significant changes in the rates of reaction (1) were observed when the D-isomer or the DL-racemic mixture of methionine were used instead of the L-isomer.

Discussion

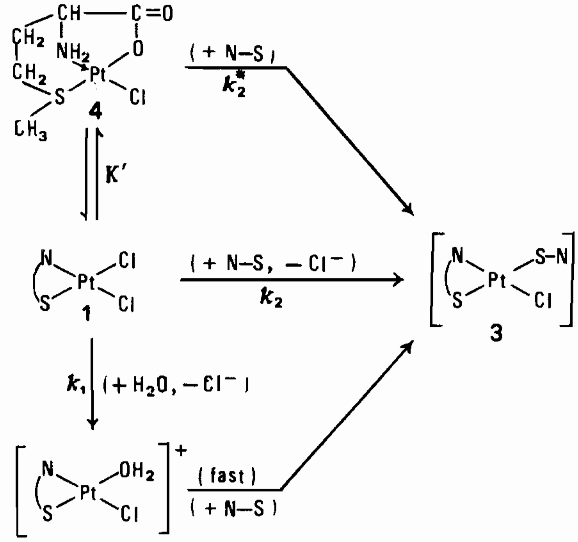
It has been reported that methionine can act as a tridentate ligand through coordination of the carboxylate group.[22] Therefore, in aqueous solution the equilibrium (**4**) is established;



(4)

In fact, changes have been observed in the spectrum of compound (**1**) in aqueous solution in the region 350-240 mμ on changing the chloride concentration and/or the pH.

The complex (**4**) is less reactive towards the entering L-methionine than the parent dichloro complex, and the rate constant for substitution of a polydentate ligand has been shown to be lower that the corresponding rate of a monodentate ligand.[7] Accordingly, mechanism (5) is proposed for the first step of reaction (1).



(5)

This mechanism is in ageement with the rate law (2), if the contribution of k_2^* to the reaction rate is neglected, on accounts of the lower reactivity of compound (**4**) relative to compound (**1**).

The value of $k_2 = 29.1 \pm 1.8$, sec^{-1} M^{-1}, is considerably higher than the corresponding value found for the substitution of Cl^- in [Pt(bipy)Cl_2] by thioethers in methanol,[23,24] and this is related to the higher *trans-effect* of sulfur relative to nitrogen in these systems.[25] K′ in (4) and (5) is related to K in eq. (2) by the relationship: $K' = K \times [H^+]$.

As for the second step of the reaction (k''_{obs}, sec^{-1}, equation (3)) this is interpreted as involving the closure of the methionine ring, as shown in scheme (6).

The activation parameters, calculated from the average values of k''_{obs} pH = 4.20, are $\Delta H^* = 15.4$

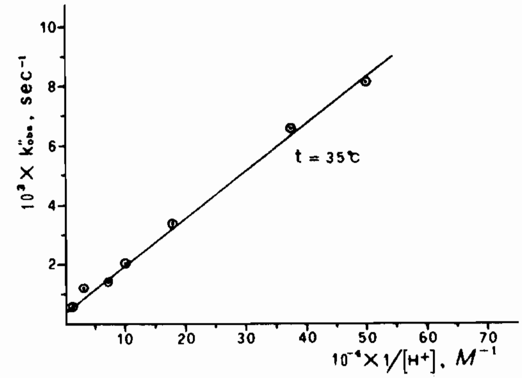


Figure 4. Dependence of k''_{obs} from 1/[H^+] at 35°C.

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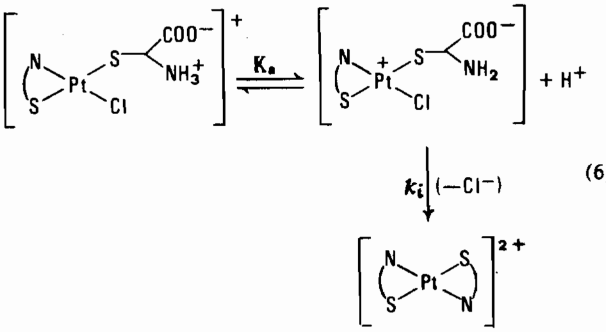
($\pm$0.3) kcal/mole, and $\Delta S^* = -23$ ($\pm$1) e.u.

The ring closure in *trans*-$[Pt(Gl)_2Cl_2]^{2-}$ was found to be slow and this was explained in terms of the *trans*-effect of Cl^- and the low nucleophilic of the group $-COO^-$.[15] In our case, however, the slowness of the ring closure is only apparent. In fact, the reacting amine group of L-methionine is almost completely protonated under the experimental conditions used. Consistently, the rate constants k^{II}_{obs} increase wih increasing pH.

The k^{II}_{obs}'s at different pH values at 35°C are reported in Table III. On plotting these rate constants *vs.* $1/[H^+]$ in the pH range 5-6 a satisfactory straight line is obtained with a slope of $(15.5\pm0.5\times 10^{-9}$, *M.* sec^{-1} (Figure 4). Owing to the fact that the free amine group must be unprotonated in order to attack the platinum, the following reaction scheme is proposed:



(6)

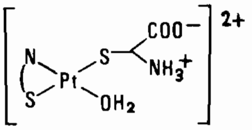
The slope of the plot of k^{II}_{obs} *vs.* $1/[H^+]$ is $K_a k_i$, according to the equation:

$$k^{II}_{obs} = k_S + \frac{K_a k_i}{K_a + [H^+]} \tag{7}$$

where K_a is negligible in the pH range examined.

To the extent that the K_a may be assumed to be the same for both free and sulfur-coordinated L-methionine (*i.e.* $pK_a = 9.21$), the true rate constant for the ring closure at 35°C is calculated $k_i = 25.1 \pm 0.9$ sec^{-1}. In any case, whatever the K_a, this value is comparable with that obtained in the ring closure of $[Pt(enH)_2Cl_2]^{2+}$ where a large kinetic *chelate-effect* was found,[11] and it seems clear from this study that this effect is operative in the amino acid ring closure of Pt^{II}.

From the plot of Figure 4 the extrapolated intercept is $k_S = (4.9\pm1.4)\times 10^{-4}$, sec^{-1}. Although this value is not reliable owing to its large standard deviation, it might be rationalized as corresponding to a solvent contribution to the rate of the second step of reaction (1) *via* formation of a solvated species such as



as in classical Pt^{II} substitution reactions.[1]

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