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Mechanistic Insight from a Volume Profile for Electron Transfer between Promazine and Hexaaquairon(III)

Joanna Wiśniewska[†] and Rudi van Eldik*

Institute for Inorganic Chemistry, University of Erlangen-Nürnberg, Egerlandstr. 1,
91058 Erlangen, Germany

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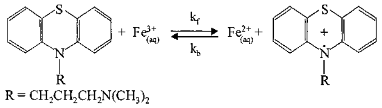
The kinetics of the outer-sphere electron-transfer reaction between promazine (dimethyl-(3-phenothiazin-10-yl-propyl)-amine) and hexaaquairon(III) was studied using a high-pressure stopped-flow technique. The effect of pressure (over the range 0.1–130 MPa at 25 °C and ionic strength 1.0 M) on the reaction rate in aqueous perchloric acid solution resulted in volumes of activation of –6.2 ± 0.4 and –12.5 ± 0.5 $cm^3\ mol^{-1}$ for the forward and reverse processes, respectively. The effect of pressure on the overall equilibrium constant revealed a reaction volume of +5.0 ± 0.2 $cm^3\ mol^{-1}$. The reported volume profile reveals mechanistic information on the electron-transfer process in terms of volume changes along the reaction coordinate. The volume of activation for the promazine/promazine$^{+\bullet}$ self-exchange reaction was calculated on the basis of the Marcus cross relationship.

Kinetic studies on the redox behavior of organic compounds in the presence of metal complexes play an important role in the understanding of electron-transfer reaction mechanisms, in general, and provide more information on the redox properties of the organic species, in particular. N-Substituted phenothiazines are a pharmaceutically important class of tricyclic compounds. These compounds modulate a variety of biochemical processes such as the uptake of norepinephrine, dopamine, and acetylcholine neurotransmission, and the biological effect of histamine.[1] One of the recent studies on the pharmacological activities of phenothiazines reports on their efficiency to affect the antibiotic resistance of bacteria and tumor cells.[2] As a result of new pharmacological investigations, they are applied as antiarrhythmic drugs, lipid peroxidation inhibitors, and photodynamic virus inactivators.[3] Their low oxidation potential and the formation of stable radical cations are important reasons for their physiological activities.[4,5] In terms of their chemical behavior, the analysis of redox and photolytic properties remains important.

Pelizzetti et al.[6] reported kinetic and equilibrium data for the electron-transfer reaction of hexaaquairon(III) with a series of phenothiazines. Our study reveals further mechanistic details on the basis of a volume profile constructed from high-pressure kinetic and thermodynamic data. The electron-transfer reaction between promazine (dimethyl-(3-phenothiazin-10-yl-propyl)-amine) and hexaaquairon(III) occurs according to the overall reaction presented in Scheme 1.

Scheme 1



In this reaction, the second-order rate constants, k_f and k_b, are quantities of the same order of magnitude, viz. 1.3 × 10^2 and 1.0 × 10^2 $M^{-1}\ s^{-1}$ at 25 °C, respectively.[6] All kinetic measurements were performed under pseudo-first-order conditions; that is, both the Fe^{III} and Fe^{II} concentrations were in at least 10-fold excess. The rate law can then be expressed by eq 1, in which the observed pseudo-first-order rate constant, k_{obs}, is related to the selected concentrations of both Fe^{III} and Fe^{II}.

$$k_{obs} = k_f[Fe^{III}] + k_b[Fe^{II}] \qquad (1)$$

A high-pressure stopped-flow instrument with spectrophotometric detection was used to study the pressure dependence of the reaction. The rate of the electron-transfer reaction was determined by monitoring the increase in absorbance of the promazine radical at 514 nm as a function of Fe^{III} concentration and pressure ($[Fe^{III}] = (1-5) \times 10^{-3}$ M, $[Fe^{II}] = 1 \times 10^{-3}$ M, [promazine] $= 1 \times 10^{-4}$ M, pH = 0, $I = 1.0$ M ($HClO_4$), $T = 25$ °C, pressure = 10, 50, 90, 130 MPa, $l = 1$ cm). The results are presented in Figure 1. From the linear plots of k_{obs} versus $[Fe^{III}]$, the second-order rate constant for the forward reaction, k_f, can, according to eq 1, be obtained from the slope, and the second-order rate constant for the back reaction, from the intercept, viz.

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* To whom correspondence should be addressed. E-mail: vaneldik@chemie.uni-erlangen.de.

[†] On leave from the Department of Chemistry, Nicholas Copernicus University, Gagarina 7, 87-100 Toruñ, Poland.

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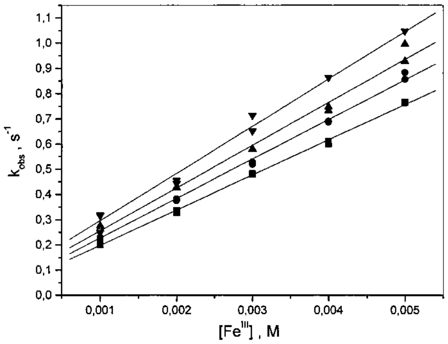

Figure 1. Plots of k_{obs} versus [Fe^{III}] for the electron-transfer reaction between promazine and hexaaquairon(III) at different pressures. Experimental conditions: [promazine] = 1×10^{-4} M, [Fe^{III}] = $(1-5) \times 10^{-3}$ M, [Fe^{II}] = 1×10^{-3} M, pH = 0, $I = 1.0$ M ($HClO_4$), $T = 25$ °C, pressure = 10 (■), 50 (●), 90 (▲), 130 (▼) MPa.

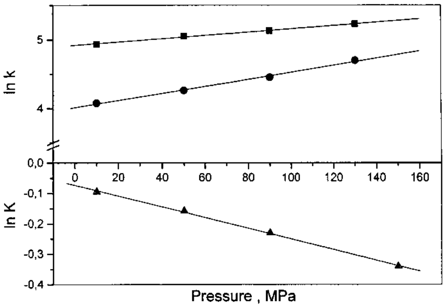

Figure 2. Plots of ln(k_f) (■), ln(k_b) (●), ln(K) (▲) versus pressure for the electron-transfer reaction between promazine and hexaaquairon(III). Experimental conditions: [promazine] = 1×10^{-4} M, [Fe^{III}] = $(1-5) \times 10^{-3}$ M, [Fe^{II}] = 1×10^{-3} M, pH = 0, $I = 1.0$ M ($HClO_4$), $T = 25$ °C.

k_b[Fe^{II}]. As expected, the error limits of the intercepts are much larger than those of the slopes (see Table S1, Supporting Information). Both k_f and k_b increase significantly with increasing pressure, which means that the transition state of the redox reaction occupies a smaller partial molar volume than either the reactant or product states. The corresponding volumes of activation, $\Delta V^{\ddagger}$, were calculated from the slopes ($=-\Delta V^{\ddagger}/RT$) of ln(k_f) and ln(k_b) versus pressure, as shown in Figure 2, from which it follows that $\Delta V^{\ddagger}(k_f) = -6.2 \pm 0.4$ cm^3 mol^{-1} and $\Delta V^{\ddagger}(k_b) = -12.5 \pm 0.5$ cm^3 mol^{-1}. Because the overall equilibrium constant for reaction 1 can be expressed as $K = k_f/k_b$, the overall reaction volume can be expressed as $\Delta V = \Delta V^{+}(k_f) - \Delta V^{+}(k_b) = +6.3 \pm 0.7$ cm^3 mol^{-1}; that is, there is a significant volume increase during the redox process.

The effect of pressure on the overall equilibrium (Scheme 1) was studied by recording UV−vis spectra of an equilibrium mixture as a function of pressure as shown in Figure 3. The recorded spectra of the promazine radical indicate that the overall equilibrium in Scheme 1 is shifted to the left on increasing the pressure, that is, K decreases on increasing pressure. The values of the equilibrium constant, K, were determined on the basis of the observed spectral data ([promazine] = 1×10^{-4} M, [Fe^{III}] = 2×10^{-3} M, [Fe^{II}] = 1×10^{-3} M, pH = 0, $I = 1.0$ M ($HClO_4$), $T = 25$ °C, pressure = 10, 50, 90, 150 MPa, $l = 1.5$ cm, see Table S2, Supporting Information) and are plotted as a function of pressure in Figure 2. The overall reaction volume, ΔV, calculated from the pressure dependence of ln(K), was found to be $+5.0 \pm 0.2$ cm^3 mol^{-1}, which is acceptably close to the reaction volume calculated from the activation volume data previously described and again indicates a significant overall volume increase during the electron-transfer reaction. This result is also consistent with the positive reaction entropy reported for the overall equilibrium, viz. $+58 \pm 17$ J K^{-1} mol^{-1}, in the literature.[6]

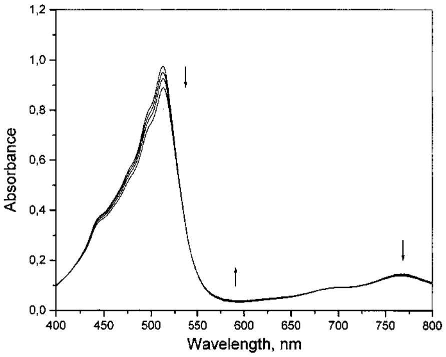

Figure 3. UV−vis spectra as a function of pressure for the equilibrium promazine + Fe^{3+}(aq) $\rightleftharpoons$ promazine$^{+\bullet}$ + Fe^{2+}(aq). Experimental conditions: [promazine] = 1×10^{-4} M, [Fe^{III}] = 2×10^{-3} M, [Fe^{II}] = 1×10^{-3} M, pH = 0, $I = 1.0$ M ($HClO_4$), $T = 25$ °C, pressure = 10, 50, 90, 150 MPa, optical path length = 15 mm.

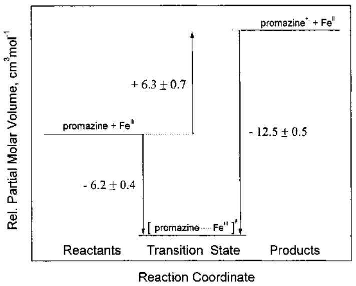

Figure 4. Volume profile for the reaction promazine + Fe^{3+}(aq) promazine$^{+\bullet}$ + Fe^{2+}(aq).

The reaction is suggested to proceed according to an outer-sphere electron-transfer mechanism.[6] This is supported by the fact that the rate constant is independent of the [H^+] in the pH range 0−2.[6] In the case of an inner-sphere electron-transfer mechanism, the rate constant is expected to increase significantly with decreasing [H^+] because of the formation of the monohydroxoiron(III) complex which is known to be significantly more labile than the hexaaquairon(III) complex.[7] The volume profile for the overall redox reaction based on the kinetic data (reported in Figure 4) clearly shows that the transition state has a smaller partial molar volume than either the reactant or product states. In contrast, the overall reaction volume is significantly positive, which suggests that the overall reaction involves "charge dilution" in going from Fe^{3+}(aq) and promazine to Fe^{2+}(aq) and the promazine cation radical, and "charge concentration" (increase in electrostriction) in the opposite direction of the redox process. The compact nature of the transition state, which is more prominent for the back than for the forward electron-transfer reaction, suggests that a significant volume collapse is associated with the redox process in the transition state. This could be due to the formation of a precursor contact pair in

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both the forward and back reactions, where the volume decrease associated with such a process will be more significant for the back reaction because of the additional effect of charge concentration and the associated increase in electrostriction. Alternatively, the value of $\Delta V^{\ddagger}(k_b)$ is very close to the half-cell reaction volume reported for the oxidation of hexaaquairon(II) as determined from the pressure dependence of its redox potential, viz. -14 ± 1 cm^3 mol^{-1} in 1.0 M $HClO_4$.[8] The latter value was attributed to equal contributions from an intrinsic volume collapse and an increase in electrostriction in going from Fe^{2+}(aq) to Fe^{3+}(aq). Furthermore, the value of $\Delta V^{\ddagger}(k_f)$ can be attributed to an increase in electrostriction during the formation of the promazine cation radical. On the basis of these arguments, it can be suggested that the transition state has an iron(III)−promazine cation radical character.

Results available from the literature[6] reveal that the thermal activation parameters for the forward reaction are $\Delta H^{\ddagger} = 41 \pm 5$ kJ mol^{-1} and $\Delta S^{\ddagger} = -67 \pm 17$ J K^{-1} mol^{-1}, and for the slower reverse reaction, $\Delta H^{\ddagger} = 24 \pm 5$ kJ mol^{-1} and $\Delta S^{\ddagger} = -125 \pm 17$ J K^{-1} mol^{-1}. The sign and magnitude of the activation entropies nicely parallel those of the activation volumes reported here and indicate that an increase in electrostriction plays a major role especially in the back reaction. Thus, solvent rearrangement and precursor formation prior to the actual electron-transfer step must account for the compact nature of the transition state in both directions of the process. Volume contributions from intrinsic volume changes associated with the redox process are not expected for the oxidation of promazine because changes in the chemical bond length in the phenothiazine species are small and negligible,[9] but reduction of Fe^{3+}(aq) has been suggested to involve an intrinsic volume increase of ca. 7 cm^3 mol^{-1}.[8] By way of comparison, volume profiles for intermolecular electron-transfer reactions between cytochrome *c* and a series a ruthenium ammine complexes[10] indicated that the transition state for the reversible electron-transfer reaction is located exactly halfway between the reactant and product states in terms of volume changes along the reaction coordinate. In this case, the volume changes are controlled by changes in electrostriction as a result of the reduction or oxidation of the Ru ammine complexes.[11]

On the basis of the Marcus−Hush theory,[12−15] we were also able to calculate the volume of activation for the self-exchange reaction of the promazine/promazine$^{+\bullet}$ couple, $\Delta V^{\ddagger}_{22}$, from the reaction and activation volumes for the cross-reaction determined in this study, and the activation volume for the self-exchange reaction of the $Fe^{3+/2+}$ couple, $\Delta V^{\ddagger}_{11}$, according to eq 2, where $\Delta V^{\ddagger}_{11} = -11.1$ cm^3 mol^{-1},[16] $\Delta V^{\ddagger}_{12} = -6.2$ cm^3 mol^{-1}, and $\Delta V_{12} = +6.3$ cm^3 mol^{-1}.

$$\Delta V^{\ddagger}_{12} = \frac{1}{2}(\Delta V^{\ddagger}_{11} + \Delta V^{\ddagger}_{22} + \Delta V_{12}) \tag{2}$$

The calculated value of $\Delta V^{\ddagger}_{22}$, viz. -7.6 cm^3 mol^{-1}, indicates that the self-exchange electron-transfer process is characterized by a significantly negative activation volume that is very similar to the activation volume found for the forward electron-transfer reaction with aquated Fe^{III}. In a similar way, the back reaction in Scheme 1 exhibits almost the same volume of activation as found for the self-exchange reaction of $Fe^{3+/2+}$. The comparison of the activation volumes for the forward and reverse cross reactions in Scheme 1 with those for the self-exchange reactions of the two redox partners suggests that the oxidation of promazine seems to control the volume changes associated with the forward reaction, whereas the oxidation of iron(II) seems to control the volume changes associated with the back reaction. To our knowledge, this is the first time that such a correlation has been observed for reversible cross reactions. Precursor formation and changes in solvent electrostriction must be the major source of the observed volume changes associated with the reorganization of the molecules prior to the actual transfer of an electron in the transition state.

All chemicals were AR grade quality and were used without further purification. $HClO_4$ (60%), $Fe(ClO_4)_3$, and $Fe(ClO_4)_2$ were supplied by Aldrich. Promazine was purchased from Sigma. Aqueous solutions of 2.00 M $HClO_4$, 0.05 M $Fe(ClO_4)_3$ ($I = 2.0$ M, $HClO_4$), 0.05 M $Fe(ClO_4)_2$ ($I = 2.0$ M, $HClO_4$), and 2×10^{-4} M promazine were prepared using deionized water.

UV−vis spectra were recorded on a Shimadzu UV-2101 PC spectrophotometer. Stopped-flow kinetic measurements were performed on an Applied Photophysics SX 18 MV stopped-flow spectrophotometer coupled to an online data acquisition system. High-pressure stopped-flow kinetic measurements were carried out on a homemade high-pressure stopped-flow system.[17] Further experimental details on the kinetic and thermodynamic measurements are given as Supporting Information.

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Supporting Information Available: Two tables reporting the effect of pressure on the forward rate constant, the reverse rate constant, and the overall equilibrium constant of reaction 1. Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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