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Kinetics of Mercuration of 2- and 4-Methyl-containing Salts of Heterocyclic Cations

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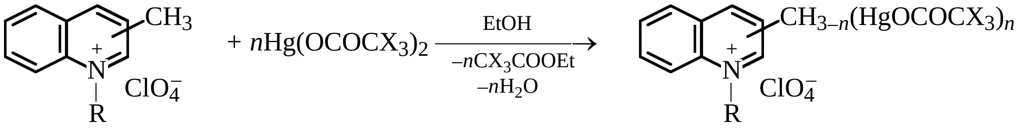
Abstract—Kinetics of the monomercuration by the active methyl groups of 2- and 4-methyl-containing salts of quinolinium, pyridinium, benzothiazolium, and pyrrilium with mercury(II) acetate and trifluoroacetate in a mixture of anhydrous ethanol and acetonitrile (3 : 1) at 50–70°C were studied by means of acid–base potentiometric titration. The apparent second-order rate constants of these reactions were estimated, and factors affecting their rate were considered. A mechanism of the reactions was offered.

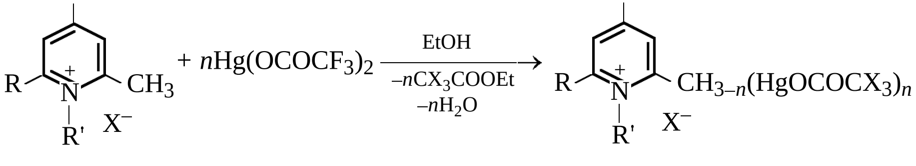
Previously we accomplished [1] numerous mercurations of 2- and 4-methyl-containing salts of heterocyclic cations to obtain 2- and 4-methylenemercurated compounds in high yields. The latter present a preparative interest in organic synthesis and hold promise as potential biologically active compounds [2]. Developing this research and aiming at elucidating structure–reactivity relationships for 2- and 4-methyl-containing salts of heterocyclic cations in the present work we have studied the kinetics and mechanism of the above-mentioned reaction.

Mercuration of a series of quaternary salts of quinolinium (**I**–**IV**), pyridinium (**V**–**VII**), benzothiazolium (**VIII**), and pyrrilium (**IX**–**XIII**) salts containing active methylene groups in positions 2 and 4 of the heteroring was chosen as an object for study. In the previous works [2–5] we found that the above-mentioned salts (mainly as perchlorates and tetrafluoroborates) all are eagerly mercurated with mercury(II) acetate and trifluoroacetate when refluxed in anhydrous ethanol. Under these reactions conditions, depending on the reagent molar ratio, mono-, di-, and trimercuration products are formed by the substitution of hydrogen atoms of the active methyl groups by mercury-containing groups according to the following schemes.



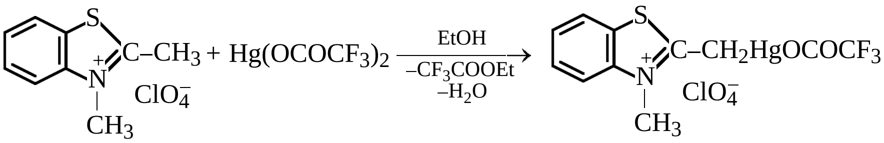
I–**IV**

4-CH_3 (**I**), 2-CH_3 (**II–IV**); R = C_6H_5 (**I, II**), CH_3 (**III**), C_2H_5 (**IV**); X = H, F; n = 1–3.

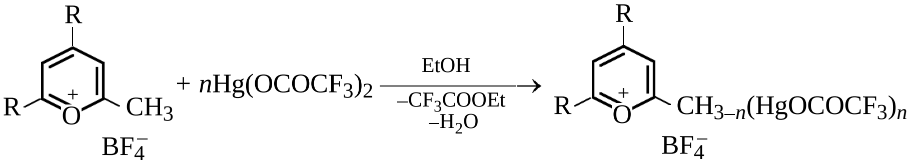


V–**VII**

R = H (**V**), C_6H_5 (**VI**), 4-$CH_3OC_6H_4$ (**VII**); R' = C_2H_5 (**V**), CH_3 (**VI, VII**); X = ClO_4 (**V**), BF_4 (**VI, VII**); n = 1–3.



VIII



IX–XIII

R = CH_3 (**IX**), 4-$CH_3OC_6H_4$ (**X**), 4-$C_2H_5OC_6H_4$ (**XI**), 4-$C_4H_9OC_6H_4$ (**XII**), 4-*i*-$C_4H_9OC_6H_4$ (**XIII**); *n* = 1–3.

The starting reagents, salts **I**–**XIII**, mercury(II) acetate and trifluoroacetate, and mercury(II) bromide and chloride, were prepared for kinetic measurements according to published procedures (see references in [3–6]). The reagent molar ratio (concentration 10^{-1}–10^{-3} M) for kinetic measurements was 1:1. The mercuration rate was followed by the acid contents of the samples taken from the reaction mixture and analyzed by nonaqueous potentiometric titration with a standard solution of sodium ethoxide in anhydrous ethanol.

The reaction of quinolinium salts **I, II** with mercury(II) trifluoroacetate was used as a model reaction in special experiments. It was established that the rates of the mercuration reactions were convenient to measure only if the reactions were carried out above 50°C in a mixture of anhydrous acetonitrile and ethanol (3:1, v/v). In other aprotic solvents, such as dimethylformamide, dimethyl sulfoxide, and pure acetonitrile, no reaction was observed. By contrast, the reaction rates in anhydrous ethanol were sufficiently high, but the evolving trifluoroacetic acid was deeply esterified with ethanol to give ethyl trifluoroacetate. In preparative mercuration reactions [3–5], the yield of ethyl trifluoroacetate was 70–80% (GLC data).

The kinetics of monomercuration of salts **I**–**XIII** in the temperature range 50–70°C at various reagent ratio (under pseudo-first-order reaction conditions) point to a second overall reaction order, first in each components. This is confirmed by a linear dependence of the reciprocal current concentration on time. Therefore, with equal initial concentrations of salts **I**–**XIII** and the mercurating agent we estimated the apparent second-order reaction rate constants (k_{app}) by the following formula [7].

$$k_{\mathrm{app}} = \frac{1}{t}\frac{x}{a(a-x)}.$$

Here t is the reaction time, s, a is the initial reagent concentration equal to 10^{-3} M, x is the current reagent concetration, M, obtained by potentiometric titration.

The resulting k_{app} values for compounds **I**–**XIII** at various temperatures and with mercurating agents are listed in the table.

As seen from the table, *N*-alkylquinolinium salts **III, IV** are mercurated slower than *N*-phenylquinolinium salts **I, II**. 2-Methyl-substituted quinolinium salts **II**–**IV** proved to be more active compared with 4-methyl-substituted salt **I**. The mercurating activity of mercury(II) trifluoroacetate was 3–10 times higher compared with mercury(II) acetate, which correlates with the electrophilic activity of these compounds [8].

2-Methylpyridinium salts **V**–**VII** are sufficiently close in reactivity to quinolinium salts **III, IV**, though the latter sometimes prove slightly more reactive. Benzothiazolium salt **VIII** in about 3 times less active in the mercuration reaction compared to quinolinium and pyridinium salts **I**–**IV** and **I**–**IV**. Finally, pyrilium salts **IX**–**XII** are mercurated still slower than salts **I**–**VIII**. Note here that 2,4,6-trimethylpyrilium salt **IX** is about 2–2.5 times more active than 4,6-diaryl-substituted salts **X**–**XIII**, which is evidently connected with different thermodynamic stabilities of the transition states of these reactions.

Interesting kinetic results were obtained for mercuration of quinolinium iodides **III, IV** with mercury trifluoroacetate. The salts proved to be scarcely active, and the mercuration rate could only be measured at 70°C and a reagent concentration of 10^{-2} M. In this case, k_{app} was 5.68×10^{-4} and 6.20×10^{-4} for iodides **IV** and **III**, respectively.

The temperature dependence of the reaction rate were used to estimate, by the Arrhenius equation [7], the activation energy (E_a 101.40–123.60 kJ/mol) and

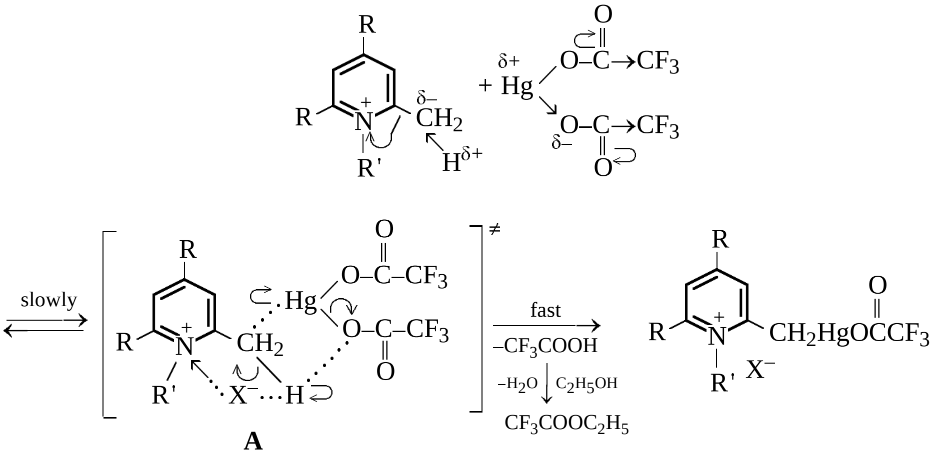
Apparent rate constants of monomercuration of compounds **I**–**XIII**

Comp. no	X in $Hg(OCOCX_3)_2$	k_{app} $l\ mol^{-1}\ s^{-1}$ [a]				
		323 K	328 K	333 K	338 K	343 K
I	H				$(1.12\pm0.02)\times10^{-3}$	$(3.42\pm0.03)\times10^{-3}$
I	F		$(1.96\pm0.02)\times10^{-3}$	$(2.67\pm0.04)\times10^{-3}$	$(4.83\pm0.05)\times10^{-3}$	$(8.91\pm0.06)\times10^{-3}$
II	H				$(2.36\pm0.02)\times10^{-3}$	$(4.72\pm0.04)\times10^{-3}$
II	F	$(3.58\pm0.02)\times10^{-3}$	$(5.92\pm0.02)\times10^{-3}$	$(9.84\pm0.06)\times10^{-3}$	$(1.58\pm0.03)\times10^{-2}$	$(4.61\pm0.03)\times10^{-2}$
III	H			$(1.27\pm0.03)\times10^{-3}$	$(1.96\pm0.03)\times10^{-3}$	$(3.84\pm0.04)\times10^{-3}$
III	F	$(3.37\pm0.02)\times10^{-3}$	$(5.88\pm0.04)\times10^{-3}$	$(9.20\pm0.06)\times10^{-3}$	$(1.42\pm0.04)\times10^{-2}$	$(4.12\pm0.05)\times10^{-2}$
IV	F			$(4.03\pm0.04)\times10^{-3}$	$(8.46\pm0.06)\times10^{-3}$	$(1.28\pm0.07)\times10^{-2}$
V	F			$(3.96\pm0.04)\times10^{-3}$		$(1.36\pm0.06)\times10^{-2}$
VI	F			$(3.21\pm0.03)\times10^{-3}$		$(1.16\pm0.06)\times10^{-2}$
VII	F			$(2.87\pm0.04)\times10^{-3}$		$(9.08\pm0.05)\times10^{-3}$
VIII	F			$(1.09\pm0.03)\times10^{-3}$	$(2.96\pm0.04)\times10^{-3}$	$(4.61\pm0.05)\times10^{-3}$
IX	F				$(9.31\pm0.07)\times10^{-4}$	$(2.00\pm0.05)\times10^{-3}$
X	F				$(3.62\pm0.06)\times10^{-4}$	$(9.83\pm0.08)\times10^{-4}$
XI	F				$(5.86\pm0.04)\times10^{-4}$	$(1.05\pm0.03)\times10^{-3}$
XII	F				$(5.97\pm0.05)\times10^{-4}$	$(1.12\pm0.04)\times10^{-3}$
XIII	F				$(6.18\pm0.06)\times10^{-4}$	$(1.27\pm0.03)\times10^{-3}$

[a] Average of 3–4 measurements

the activation entropy ($\Delta S^{\neq}$ +13.4±1.5 to –44.3± 2.5 $J\ mol^{-1}\ K^{-1}$.

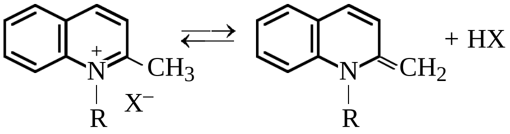
The experimental kinetic data for monomercuration of salts **I**–**XIII** as perchlorates or tetrafluoroborates suggest that the most probable transition state is four-centered of type **A**, in which the mercury atom is three-coordinate. The subsequent fast electron density redistribution in transition state **A** (shown by arrows in the scheme for pyridinium salts as example) leads to corresponding mercury-containing salts of heterocyclic cations and carboxylic acids (CF_3COOH, CH_3COOH) whose at least partial esterification with ethanol shifts the equilibrium to the target mercuration products.



X = ClO_4, BF_4.

Scheme 1 most completely explains the available experimental data. It is evident from this scheme that the rate of formation of transition state **A** depends on the concentration of both reagents, and k_{app} is determined by the charges on atoms involved directly into formation of structure **A**. Probably, the larger is the difference in these charges (not considering solvation) in the same solvent, the higher is k_{app}.

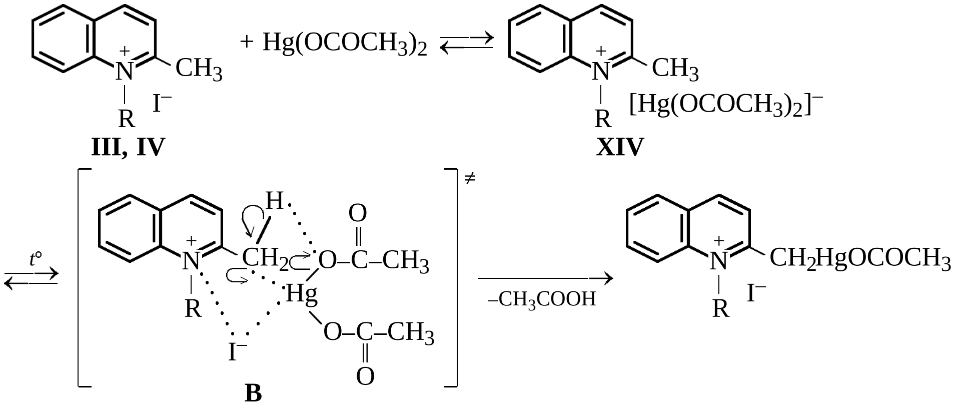
It can be suggested that the equilibrium stage of formation of transition state **A** is limiting in the overall chemical process. Evidence for this suggestion comes from the fact that the k_{app} values well correlate with the pK_a values [9] of certain quinolinium and pyrilium salts. Consequently, the higher is the CH acidity of the mercurated salt, the higher is the reaction rate. It is clear that here we contemplate the thermodynamic acidity determined by the following equilibrium process.



If one first prepares a methylene base of type **B** (for example, by treatment of quarternary salts with sodium methoxide) and adds the corresponding mercury(II) salt, a very fast (almost immediate) addition of the electrophilic agent by the exocyclic double bond of base **B** takes place [3–6], formally leading to the same mercuration products. From that it follows that the roles of transition state **A** and base **B**, that lie on the coordinate of the mercuration reaction of 2- and 4-methyl-containing salts of heterocyclic cations, are approximately equal, and just the rate of their formation most significantly affects the kinetics of the overall chemical process.

It is undoubtful that the effectiveness of formation of transition state **A** also depends on many other factors whose role can hardly be predicted. Specifically, this relates to solvent effects. The fact that salts **I**–**XIII** are scarcely mercurated in strongly polar aprotic solvents (DMF, DMSO, acetonitrile) points to significant solvation of polar reagents, rendering the latter less active in the reaction that gives rise to a less polar (as evidenced by the relatively high activation entropy $\Delta S^{\neq}$) transition state **A**. The role of the less polar solvent, ethanol, in which salts **I**–**XIII** are best mercurated under reflux, appears to consist largely in specific solvation of transition state **A** to reduce the activation energy and thus accelerate reaction. Furthermore, ethanol plays a significant role by binding the carboxylic acid liberated by mercuration into its ethyl ester and thus preventing the reverse reaction, protodemercuration of the resulting products. The last fact probably explains why halogen-containing mercury salts formally failed to mercurate salts **I**–**XIII**. Naturally, these reactions would provide hydrohalic acids which do not react with ethanol under the mercuration conditions and, at the same time, are effective protodemercurating agents [3–6].

We found that the nature of the anion of salt **I**–**XIII** exerts a significant rate effect. Hence, hard Pearson bases [10], such as ClO_4^- and BF_4^-, will prefer (according to the Pearson hard and soft acids and bases principle) to coordinate with a more hard acid, i.e. proton, thus favoring formation of transition state **A** and its subsequent electron density redistribution, and leading to the mercuration products. In the case of quinolinium iodides **III, IV**, a soft base, the iodide ion, will coordinate with a soft acid, the mercuty cation Hg^{2+}. Initially, this may lead to formation of a quarternary quinolinium salt **XIV** with a mercury-containing complex anion [4]. On heating these salts can transform to transition state **B** whose subsequent decomposition to the final mercuration products occurs difficultly and thus slower compared to transition state **A**. Just this effect we observed in the kinetic experiment.



EXPERIMENTAL

Kinetic studies of the mercuration reactions were carried out under temperature-controlled conditions (±0.5°C) with stirring and protection from air moisture. Samples taken in the course of reaction were diluted with 20 ml of acetonitrile and immediately subjected to potentiometric titration with a solution of sodium ethoxide in anhydrous ethanol in an inert atmosphere at 20 ± 1°C, using an EV-74 pH-meter with an ESL-63-07 glass electrode and an EVL-1M3 silver chloride electrode filled with a saturated solution of potassium chloride in anhydrous methanol.

Solvents used in kinetic studies were purified by known procedures [11].

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