KINETICS OF ORGANIC SUBSTITUTION REACTIONS IN MOLTEN ACETATE AND THIOCYANATE SALTS

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Methyl 3,5-dihydroxybenzoate, like many polyhydroxy compounds, is soluble in molten potassium thiocyanate and in the eutectic Na⁺K⁺SCN⁻, and reacts by nucleophilic attack of thiocyanate ion on the methyl group. The rate of this solvolysis for the ethyl ester is only 0.02 times that of the methyl at 150°C. Methyl 2,4-dihydroxybenzoate decarboxylates subsequently to displacement but the kinetics show no catalysis by the neighboring hydroxyl group.

Alkyl p-hydroxybenzoates undergo similar nucleophilic displacements in molten acetates such as Li⁺, Na⁺, K⁺OAc⁻. In contrast to the thiocyanate melt, the fused acetate is basic as well as nucleophilic. In this medium at 181-250°C, methyl, ethyl, propyl, isopropyl, 2-butyl and neopentyl p-hydroxybenzoates show the progressively decreasing rates typical of SN₂ reactions. The 2-butyl ester undergoes elimination as well as displacement; optically active substrate is 58% inverted, 42% racemized. Neopentyl p-hydroxybenzoate yields neopentyl acetate without rearrangement.

The rate of isomerization of phenyl ammonium thiocyanate has been determined over the entire concentration range, from dilute solution to fused thiocyanate eutectic.

Nucleophilic substitutions comprise a class of reactions very important in, though not limited to, organic chemistry. In the general case (1) and the example (2), the nucleophile X and the leaving group Y are bases:

\[ X^- + R-Y \rightarrow R-X + Y \]  \hspace{1cm} (1)
\[ \text{OH}^- + \text{CH}_3\text{Cl} \rightarrow \text{CH}_3\text{OH} + \text{Cl}^- \]  \hspace{1cm} (2)
Thiocyanate ion is a more reactive nucleophile than hydroxide \((3)\). Potassium thiocyanate moreover is a low-melting salt (mp 177°C). These facts suggested to us the possibility of carrying out nucleophilic displacement reactions in molten KSCN at temperatures compatible with organic substrates. Heterogeneous reactions of the vapor of simple alkyl halides bubbled through such melts had already been noted \((4)\). This paper reports results obtained with homogeneous solutions in fused thiocyanate salts and extension of the research to fused Group I acetates.

Molten Sodium-Potassium Thiocyanate

The working temperature was lowered by making use of the binary eutectic \((5)\) \(\text{Na}_x\text{K}_{1-x}\text{SCN}^-, 25-75\%, \text{mp} 133°C\) which we designate \(\text{M}^+\text{SCN}^-\). Most substrates for conventional substitution reactions in common organic solvents--alkyl halides, for example--are insoluble in this ionic, aprotic liquid. We found, however, that compounds having at least two hydroxyl groups per molecule for hydrogen bonding to thiocyanate ion were generally soluble in \(\text{M}^+\text{SCN}^-\), just as in ammonium nitrate melts \((6)\). Ethylene glycol, pentaerythritol, hydroquinone and glucose are all quite soluble, for example \((7)\). Some monohydroxy compounds such as water, methanol and benzoic acid are very soluble while higher alcohols and phenols are not. Although quantitative acid-base studies are precluded by the instability of HSCN, simple indicator experiments show that the hydroxyl groups of the soluble alcohols are unionized in the fused salt. The NMR spectrum of pentaerythritol in \(\text{M}^+\text{SCN}^-\) at 150°C shows singlets for \(\text{CH}_2\) and \(\text{OH}\) separated by 0.4 ppm at 60 MHz. The freezing point-composition curve of the hydroquinone (mp 171°C)-KSCN (mp 177°C) system shows a minimum, 140°C at about 60 mol % hydroquinone, and complete miscibility above 177°C \((7)\).

In a search for suitable substrates, sodium chloroacetate proved insoluble in anhydrous \(\text{M}^+\text{SCN}^-\) \((8)\) and 1-chloro-2,3-propanediol underwent undesirable cyclizations. Alkyl dihydroxybenzoates, however, were soluble and reacted at a convenient rate at 140-160°C, by attack of thiocyanate ion on the \(\alpha\)-carbon atom of the alkyl group \((9)\):

\[
\begin{align*}
\text{HO} & \text{COOR} + \text{SCN}^- \rightarrow \text{HO} \text{COO}^- + \text{RSCN} + \text{RNCS} \\
\text{HO} & \text{COOR} + \text{SCN}^- \rightarrow \text{HO} \text{COOH} + \text{CO}_2 + \text{RSCN} + \text{RNCS}
\end{align*}
\]
Though recognized early by Ingold (10) as a possible mechanism of hydrolysis, nucleophilic attack at this position is atypical of esters and occurs only when carbonyl attack is impossible. In one striking demonstration, methyl benzoate with sodium methoxide slowly yielded dimethyl ether (11):

\[
C_6H_5COOCH_3 + CH_3O^- \rightarrow C_6H_5COO^- + CH_3OCH_3
\]

In our case, the affinity of thiocyanate ion for \(\text{Sp}^3\) carbon is apparently much higher than for \(\text{Sp}^2\).

The kinetics of reaction 3 were followed by trapping the volatile products, methyl thiocyanate and methyl isothiocyanate. (One of the few convenient properties of molten salts is low volatility.) An air pressure of 20 Torr was maintained in the vacuum system to prevent volatilization of the substrate \(S_1\). The products were redistilled through calcium chloride and weighed. Since methyl 2,4-dihydroxybenzoate \(S_2\) undergoes decarboxylation as in equation 4, this reaction could easily be followed by measuring the volume of carbon dioxide evolved. But unlike the first-order reaction of \(S_1\), the substrate \(S_2\) proceeded only 50% to completion with kinetics according to equation 5:

\[
\frac{1}{2} \ln \frac{a}{a-2a} = kt
\]

This observation is consistent with the fact that resorcinol distils out of the solution, leaving \(S_2\) as an unreactive and probably insoluble anion, effectively removing one mol of \(S_2\) for each mole undergoing displacement.

The rate constants for reactions 3 and 4 at 150.5°C are respectively \(3.2 \times 10^{-4} \text{ S}^{-1}\) and \(4.7 \times 10^{-5} \text{ S}^{-1}\). The fact that the 2,4-dihydroxy ester reacts more slowly than the 3,5 shows that acid catalysis by the hydroxyl group adjoining the reaction center is absent. It also strongly suggests that decarboxylation occurs subsequently to displacement rather than concurrently, since extra driving force (or lowering of free energy of activation) of concerted fragmentation reactions is usual.

Further evidence for non-participation of the ortho hydroxy group in \(S_2\) is the lack of any appreciable kinetic isotope effect when both OH groups were replaced by OD \((k = 4.8 \times 10^{-5} \text{ S}^{-1})\).

The product from both substrates was 96% \(\text{CH}_3\text{SCN}\) and 4% \(\text{CH}_3\text{NCS}\), C-S bond formation predominating as in \(\text{SN2}\) reactions at room temperature. Ethyl 3,5-dihydroxybenzoate is 1/50 as reactive as the methyl ester \(S_1\). This is typical of bimolecular displacements. Nearly 50% of the product is \(\text{C}_6\text{H}_5\text{NCS}\), an unexpected result indicating some ionic character in the transition state or some other structural effect on its interaction with the nucleophilic solvent. Esters
higher than ethyl are not sufficiently soluble in M⁺SCN⁻ for further studies of the effect of structure on reactivity.

Molten Lithium-Sodium-Potassium Acetate

The second fused salt used as a solvent was a eutectic (M⁺OAc⁻) of three Group I acetates: Li⁺,Na⁺,K⁺/OAc⁻ (32, 30, 38 mol %) mp 162°C (12). Like the MSCN melt discussed above, M⁺OAc⁻ dissolves organic alcohols and phenols, which however include many monohydroxy compounds. The acetate melt is much more basic than the thiocyanate, as expected from the 10⁷-fold greater basicity of acetate compared with thiocyanate ion in aqueous solution at 25°C. 2,4-dinitroaniline (pKₐ 15.00) but not p-nitroaniline (pKₐ 18.37) is ionized to ArNH⁻ in M⁺OAc⁻ at 200°C (13).

Acetic acid is soluble in the fused salt; its tendency to associate with the solvent anion to form the hydrogen-bonded species CH₃COO⁻...HOOCC₃H₆("homocounguration") (14) is shown by large deviations of the vapor pressure of the solutions from ideality (15). The presence of acetic acid is required for ready solubility of phenoxides and certain carboxylates such as sodium benzoate, which are likely associated with the acid molecules. The fused salt, M⁺OAc⁻, if it could be freed initially of all traces of water and acetic acid, would seem to be an aprotic solvent though the observed exchange of alpha hydrogen atoms between acetate ions shows that this is not strictly true (13). Clearly, however, the presence of ionized phenols in all our experiments and of acetic acid itself in most, introduced the possibility of acid-base interactions and catalysis in our reactions.

The nucleophilic displacements we chose to study in the acetate melt were analogous to reactions 3 and 4, but since alkyl p-hydroxybenzoates were soluble, it was unnecessary to employ dihydroxy compounds:

\[
CH₃COO⁻ + C₆H₅OCOC₆H₄O⁻ + CH₃COOH \rightarrow CH₃COOC₆H₅ + CO₂ + C₆H₅O⁻ + CH₃COO⁻
\]  

(6)

The above example shows the attack of acetate ion on the ethyl group of ethyl p-hydroxybenzoate to give ethyl acetate. The substrate and the phenol formed by decarboxylation are both ionized and hydrogen-bonded to acetic acid. p-Hydroxybenzoic acid, like 2,4-dihydroxybenzoic acid (eq. 4) is known to decarboxylate at this temperature; the ring position vacated by carbon dioxide is filled by a proton from acetic acid, if available, or from another substrate molecule. In all kinetic studies, a constant concentration of acetic acid was maintained in the M⁺OAc⁻ solvent, by saturating a stream of nitrogen with acetic acid at 240°C and passing it through the molten salt. The gas
served to sweep out carbon dioxide into absorption tubes for following the kinetics.

Reactions were first order in the substrate ester under these conditions, while in the absence of added acetic acid, equation 5 described the kinetics. These observations might be explained by the necessity of one mol of acetic acid in the melt to solvate the phenoxide ion, $S_3^-$. If the acid is consumed as it donates a proton in the decarboxylation, $S_3^-$ is insoluble and is effectively removed analogously to the removal of the unionized substrates $S_1$ and $S_2$, used in the molten salt $M^{+}SCN$.

In one experiment, however, acetic acid vapor was introduced only after the reaction had proceeded 36% to completion and the plot of $\ln a/(a-x)$ vs time had begun to taper off. The presence of acetic acid then caused the reaction to accelerate to a rate higher than normal, the last point falling on the linear plot expected in the presence of acetic acid. This "catching up" would not have been caused by the redissolving of $S_3^-$ temporarily removed from solution; it suggests the accumulation of an intermediate such as the primary displacement product $-OC_6H_4COO^-$ which cannot decarboxylate in the absence of a proton donor.

The rate constants (15) for reaction of several alkyl p-hydroxybenzoates in $M^{+}0Ac^-$ at 200°C are shown in Table I.

Table I. Rate Constants for Reaction of p-HOC$_6$H$_4$COOR with Molten $M^{+}0Ac^-$ at 200°C

| R          | $k, s^{-1}$ | no. of runs | av dev, % | k calcd 25°C |
|------------|------------|-------------|-----------|--------------|
| CH$_3$     | $9.5 \times 10^{-5}$ | 3           | 0.8       | 30           |
| CH$_3$CH$_2$ | $1.65 \times 10^{-5}$ | 2           | 0.6       | (1)          |
| CH$_3$CH$_2$CH$_2$ | $8.1 \times 10^{-6}$ | 2           | 1.8       | 0.4          |
| (CH$_3$)$_2$CH | $4.8 \times 10^{-6}$ | 2           | 3.3       | 0.025        |
| CH$_3$CH$_2$(CH$_3$)CH | $2.63 \times 10^{-6}$ | 2           |           |              |
| CH$_3$     | $9.1 \times 10^{-5}$ | 1$^b$       |           |              |

$^a$Containing CH$_3$COOH from nitrogen stream saturated at 24°C.

$^b$Nitrogen stream saturated with CH$_3$COOD.

$^c$Relative to the ethyl ester.
The decrease in rate with increasing $\alpha$ or $\beta$ substitution at the reaction center is again characteristic of SN2 reactions.

An Arrhenius plot for the methyl ester over the temperature range 181-220°C is given by $k(S^{-}) = 1.49 \times 10^{9}e^{-19000/RT}$. Using this activation energy for methyl and adding average increments for the other groups in displacement reactions (16) we calculated the hypothetical relative rates at 25°C shown in the last column of Table I which are more closely comparable with known reactions than the 200°C data.

We used two additional experimental probes which are obligatory in the study of nucleophilic solvolytic reactions. The first was to employ an optically active substrate, 2-butyl p-hydroxybenzoate, the fifth entry in Table I. The product was 58% inverted, 42% racemized 2-butyl acetate. A one-step bimolecular displacement would cause 100% inversion, but our result is more typical of solvolytic reactions of secondary substrates.

The second experimental variation was to introduce a second nucleophile into the solvent to determine the effect of its concentration on the rate and product composition. Potassium thiocyanate, which is miscible with the molten acetate, $M^{+}OAc^{-}$, indeed accelerated the displacement in concentrations up to 4M or about 25 mol per cent. The acceleration moreover appeared to be greater than would be expected on the basis of the thiocyanate consumed; in other words, thiocyanate ion not only reacted to form RSCN but catalyzed the formation of ROAc. While this suggests an ion-pair intermediate, such a postulate should be supported by correlation of the product ratio with the rates.

One further classical experiment was carried out in the molten salt $M^{+}OAc^{-}$. Neopentyl p-hydroxybenzoate ($R = (CH_3)_{3}CCH_2^{-}$) was used as the substrate in eq. 6. If the reaction proceeded via a free neopentyl cation in this ionic, high-temperature medium, the rearranged product, 2-methyl-2-butyl acetate would be expected. Only the unrearranged product, neopentyl acetate, was obtained, proof that the alkyl group does not exist as a carbonium ion and confirmation of the proposed SN2 mechanism.

From Dilute Solution to Fused Salt

One of the original goals of this research was to determine the rate of an organic reaction as a function of ionic strength "from dilute solution to fused salt (17)." We now report the first such study, utilizing the Wöhler isomerization of anilinium thiocyanate to phenyl thiourea in $M^{+}SCN^{-}$:

$$C_6H_5NH_3^+ + SCN^- \rightarrow C_6H_5NHCSNH_2$$
The reaction was followed by acid-base titration. Anilinium chloride was used in the aqueous solutions, with increasing concentrations of sodium and/or potassium thiocyanate. In molten $M^\text{SCN}^-$, anilinium thiocyanate was used as the substrate. This compound, prepared by precipitating potassium chloride from anilinium chloride and potassium thiocyanate in absolute ethanol, was more soluble in $M^\text{SCN}^-$ than was anilinium chloride.

Figure 1 is a plot of $\log k$ (second-order) vs (ionic strength)$^{1/2}$ at $10^6$°C. The Debye-Hückel limiting slope for the cation-anion reaction is shown by the dotted line. The increase in rate constant with ionic strength at higher concentrations may be related to the decreasing dielectric constant of the medium: the triangle shows the similar effect of ethanol.

At $138^\circ$C, just above the melting point of the molten salt eutectic, the reaction was too fast to obtain accurate rate constants; values of $k_2$ ranged from $1.1 \times 10^{-3}$ to $2.6 \times 10^{-3}$ 1/mol-s for the rearrangement in molten $M^\text{SCN}^-$, which is 17 M. A series of rate measurements with 15.2 M solutions was made at $100^\circ$C, $106^\circ$C and $113^\circ$C, giving an Arrhenius plot from which an extrapolated value of $1.0 \times 10^{-3}$ 1/mol-s was calculated for $138^\circ$C. We conclude that the increase in $k$ from 15.2 M solution to the molten salt is probably not more than about 2 to 3-fold.

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Figure 1. Rate of reaction of anilinium thiocyanate to form phenylthiourea at 106° C, in aqueous solutions of thiocyanate salts; O NaSCN; • KSCN; ○ Na⁺, K⁺SCN⁻; △ KSCN in 50% C₂H₅OH-H₂O. Horizontal axis terminates at the concentration of the anhydrous molten salt Na⁺, K⁺SCN⁻.