# Chemistry

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## Abstract

## Full Text

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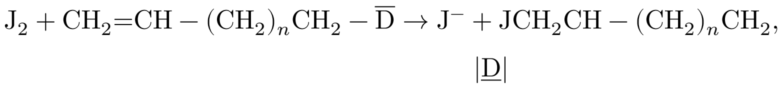
## On the Question of the Significance of Cyclic Transition Complexes in the Mechanism of Organic Reactions

In reactions of organic compounds, a tendency toward the formation of cyclic transition complexes has long been noted (1); however, the theory of this phenomenon still remains controversial (2). In order to obtain quantitative data on the question of cyclic complexes in addition reactions, we carried out kinetic measurements for several iodination reactions of unsaturated compounds with ring closure of the type



$$\begin{array}{c} J_2 + CH_2{=}CH-(CH_2)_nCH_2-\overline{D} \rightarrow J^- + JCH_2CH-(CH_2)_nCH_2, \\ |\underline{D}| \end{array}$$

where D is an anionoid group.

We carried out iodination in aqueous solutions containing potassium iodide. In these media iodine does not add to a double or triple bond if the possibility of formation of a ring compound is excluded and if the compound being iodinated is not excessively active. On the contrary, iodination reactions with ring formation proceed, for the most part, readily, and in kinetic measurements the reaction usually has to be slowed down by various methods. We found that the rate of iodination in all cases is expressed by the equation

$$-\frac{d(J)}{dt} = \frac{kM(J)}{[J^-]}, \tag{1}$$

where $M$ is the concentration of the unsaturated compound, and (J) is the total concentration of active iodine, equal to the sum $[J_2] + [J_3^-]$.

According to the equilibrium law $[J_2][J^-] = K[J_3^-]$, and since the constant $K$ is small, even at low concentrations of iodide ion $[J_3^-] \simeq (J)$, and, consequently, equation (1) is equivalent to the equation $-d(J)/dt = (k/K)M[J_2]$, or, if the reaction rate is referred to the active form of the unsaturated compound, $M_0$, then $-d(J)/dt = k_0M_0[J_2]$.

Thus the active agent in iodocyclization proves to be free iodine. In contrast to hydrogen substitution in the iodination of aromatic compounds (3), we find no signs of participation by iodine-cation complexes in the mechanism of iodocyclization.

In one series of our experiments (carried out by E. N. Rengevich), data were obtained on the iodination of a series of salts of unsaturated acids that form iodomethyl lactones with different numbers of members in the ring.

The products of these reactions were for the most part known previously ($^4$). Newly obtained and identified were the lactones of ortho-($\beta$-iodo-$\alpha$-oxyethyl)benzoic acid (m.p. 67.6°) and 5-iodo-4-oxy-$\omega$-pentenoic acid (m.p. 75-76°).

The initial concentrations of the reagents were (in mol/l): salts of the unsaturated acid 0.005-0.01, iodine 0.005-0.02, potassium iodide 0.05-0.1. Temperatures were 0-50° ($±$0.05°). For very slow reactions, measurements were made only at higher temperatures, and for excessively fast ones—only at lower temperatures.

Table 1 combines the values of the rate constant of iodolactonization, $k_0$, the activation energies, and the preexponential factor from the Arrhenius equation. Val—

the value of the equilibrium constant $K$ in the system $J_2$—KJ were determined anew for different temperatures under conditions close to those of our kinetic experiments ($^5$).

Considering the data of Table 1, we find for aliphatic iodomethyl lactones the usual regularity in such cases: the five-membered ring is formed fastest of all, followed by six-, seven-, and, finally, four-membered rings; crotonate and acrylate ions, which could give a three-membered lactone, do not react at all with iodine.

**Table 1**

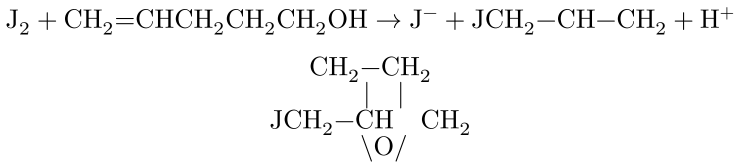
| Iodinated compound | $(k_2)_{20^\circ}$, l · mol$^{-1}$ · sec$^{-1}$ | $E$, kcal/mol | lg $A$ |
|---|---|---|---|
| $\cdot CH_2{=}CH{-}CO_2^-$ | 0 | – | – |
| $\cdot CH_2{=}CH{-}CH_2{-}CO_2^-$ | 0.012 | 21 | 13.8 |
| $\cdot CH_2{=}CH{-}(CH_2)_2{-}CO_2^-$ | 78.6 | 13.3 | 11.8 |
| $\cdot CH_2{=}CH{-}(CH_2)_3{-}CO_2^-$ | 10.9 | 13.2 | 10.9 |
| $\cdot CH_2{=}CH{-}(CH_2)_4{-}CO_2^-$ | 0.17 | 13.2 | 9.1 |
| $\cdot o\text{-}CH_2{=}CH{-}C_6H_4CO_2^-$ | 3.12 | 16.4 | 12.7 |
| $\cdot o\text{-}CH_3CH{=}CH{-}C_6H_4CO_2^-$ | 5.3 | 16.8 | 13.3 |
| $\cdot CH{\equiv}C{-}CH_2CH_2CO_2^-$ | 1.9 | 14.1 | 10.8 |

Ring closure at the benzene nucleus proceeds noticeably more slowly than in aliphatic compounds in the formation of iodomethyl lactones with the same number of members in the ring. Replacement of a double bond by a triple bond also somewhat slows iodolactonization.

It is noteworthy that the activation energies in the formation of five-, six-, and seven-membered rings have very close values (~ 13 kcal), and the differences in the rates of cyclization are associated only with the frequency factor.

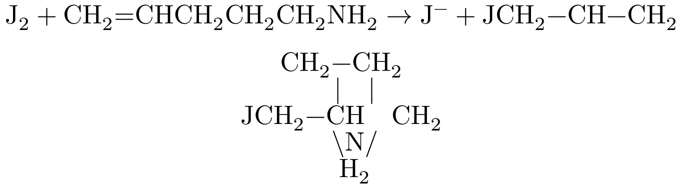
The difference between the activation energies in the formation of four-membered and higher rings approximately corresponds to the strain energy of four-membered rings. The increase in energy in the formation of aromatic lactones is apparently connected with the reduced nucleophilicity of the corresponding double bonds.

In another series of experiments, carried out by V. I. Staninets, the number of members in the ring being formed was always the same (five), but the composition and nature of the heterofunction closing the chain into the ring were varied. To measure the rate of iodocyclization, the following compounds were taken: pent-1-en-5-ol (I), 4,6-dichloro-2-allylphenol (II), methyl $\omega$-pentenyl sulfide (III), $\omega$-pentenylamine (IV), $\omega$-pentenyldimethylamine (V), and the amide of $\omega$-pentenoic acid (VI). The products of iodocyclization of these compounds are derivatives of tetrahydrofuran, tetrahydrothiophene, and tetrahydropyrrole, formed according to the following typical schemes:



$$J_2 + CH_2{=}CHCH_2CH_2CH_2OH \rightarrow J^- + JCH_2{-}CH{-}CH_2 + H^+$$

$$\begin{array}{c} CH_2{-}CH_2 \\ |\quad\ | \\ JCH_2{-}CH\quad CH_2 \\ \backslash O / \end{array}$$



$$J_2 + CH_2{=}CHCH_2CH_2CH_2NH_2 \rightarrow J^- + JCH_2{-}CH{-}CH_2$$

$$\begin{array}{c} CH_2{-}CH_2 \\ |\quad\ | \\ JCH_2{-}CH\quad CH_2 \\ \backslash N / \\ H_2 \end{array}$$

Of the cyclic compounds obtained, one (formed in iodocyclization V) was known previously ([6]), while the others were obtained for the first time. These include: 2-iodomethyltetrahydrofuran, b.p. 68–70° at 13 mm; 5,7-dichloro-2-iodomethylbenzodihydrofuran, m.p. 78–79°; S-methyl-2-iodomethyltetrahydrothiophene, m.p. > 320°; 2-iodomethylpyrrolidinium iodide, m.p. 208° (decomp.); the hydroiodide salt of 4-iodomethylpyrrolidone-2, m.p. 156° (decomp.). These compounds were isolated in pure form, and their composition was checked by analysis. To establish whether the unsaturated molecule reacts in the form ion or in the form of a neutral compound, we determined the dependence of the iodination rate on pH and found that I is iodinated in the form of the alcohol, II as the phenolate, and the amines only as free bases.

In order to relate the reaction rate to the concentrations of the active forms, it was necessary to determine the electrolytic dissociation constants of the amines and phenol studied at several temperatures and salt concentrations close to the conditions of the kinetic experiments. By electrometric titrations with a glass electrode the following values of $pK_b$ were obtained: 4,6-dichloro-2-allylphenol $5.8_{21^\circ}$, $5.23_{40^\circ}$; $\omega$-pentenylamine $4.36_{0^\circ}$, $3.59_{20^\circ}$, $3.02_{40^\circ}$; $\omega$-pentyldimethylamine $4.14_{0^\circ}$, $3.46_{20^\circ}$, $2.89_{40^\circ}$. The initial analytical concentrations of the reagents in the kinetic experiments (in mole/liter) were: unsaturated compound 0.001–0.02, iodine 0.00125–0.005, KJ 0.01–0.2.

The values of the rate constants as a function of the reaction temperature are given in the form of a plot of $\lg k_0 — \frac{1}{T}$ in Fig. 1.

**Table 2**

| Iodinated compound | $(k_0)_{20^\circ}$, l · mole$^{-1}$ · sec$^{-1}$ | $E$, kcal/mole | lg $A$ |
|---|---|---|---|
| R—CH$_2$SCH$_3$ (III) | 0.003 | 17.3 | 8.0 |
| R—CONH$_2$ (VI) | 0.67 | 12.2 | 8.9 |
| R—CH$_2$OH (I) | 1.47 | 8.9 | 7.8 |
| $ClC_6H_2(O^-)(CH_2CH{=}CH_2)Cl$ (II) | 170 | 4.2 | 4.6 |
| R—CH$_2$NH$_2$ (IV) | $1.41 \cdot 10^5$ | 2.8 | 7.2 |
| R—CH$_2$N(CH$_3$)$_2$ (V) | $2.83 \cdot 10^5$ | 1.9 | 6.9 |

The plot demonstrates, above all, enormous differences in the rates of these analogous reactions, amounting to 8 orders of magnitude on going from III to V. It may further be seen that, in the temperature interval studied, the reactions obey the Arrhenius equation and make it possible to calculate the values of $E$ and $A$.

These values are presented in Table 2, where R = $CH_2{=}CH—CH_2CH_2$.

Comparing the values of $k_0$ and $E$ with the structure of the reacting molecule, we note that the reaction rate in this series of compounds increases and the activation energy decreases as the nucleophilicity of the terminal group is strengthened. This conclusion is consistent with the fact that the $\omega$-butenylsulfonate

Figure 1

Figure 1: Figure 1

ion, which might seemingly form iodomethylsultone, does not react at all with a solution of iodine and potassium iodide under ordinary conditions.

The results of our experiments make it possible to judge the driving forces and the mechanism of iodocyclization.

Obviously, what is involved is a synchronous acceptor-donor reaction, an example of which may be the iodocyclization of II:

$$\begin{aligned} &\mathrm{J_2 + CH_2{=}CH{—}CH_2{—}C_6H_2Cl_2O^-} \rightleftharpoons \mathrm{J \leftarrow J \cdots CH_2}\langle\cdots \mathrm{CH} \\ &\qquad \cdots \mathrm{O} \cdots \mathrm{C_6H_2Cl_2} \longrightarrow \mathrm{J^- + JCH_2{—}CH}\langle \mathrm{CH_2{—}O{—}C_6H_2Cl_2} \end{aligned}$$

This reaction is analogous to the known mixed additions to multiple bonds, but differs from them in the unusual ease of the transformation. For comparison it may be pointed out that the seemingly analogous reaction of iodination of allyl alcohol in the presence of the 2,4,6-trichlorophenolate ion,

$$\mathrm{J_2 + CH_2{=}CH{—}CH_2OH + {}^-O{—}C_6H_2Cl_3} \longrightarrow \mathrm{J^- + JCH_2{—}CH} \left( \begin{matrix} \mathrm{CH_2OH} \\ \mathrm{O{—}C_6H_2Cl_3} \end{matrix} \right)$$

does not proceed at all under identical experimental conditions.

Such a difference may be connected with the fact that the second stage of iodocyclization is a monomolecular reaction. With ordinary pre-exponents this circumstance leads to the result that, other conditions being equal, the rate of iodocyclization should be considerably greater than the rate of the analogous reaction without ring closure.

However, the effect of accelerating the reaction upon formation of cyclic complexes is not reducible to its monomolecularity. It must be assumed that the favorable configuration of the intermediate complex brings the donor end of the molecule into action already at the first stage of addition, when formation of the $\pi$-complex causes the appearance of a positive charge on the saturated carbon atoms. The participation of the nucleophilic agent lowers the activation energy and accelerates addition. That it is specifically nucleophilic affinity that is important, and not electric charge, is shown by the dependence of the rate constant and activation energy on the structure of the nucleophilic group (Table 2).

**Fig. 1.** The numerals at the straight lines denote the unsaturated compounds given in the text and in Table 2.

Meanwhile, in the formation of acyclic mixed compounds the nucleophilicity of the donor is of no great importance [7]. Apparently, unbound anionoid molecules, including molecules of a polar solvent, are so mobile that they cannot form a sufficiently stable complex that could manifest its nucleophilic affinity.

Therefore, for the addition reaction to proceed through an acyclic transition complex, it is necessary that the complex formed by the electrophilic agent reach a high degree of polarization, approaching the state of an ion pair, and only then does the anionoid component of the system acquire the possibility of acting.

Unlike chlorine and bromine, iodine is such a weak electrophile that it can bring an olefin into the required active state without the aid of a nucleophilic agent.

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*Note: Figure translations are in progress. See original paper for figures.*

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