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Studies on the Reaction between Polynitrobenzene Compounds and Active Methylene Groups. XI.[1] Kinetic Study on the Janovsky Reaction of Trinitrobenzene with Cyclohexanone in Methanol[2]

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The Janovsky reaction of 1,3,5-trinitrobenzene with cyclohexanone was studied kinetically. The rate-determining step is the addition of cyclohexanonate anion to trinitrobenzene. Kinetic and thermodynamic parameters are compared with those of the reaction with acetone. And the mechanism of the Zimmermann reaction of *m*-dinitrobenzene is suggested.

In the preceding paper,[1] it was shown that the rate-determining step of the Janovsky reaction of 1,3,5-trinitrobenzene (TNB) with acetone in methanol is not the deprotonation of acetone but the attack of acetonate ion to TNB, and the kinetic and thermodynamic parameters of the reaction were determined. The present paper has three main objects: first, the application of the kinetics to the Janovsky reaction with cyclohexanone; second, the comparison of the nature of the Janovsky complex of cyclohexanone with that of the Janovsky complex of acetone and with that of Meisenheimer complexes depending on the kinetic and thermodynamic parameters; third, the discussion on the mechanism of the Zimmermann reaction of *m*-dinitrobenzene.[4]

Experimental

Commercial cyclohexanone was purified by means of the bisulfite addition complex, which was decomposed with sodium carbonate and then distilled,[5] bp 155—156°. Other materials, instruments and the procedure of the color development previously described[1] were employed.

Result and Discussion

Sodium methoxide solution was added to a mixture of TNB and cyclohexanone in methanol and the change of the absorption spectrum was followed. Although instantaneously

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1) Part X: N. Obi and M. Kimura, *Chem. Pharm. Bull.* (Tokyo), **20**, 2295 (1972).

2) A part of this paper was presented at the Meeting of Hokkaido Branch of Pharmaceutical Society of Japan, Feb. 1968.

3) Location: *Nishi-6-chome, Kita-12-jo, Sapporo, 060, Japan.*

4) A review on Zimmermann reaction and Janovsky one has been described (T. Nambara, *Japan Analyst* (Bunseki Kagaku), **13**, 184 (1964)).

5) C.E. Garland and E.E. Reid, *J. Am. Chem. Soc.*, **47**, 2333 (1925).

after the start of the reaction two maxima due to the complex II (Chart 1) were found at 425 and 495 mμ, very soon other two maxima due to the complex I (Chart 1) appeared at 463 and 544 mμ and gradually increased, and the maxima due to II were hidden and only two maxima were observed at 463 and 544 mμ. But long after the start of the reaction——more than 10 hours at the conditions shown in Fig. 1——another new maximum appeared at 518 mμ and increased very slowly while the absorbance at 463 and 544 mμ decreased. This maximum may be due to compound III.[6] This spectrum change is similar to that of the Janovsky reaction of TNB with acetone.[1,7] Since the formation of III is very slow compared with the formation of I, equation (1) to (3) in Chart 1 may be satisfactry for the kinetics of the formation of I, where K and k designate the equilibrum constant and the rate one, respectively, and the suffix shows the number of equation and the direction of the reaction. Complex I and II are Meisenheimer type complexes——anionic σ complexes[8] and there have been several reviews on this field[9] and all the equations in Chart 1 are reversible without doubt.

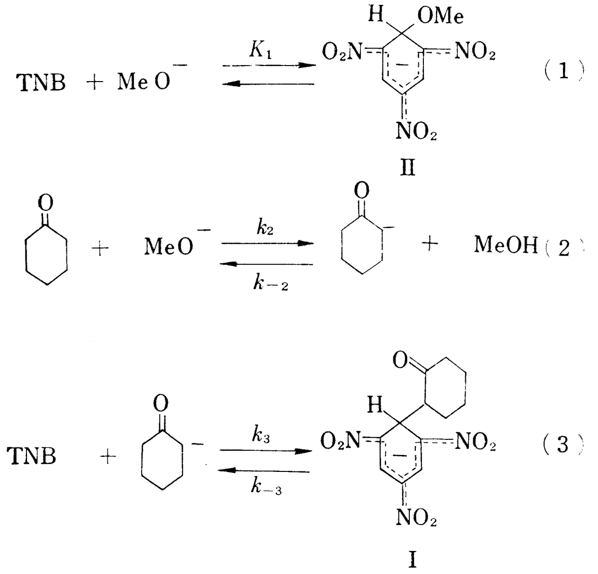
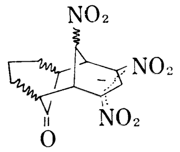
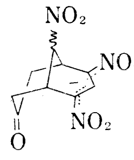


Chart 1



III



IV

The rate of the formation of I may be given by equation (4).

$$d[\mathrm{I}]/dt = \frac{k_2k_3[\mathrm{C_6H_{10}O}][\mathrm{MeO^-}][\mathrm{TNB}]-k_{-2}k_{-3}[\mathrm{I}]}{k_{-2}+k_3[\mathrm{TNB}]} \qquad (4)$$

If $k_{-2} \gg k_3[\mathrm{TNB}]$, equation (4) is as follows:

$$d[\mathrm{I}]/dt = K_2k_3[\mathrm{C_6H_{10}O}][\mathrm{MeO^-}][\mathrm{TNB}] - k_{-3}[\mathrm{I}] \qquad (5)$$

If $k_{-2} \ll k_3[\mathrm{TNB}]$, equation (4) is as follows:

$$d[\mathrm{I}]/dt = k_2[\mathrm{C_6H_{10}O}][\mathrm{MeO^-}] - k_{-2}[\mathrm{I}]/K_3[\mathrm{TNB}] \qquad (6)$$

In the experiment shown in Fig. 1, the initial rate of the formation of complex I depends on the concentration of TNB in the first order, approximately. Therefore, the kinetics may be

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6) K. Kohashi, Y. Ohkura, and T. Momose, The Symposium on Absorption Spectrochemical Analysis and Fluorometric Analysis of the Pharmaceutical Society of Japan, Gifu, Nov. 1970, Abstracts of Papers, p. 73.

7) K. Kohashi, Y. Ohkura, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **19**, 2065 (1971).

8) Meisenheimer complex is a stable intermediate in the aromatic nucleophilic substitution and is called an anionic σ complex in contrast to donor-acceptor π complex and in a wide sense all the anionic σ complexes are called Meisenheimer type complexes including Janovsky complexes.

9) R. Foster and C.A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); E. Buncel, A.R. Norris, and K.E. Russel, *Quart. Rev.* (London), **22**, 123 (1968); P. Buck, *Angew. Chem. Intern. Ed. Engl.*, **8**, 120 (1969); M.R. Crampton, "Advances in Physical Organic Chemistry," Vol. 7, ed. by V. Gold, Academic Press, London and New York, 1969, p. 211; M.J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

followed according to equation (5) and the rate-determining step of the formation of I is the forward reaction of equation (3). Integration of equation (5) with considering the competition of reaction (1), gives the rate equation (7) as described previously,[1]

$$\log \{[\mathrm{TNB}]_{\mathrm{st}} - (1 + k_{-3}/mK_2k_3)[\mathrm{I}]\} = -0.4343(mK_2k_3 + k_{-3})t + \log [\mathrm{TNB}]_{\mathrm{st}} \qquad (7)$$

where $[\ \ ]_{\mathrm{st}}$ shows the stoichiometric concentration and m is as follows:

$$m = \frac{[\mathrm{MeO^-}]_{\mathrm{st}}[\mathrm{C_6H_{10}O}]_{\mathrm{st}}}{1 + K_1[\mathrm{MeO^-}]_{\mathrm{st}}} \qquad (8)$$

The concentration of I is obtained from equation (9) in analogy with the case in the preceding paper,[1]

$$[\mathrm{I}] = \frac{E(1 + K_1[\mathrm{MeO^-}]_{\mathrm{st}}) - \varepsilon_{\mathrm{II}}K_1[\mathrm{MeO^-}]_{\mathrm{st}}[\mathrm{TNB}]_{\mathrm{st}}}{\varepsilon_{\mathrm{I}} + K_1[\mathrm{MeO^-}]_{\mathrm{st}}(\varepsilon_{\mathrm{I}} - \varepsilon_{\mathrm{II}})} \qquad (9)$$

where ε_{I} and $\varepsilon_{\mathrm{II}}$ are the molar extinction coefficients of I and II, respectively, and E is the observed absorbance.

The values ε_{I} and $\varepsilon_{\mathrm{II}}$ were determined as 2.66×10^4 and $1.98 \times 10^4\ \mathrm{M^{-1}cm^{-1}}$ at 463 mμ, respectively, and K_1 was obtained as shown in Table I.[10] From these values and the absor-

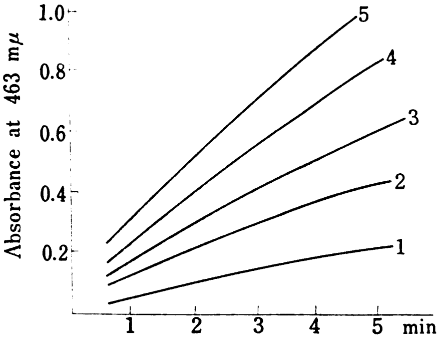

Fig. 1. Color Development of the Janovsky Reaction for Various Concentration of TNB

condition: reaction temperature 15°
$[\mathrm{MeO^-}]_{\mathrm{st}} = 2.40 \times 10^{-3}\mathrm{M}$
$[\mathrm{C_6H_{10}O}]_{\mathrm{st}} = 1.00 \times 10^{-1}\mathrm{M}$
$[\mathrm{TNB}]_{\mathrm{st}} = 2.00 \times 10^{-5}\mathrm{M}$……1
$[\mathrm{TNB}]_{\mathrm{st}} = 4.00 \times 10^{-5}\mathrm{M}$……2
$[\mathrm{TNB}]_{\mathrm{st}} = 6.00 \times 10^{-5}\mathrm{M}$……3
$[\mathrm{TNB}]_{\mathrm{st}} = 8.00 \times 10^{-5}\mathrm{M}$……4
$[\mathrm{TNB}]_{\mathrm{st}} = 1.00 \times 10^{-4}\mathrm{M}$……5

Table I. K_1 in Methanol Containing Various Concentration of Cyclohexanone

$[\mathrm{C_6H_{10}O}]$ × 10 (M)	Temperature			
	10°	15°	20°	25°
0.000	11.1M^{-1}	12.1M^{-1}	13.6M^{-1}	—M^{-1}
0.250	—	13	—	—
0.500	13	14	14	—
1.000	15	16	16	17
1.500	18	18	19	—
2.000	22	22	23	—
2.500	25	26	27	—

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10) The equilibrium constant K_1 may be independent of the concentration of cyclohexanon. In practice, however, K_1 was affected by medium composition. This is the same as the previous paper.[1] Recently, σ complex formation between TNB and hydroxide ion was studied quantitatively as a function of medium composition in part of the dimethylformamide–water solvent system.[11] In this paper, it was reported that only a small content of dimethylformamide increased the equilibrium constant considerably. In the present case, the increase in K_1 may be ascribed to increased solvation of the large polarizable σ complex(II) as the protic solvent (methanol) is replaced by the dipolar aprotic component(cyclohexanone).[12] Since acetone is a dipolar aprotic solvent,[12] cyclohexanone may reasonably classified into this group.

11) E.A. Symons and E. Buncel, *Can. J. Chem.*, **50**, 1729 (1972).

12) A.J. Parker, *Quart. Rev.* (London), **16**, 163 (1962); *idem*, "Advances in Organic Chemistry: Methods and Results," Vol. 5, ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg, John Wiley & Sons, Inc., New York, 1965, pp. 1—46.

bance data, the concentration of I was calculated along the time-cource of the experiment using equation (9). Then this value was substituted into equation (7), and K_2k_3 and k_{-3} were determined by trial-and-error method as described in the preceding paper.[1]

Though K_2k_3 and k_{-3} are independent of the concentration of cyclohexanone in equation (4), they are influenced by its concentration——this is the same as the case of acetone.[1] At 10°, K_2k_3 and k_{-3} were determined under the experimental condition of 10^{-1}M of cyclohexanone (Table II). Together with these data, K_2k_3 and k_{-3} at other temperatures are

Table II. Rate Constants at 10° in Methanol Containing 10^{-1} M of Cyclohexanone

$[\mathrm{TNB}]_{\mathrm{st}} \times 10^5$ (M)	$[\mathrm{MeO^-}]_{\mathrm{st}} \times 10^3$ (M)	$K_2k_3 \times 10^{-2}$ ($\mathrm{M^{-2}\,min^{-1}}$)	$k_{-3} \times 10^3$ ($\mathrm{min^{-1}}$)
2.00	1.91	2.83	11.8
4.00	1.22	2.71	5.0
4.00	1.91	2.67	5.5
4.00	1.91	2.80	8.3
4.00	2.43	2.24	7.8
4.00	3.65	2.66	3.5
4.00	4.87	2.79	5.9
4.00	6.09	2.71	5.0
6.00	1.91	2.69	6.0
8.00	1.91	2.71	9.3
10.00	1.91	2.70	9.5
		mean 2.68 ± 0.09[a]	7.1 ± 2.1[a]

a) average deviation

Table III. Rate Constants in Methanol Containing 10^{-1}M of Cyclohexanone

Temperature (°C)	No. of Runs	$K_2k_3 \times 10^{-2}$ ($\mathrm{M^{-2}\,min^{-1}}$)	$k_{-3} \times 10^3$ ($\mathrm{min^{-1}}$)	$K_2K_3 \times 10^{-4}$ ($\mathrm{M^{-2}}$)
10	11	2.68 ± 0.09[a]	7.1 ± 2.1[a]	3.8
15	20	4.19 ± 0.26	12.5 ± 7.4	3.2
20	11	6.30 ± 0.19	34.0 ± 1.0	1.9
25	9	9.12 ± 0.26	41.3 ± 3.4	2.2

a) average deviation

Table IV. Kinetic and Thermodynamic Parametrs of the Janovsky Reactions of TNB in Methanol Containing 10^{-1}M of Active Methylene Compounds

	Reaction with cyclohexanone	Reaction with acetone[a]
$K_2k_3 \times 10^{-2}(\mathrm{M^{-2}min^{-1}})$[b]	4.19	0.60
$k_{-3} \times 10^3(\mathrm{min^{-1}})$[b]	12.5	6.0
$E_{K_2k_3}$(kcal mol^{-1})[c]	13.8	12.5[d]
$E_{k_{-3}}$(kcal mol^{-1})[c]	22	37.3[d]
ΔH(kcal mol^{-1})[e]	−8	−24.8[d]
$\Delta S^{\ddagger}_{K_2k_3}$(eu)[b]	−1	−9[d]
$\Delta S^{\ddagger}_{k_{-3}}$(eu)[b]	7	55[d]
ΔS[f]	−8	−64[d]

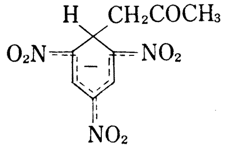
a) Reference 1; b) at 15°; c) calculated using Arrhenius equation; d) in methanol containing 5×10^{-1}M of acetone; e) calculated as $E_{K_2k_3} - E_{k_{-3}}$; f) calculated as $\Delta S^{\ddagger}_{K_2k_3} - \Delta S^{\ddagger}_{k_{-3}}$

Table V. Rate Constants in Methanol Containing Various Concentrations of Cyclohexanone
(reaction temperature: 10°, $[\mathrm{TNB}]_{st}=4.00\times10^{-5}$M, $[\mathrm{MeO^-}]_{st}=1.91\times10^{-3}$M)

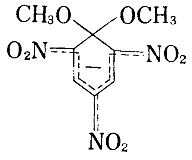
$[C_6H_{10}O]_{st}\times10$ (M)	$K_2k_3\times10^{-2}$ (M^{-2}min^{-1})	$k_{-3}\times10^3$ (min^{-1})	$K_2K_3\times10^{-4}$ (M^{-2})
0.50	2.68	8.2	3.3
1.00	2.68	7.1	3.8
1.50	2.74	4.7	5.8
2.00	2.84	4.5	6.3
2.50	2.94	5.6	5.3

given in Table III. From these values various thermodynamic parameters were calculated which are tabulated in Table IV with the data of the Janovsky reaction with acetone.[1] The data obtained under the conditions of various concentrations of cyclohexanone and the constant concentrations of TNB and sodium methoxide, are given in Table V.

Since in the case of cyclohexanone the rate-determining step and the solvent effect of cyclohexanone on the color development are similar to those described in the case of acetone,[1] only the differences of the kinetic and thermodynamic parameters between the two cases are discussed together with the thermodynamic parameters of some Meisenheimer type complexes. Although the precise comparison is not capable because of the difference of the magnitude of the solvent effect between cyclohexanone and acetone, K_2k_3 in the case of cyclohexanone is about 7 times larger than that of acetone. The equilibrium constant K_2 in methanol has not been reported. In water, however, pKa of cyclohexanone is 16.7 in keto form and11.3 in enol form, while pKa of acetone is 19—20 in keto form.[13] The enol content of aqueous cyclohexanone and acetone at 5.8×10^{-2}M ketone solution are 4.1×10^{-6} and 2×10^{-6} at 25°, respectively.[13] Though K_2 is the apparent value of the mixture of keto and enol forms of active methylene compounds, K_2 of cyclohexanone may be much larger than that of acetone from the data mentioned above. So k_3 of cyclohexanone may be fairly smaller than that of acetone. Since k_{-3} of cyclohexanone is about twice larger than that of acetone, K_3 of cyclohexanone must be smaller than that of acetone. Though the activation energy of the formation of I is nearly equal to that of σ complex with acetone (V), the activation energy of the decomposition of I is smaller than that that of V, and hence ΔH is larger in the case of cyclohexanone than that of acetone. Thermodynamic parameters of σ complexes II and VI that is one of the most stable Meisenheimer complexes has been reported as follows; the activation energies of the formation of II and VI in methanol are 10.2[14] and 13.5[15] kcal mole^{-1} respectively, and that of the decomposition of II and VI are 9.2[14] and 19.0[15] kcal mole^{-1}, respectively. These facts show that Meisenheimer type complex formed by carbanion such as I or V is more stable than that formed by alkoxide such as II or VI. It is very interesting that the entropy of activation of the decomposition is positive in the both cases of I and V, and anomalously large in the case of V. This may be related to the formation of the bicyclic type compound such as III and IV, and V may exist in very orderly conformation more



V



VI

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[13] R.P. Bell and P.W. Smith, *J. Chem. Soc.* (*B*), **1966**, 241.
[14] C.F. Bernasconi, *J. Am. Chem. Soc.*, **92**, 4682 (1970).
[15] J.H. Fendler, E.J. Fendler, and C.E. Griffin, *J. Org. Chem.*, **34**, 689 (1969).

similar to the transition state to IV compared with the transition state of the decomposition of V to TNB. Complex I may be less orderly than V and may exist in the conformation somewhat apart from the transition state to III for the steric requirement of cyclohexanonyl group. The difference in the stability between I and V may be attributable to their conformations.

It is worth remarking that the rate-determining step of the Janovsky reaction of TNB with cyclohexanone or acetone is the addition of the anion of active methylene compound to aromatic ring. Though cyclohexanone or acetone has not so large steric requirement in this reaction as fused ring active methylene compounds, for example 17-keto steroids, the rate-determining step is the addition step. This must mean that in general the rate-determining step of the Janovsky reaction of TNB is not the deprotonating step of active methylene compounds but the addition step. This may not be due to the ortho nitro groups, because they do not undergo steric inhibition of resonance in the transition state of aromatic nucleophilic substitution16) and in practice the steric hindrance of two ortho nitro groups is not pronounced in Meisenheimer compound.17) In addition to this, *m*-dinitrobenzene is far less reactive than TNB. When the mechanism of the Janovsky reaction of *m*-dinitrobenzene is considered from these points of view, the rate-determining step must be the addition step, too. This speculation can reasonably be extended to the assumption that the rate-determining step of the Zimmermann reaction of *m*-dinitrobenzene is not the deprotonating step of active methylene compound, but the same step as the Janovsky reaction or the oxidizing step of the Janovsky complex. If the rate-determining step is the oxidizing step, the color initially developed in the Zimmermann reaction must be based on the Janovsky complex. But in practice it is not true and the absorption maximum coincides with the oxidized product which is the Zimmermann complex.19) Hence, it is concluded that the rate-determining step of the Zimmermann reaction of *m*-dinitrobenzene must be the addition step of the anion of active methylene compound. Nevertheless, another speculation has been reported on the mechanism of the Zimmermann reaction. Nambara inferred that in the simple ketone the rate-determining step is the deprotonation step and in the fused ring system such as oxosteroids the rate depends not only on the relative ease of deprotonation of α-methylene but also on the steric requirement of bulky 2,4-dinitrophenyl group to be introduced.19a) Klyne described that rates of the Zimmermann reactions for some of the steroid ketones can be roughly correlated with their known properties on the basis of enolization as the rate-controlling step.19b) As these reports cited above are not based on the precise kinetic experiments, they are inadequate and further kinetic study on the Zimmermann reaction is now expected.

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16) F. Pietra, *Quart. Rev.* (London), **23**, 504 (1969).

17) This has been shown by X-ray crystal analysis of VI.18)

18) H. Ueda, N. Sakabe, J. Tanaka, and A. Furusaki, *Bull. Chem. Soc. Japan*, **41**, 2866 (1968).

19) *a*) M. Kato, M. Ohnishi, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **16**, 2398 (1968); *b*) D.N. Kirk, W. Klyne, and A. Mudd, *J. Chem. Soc.* (*C*), **1968**, 2269.