

Mechanism of the Color Reaction of Active Methylene Compounds with 1,3,5-Trinitrobenzene Derivatives. III.¹⁾ The Color Reactions of Cyclohexanone, and Acetophenone, with 1,3,5-Trinitrobenzene²⁾

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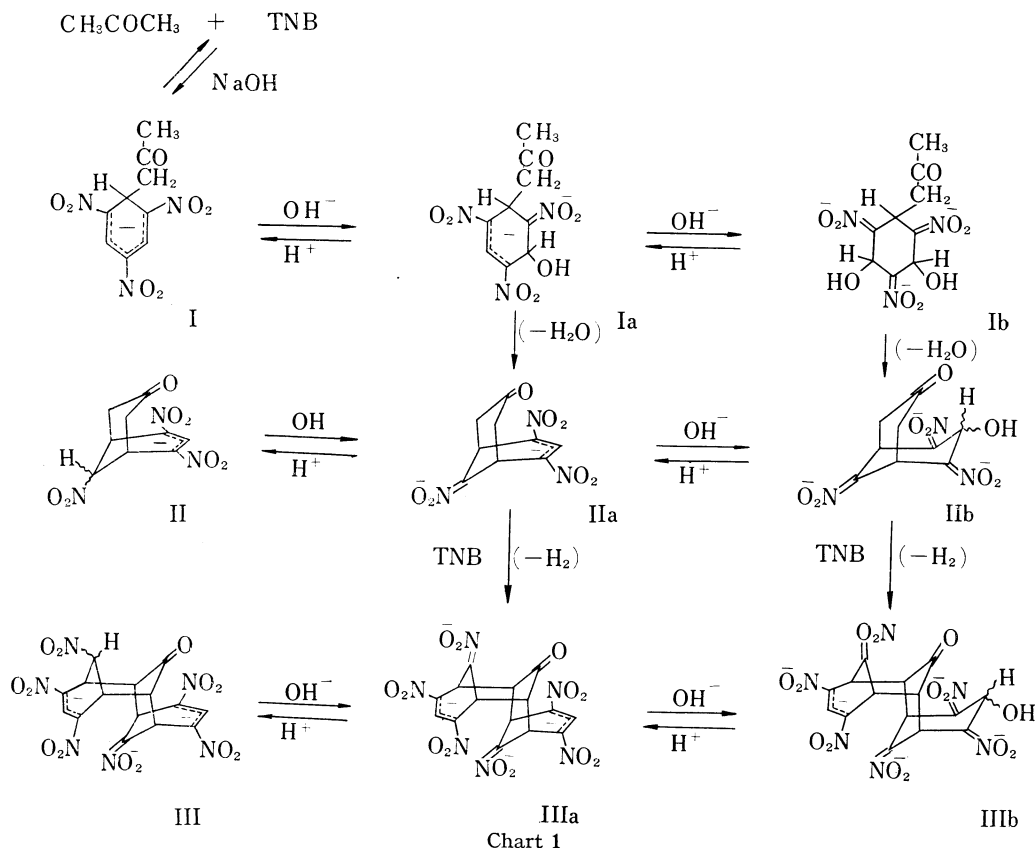
The color reactions of cyclohexanone, and acetophenone, with 1,3,5-trinitrobenzene were investigated. Two main coloring matters, a Meisenheimer type compound, IV Na and a tricyclic type compound, V Na, were isolated from the reaction mixture of cyclohexanone. In the case of the reaction of acetophenone with excessive 1,3,5-trinitrobenzene, the Meisenheimer type compound, VII Na, was the sole coloring matter. From a comparison of the absorption spectral behavior of them with the color reaction mixtures, mechanisms of the color reactions of cyclohexanone, and acetophenone, under the spot test procedure were elucidated.

It has been well known that the Meisenheimer type anions⁴⁾ are formed in the reactions of several ketones with 1,3,5-trinitrobenzene (TNB) in the presence of a base and some of them are easily transformed into the bicyclic type anions.^{1,5,6)}

In the previous paper of this series,⁷⁾ it was shown that the coloration of active methylene compounds with TNB in an aqueous sodium hydroxide solution was intensified when the alkaline reaction mixture was neutralized by sodium dihydrogen phosphate. This phenomenon has been effectively used in the spot test detection of active methylene compounds, and the color change of the reaction mixture of acetone with TNB has been explained^{1,5)} as summarized in Chart 1.

Acetone reacts with TNB in a sodium hydroxide solution to form anion I, which is in equilibrium with anions Ia and Ib in the early stage of the reaction. Then, Ia and Ib are gradually transformed into bicyclic type anions IIa and IIb, respectively. These transformations are irreversible. And further, IIa and IIb combine with one molecule of TNB to form tetracyclic type anions, IIIa and IIIb, respectively, in the presence of excessive TNB. When the alkaline reaction mixture is neutralized by sodium dihydrogen phosphate, Ia and Ib return to I, IIa and IIb to II, and IIIa and IIIb to III, respectively. These shifts of equilibria cause

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- 2) This forms "Organic Analysis LXXXVI." Part LXXXV: Y. Ohkura and T. Mizumoto, *Rinsho Kagaku*, **1**, 215 (1972).
- 3) To whom all inquiries should be addressed. Location: *Katakasu, Higashi-ku, Fukuoka*; a) Emeritus Professor of Kyushu University. Present address: *102-7, Aza-Mukai, Ohaza-Higashimisugi, Sayama, Saitama*.
- 4) a) J. Meisenheimer, *Ann.*, **323**, 209 (1902); b) M. Kimura, *Yakugaku Zasshi*, **73**, 1219 (1953). For reviews, see R. Foster and C.A. Fyfe, *Rev. Pure and Appl. Chem.*, **16**, 61 (1966); M.R. Crampton, *Adv. Phys. Org. Chem.*, **7**, 211 (1969); M.J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
- 5) T. Momose, Y. Ohkura, and K. Kohashi, *Chem. Pharm. Bull.* (Tokyo), **17**, 858 (1969); K. Kohashi, Y. Ohkura, and T. Momose, *ibid.*, **18**, 2151 (1970).
- 6) a) R. Foster, M.I. Foreman, and M.J. Strauss, *Tetrahedron Letters*, **1968**, 4949; M.I. Foreman, R. Foster, and M.J. Strauss, *J. Chem. Soc. (C)*, **1969**, 2112; b) M.J. Strauss and H. Schran, *J. Am. Chem. Soc.*, **91**, 3974 (1969); M.J. Strauss, T.C. Jensen, H. Schran, and K. O'Conner, *J. Org. Chem.*, **35**, 383 (1970); M.J. Strauss and H. Schran, *Tetrahedron Letters*, **25**, 2349 (1971).
- 7) T. Momose, Y. Ohkura, and K. Kohashi, *Chem. Pharm. Bull.* (Tokyo), **11**, 301 (1963).



the increase in the intensity of the color due to the formation of I, II and/or III. I shows a characteristic absorption spectrum in the visible region (the Meisenheimer band) (*cf.* Fig. 1, 1, Fig. 2, 1, Fig. 3, a, Fig. 5, 1 and 2, Fig. 6, 1, and Fig. 7, a) and other anions as described in Chart 1 except Ib and IIb have a dinitropropenide function of TNB ring system, which shows a maximum at about 480 nm in aqueous medium.

Strauss and his co-workers have also proposed two different mechanisms for the cyclization of the Meisenheimer type anions to the bicyclic type anions in nonaqueous basic media.^{6b)} However, their mechanisms could be inapplicable to an explanation of the color changes in the reactions of several ketones with TNB in aqueous medium.

In the present paper, we have investigated the color reactions of cyclohexanone, and acetophenone, with TNB under the conditions of the spot test procedure⁷⁾ by comparing the spectral behavior of the reaction mixtures with that of the isolated crystalline coloring matters.

The Color Reaction of Cyclohexanone with TNB

The absorption spectra of the color reaction mixture of cyclohexanone with TNB are shown in Fig. 1.

Two main coloring matters formed in the reaction were isolated in crystalline forms from the reaction mixture. One of them was assigned to the Meisenheimer type compound, sodium salt of IV (IV Na) (Chart 2) and the other to a tricyclic type compound, sodium salt of V⁸⁾ (V Na) (Chart 3).

8) The anion V was also obtained as piperidinium salt from the reaction mixture of cyclohexanone, TNB and piperidine in methanol. The piperidinium salt thus obtained (mp 195° (decomp.)) was easily converted to sodium salt by treating it with sodium hydroxide as well as in the case of piperidinium salt of II as described in the previous paper.⁵⁾

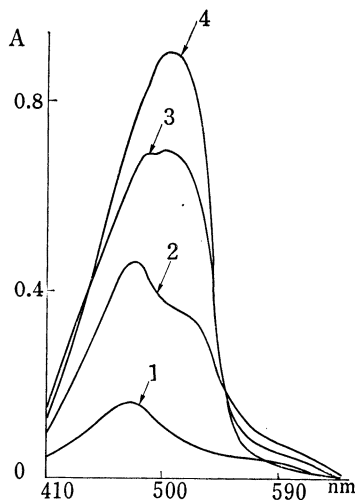


Fig. 1. Absorption Spectra of Reaction Mixtures of Cyclohexanone with TNB

To 2.0 ml of a dimethylformamide (DMF) solution of cyclohexanone ($1.4 \times 10^{-4} M$), 1.0 ml each of 0.1% TNB¹⁻⁹ and aq. 1.8% NaOH were successively added. The solution was kept at 37° for various periods, and then neutralized with 1.0 ml of aq. 18% $NaH_2PO_4 \cdot 2H_2O$.
1) 2 min; 2) 15 min; 3) 60 min; 4) 180 min
The spectra were measured against the reagent blank.

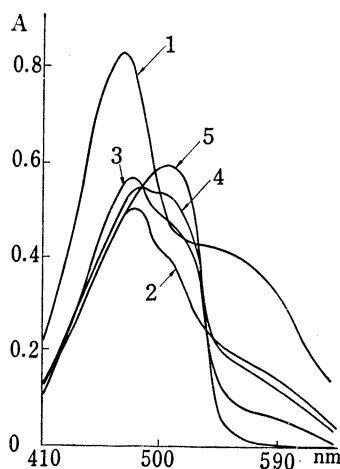


Fig. 2. Changes of Absorption Spectrum of IV Na with Time in the Presence of TNB

The reactions were carried out under the same conditions as the legend for Fig. 1 by using a DMF solution of IV Na ($2.0 \times 10^{-4} M$) instead of cyclohexanone
1) immediately; 2) 5 min; 3) 15 min; 4) 30 min; 5) 180 min
The spectra were measured against the reagent blank.

An aqueous solution of IV Na showed a typical Meisenheimer band and the mode of spectral change of the Meisenheimer band to another in the presence of TNB was similar to that of the reaction mixture (Fig. 1) as shown in Fig. 2.

When sodium hydroxide was added to the aqueous solution of IV Na, the solution showed a new band with a maximum at about 480 nm (Fig. 3, a and b). The intensity of the new band was decreased with increasing concentration of the alkali (Fig. 3, b). When these alkaline solutions were neutralized by sodium dihydrogen phosphate immediately after the solutions were made alkaline, the initial Meisenheimer band was recovered. The spectral changes were reversible, showing an isosbestic point at 318 nm. These observations indicate that IV is in equilibrium with other anions, IVa and IVb, in the alkaline solution (Chart 2). The chromogenic groups of the anions were assumed from the similarity of the absorption spectral behavior of I and its equilibrium system (Chart 1) as described in the previous paper.¹⁾ Then, the new band with a maximum at 480 nm was ascribed to the anion IVa (Fig. 3, b₁ or b₂) and the band with a maximum at 286 nm and a weak absorption in the visible region to the anion IVb (Fig. 3, b₃). These spectra showed isosbestic points at 248 and 268 nm.

When the alkaline solutions were allowed to stand for an hour or so, these bands (Fig. 3, b) did not return to the initial Meisenheimer band (Fig. 3, a) even if the solutions were neutralized. The solutions thus neutralized showed a new band with a maximum at 480 nm (Fig. 3, c), which agreed with that of an aqueous solution of V Na (Fig. 4, a). These observations suggest that such a change of IV to V is performed in aqueous alkaline media even in the absence of TNB.

The absorption spectrum of an aqueous solution of V Na was also changed by the addition of sodium hydroxide (Fig. 4, a and b) and turned to the initial one by the neutralization (Fig. 4, c). The spectra in the alkaline solutions showed an isosbestic point at 318 nm. These reversible changes of the spectra suggest that V is also in equilibrium with other anions, Va

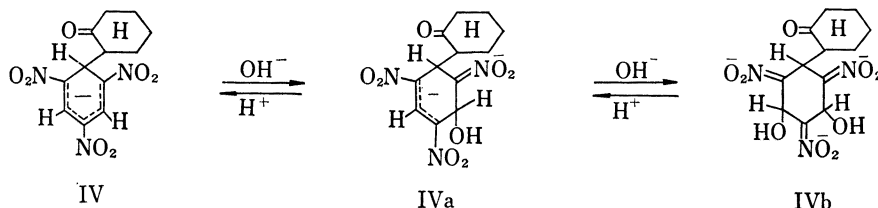


Chart 2

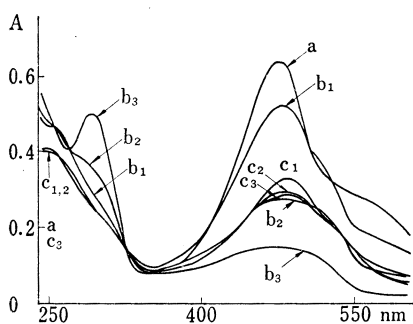


Fig. 3. Changes of Absorption Spectrum of IV Na in the Absence of TNB

- 2.0 ml of aq. solution of IV Na ($1.0 \times 10^{-4} \text{M}$) was diluted with 3.0 ml of H_2O .
- To 2.0 ml of aq. solution of IV Na ($1.0 \times 10^{-4} \text{M}$), 1.0 ml each of H_2O and NaOH (1, 0.1; 2, 0.5; 3, 2.5%) were successively added. After being mixed well, the solution were diluted with 1.0 ml of H_2O .
- Alkaline solutions of IV Na in b) were allowed to stand for 60 min at room temperature (27°), then, neutralized with 1.0 ml of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (1, 0.5; 2, 2.5; 3, 12.5%). The spectra were measured against H_2O .

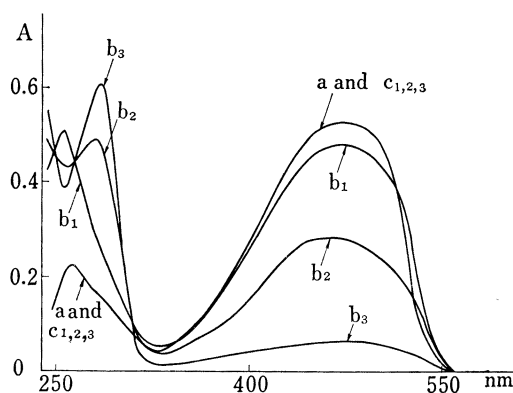


Fig. 4. Changes of Absorption Spectrum of V Na in Alkaline and Neutralized Solutions

- 2.0 ml of aq. solution of V Na ($1.0 \times 10^{-4} \text{M}$) was diluted with 3.0 ml of H_2O .
- To 2.0 ml of aq. solution of V Na ($1.0 \times 10^{-4} \text{M}$), 1.0 ml each of H_2O and NaOH (1, 0.05; 2, 0.5; 3, 2.5%) were successively added. After being mixed well, the solutions were diluted with 1.0 ml of H_2O .
- Alkaline solutions of V Na in b) were neutralized with 1.0 ml of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (1, 0.25; 2, 2.5; 3, 12.5%). The spectra were measured against H_2O .

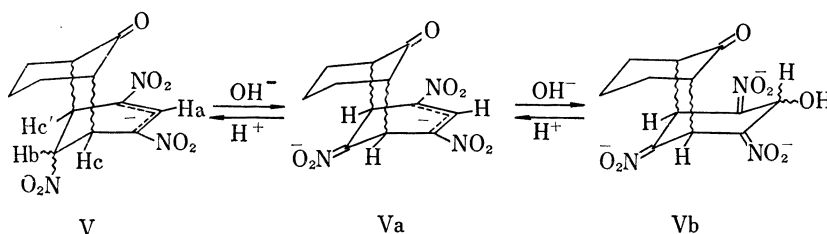
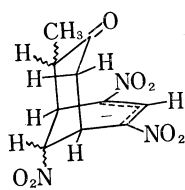


Chart 3

and Vb, in the alkaline solutions (Chart 3). The chromogenic groups of the anions were assumed from the similarity of the spectral behavior of II and its equilibrium system (Chart 1) as described in the previous paper.⁴⁾ The spectrum with two maxima at 258 and 480 nm (Fig. 4, b_1) was ascribed to the anion Va and the spectrum with a maximum at 282 nm (Fig. 4, b_3) to the anion Vb. These spectra showed isosbestic points at 248 and 268 nm.

Changes of absorption spectra of IV Na and V Na (Fig. 3 and 4) are close similar to those of sodium salts of I and II as described in the previous paper.^{1,5)} When V Na was treated with excessive TNB in alkaline medium, the increase in the absorption intensity of the visible spectral region did not occur. But when sodium salt of I or II was treated in the same way, the increase in the intensity was observed, which was proved to be due to the formation of

the tetracyclic compound, III as shown in Chart 1, and the same phenomenon was also observed in the case of the coloring matter, sodium salt of VI as shown in Chart 4, isolated from the reaction mixture of methyl ethyl ketone and TNB as described in the previous paper.⁵⁾ This fact suggested that a tetracyclic type compound was not formed in the reaction of cyclohexanone with TNB, and the reaction might proceed as follows (Chart 5).



VI
Chart 4

TNB + cyclohexanone

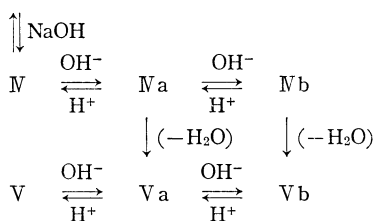


Chart 5

Cyclohexanone reacts with TNB to form IV, which is in equilibrium with IVa and IVb in alkaline medium. IVa and IVb are gradually transformed into Va and Vb, respectively. When the reaction mixture is neutralized, IVa and IVb return to IV, and Va and Vb to V.

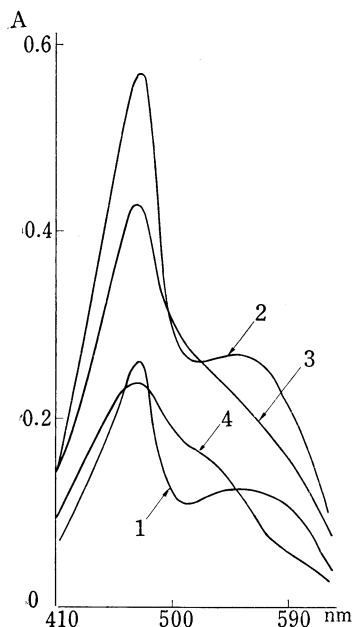


Fig. 5. Absorption Spectra of Reaction Mixture of Acetophenone with TNB

The reactions were carried out under the same conditions as the legend for Fig. 1 by using a DMF solution of acetophenone ($1.7 \times 10^{-4} \text{M}$) instead of cyclohexanone

1) 1 min; 2) 15 min; 3) 60 min; 4) 120 min

The spectra were measured against the reagent blank.

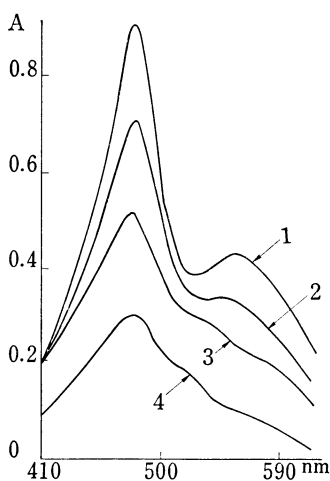


Fig. 6. Changes of Absorption Spectrum of VII Na in the Presence of TNB

The reactions were carried out under the same conditions as the legend for Fig. 1 by using a DMF solution of VII Na ($1.0 \times 10^{-4} \text{M}$) instead of cyclohexanone

1) immediately; 2) 15 min; 3) 30 min; 4) 120 min

The spectra were measured against the reagent blank.

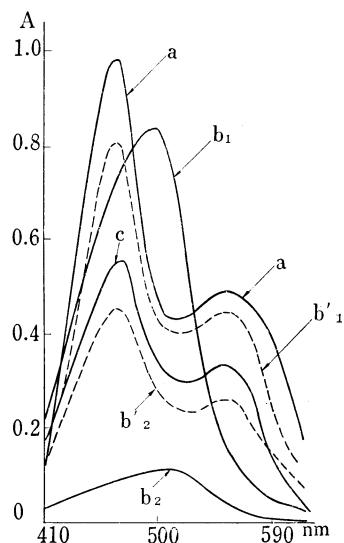


Fig. 7. Changes of Absorption Spectrum of VII Na in Alkaline and Neutralized Solutions

- 2.0 ml of aq. solution of VII Na ($1.0 \times 10^{-4} \text{M}$) was diluted with 3.0 ml of H_2O .
 - To 2.0 ml of aq. solution of VII Na ($1.0 \times 10^{-4} \text{M}$), 1.0 ml each of H_2O and NaOH (1, 0.5%; 2, 1.5%) were successively added. Immediately after being mixed well, the mixture was diluted with 1.0 ml of H_2O .
 - Alkaline solutions of VII Na in b) were neutralized with 1.0 ml of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (1, 2.5%; 2, 7.5%) instead of the addition of H_2O .
 - Aq. solution of VII Na in a) was allowed to stand for 60 min.
- The spectra were measured against H_2O .

These shifts of equilibria cause the color due to IV and/or V to become deeper. Therefore, the coloration of cyclohexanone under the conditions of the spot test procedure, in which the reaction mixture is neutralized, is ascribed to IV in the early stage of the reaction, then to the mixture IV and V, and finally to V.

The Color Reaction of Acetophenone with TNB

The absorption spectrum of the color reaction mixture of acetophenone with TNB under the conditions of the spot test procedure changes with time (Fig. 5). The intensity of the Meisenheimer band attained a maximum after 15 min (Fig. 5, 1—2) and then decreased with deforming the band shape (Fig. 5, 3—4). Similar change of the Meisenheimer band was also observed when the Meisenheimer type compound, derived from acetophenone and TNB, sodium salt of VII^{4b)} (VII Na), was treated with alkali in the presence of TNB (Fig. 6). These changes of spectra suggest that VII Na is the sole coloring matter formed under the conditions of the color reaction. The mechanism of this reaction proposed by Kimura^{4b)} was also applicable to this case, except for the reason why the Meisenheimer band appeared when the alkaline reaction mixture, which showed a strong red color, was neutralized by sodium dihydrogen phosphate (Fig. 5).

When sodium hydroxide was added to an aqueous solution of VII Na, the Meisenheimer band (Fig. 7, a) was immediately changed to a new band with a maximum at 510 nm (Fig. 7, b₁ or b₂). The intensity of this band decreased with increasing concentration of the alkali (Fig. 7, b₁ and b₂). When the alkaline solutions were neutralized by sodium dihydrogen phosphate, the Meisenheimer bands (Fig. 7, b'₁ and b'₂) recovered though their intensities were lower than that of the initial band (Fig. 7, a). These changes of spectra suggest that VII is in equilibrium with other anions, VIIa and VIIb, in the alkaline solution (Chart 6).

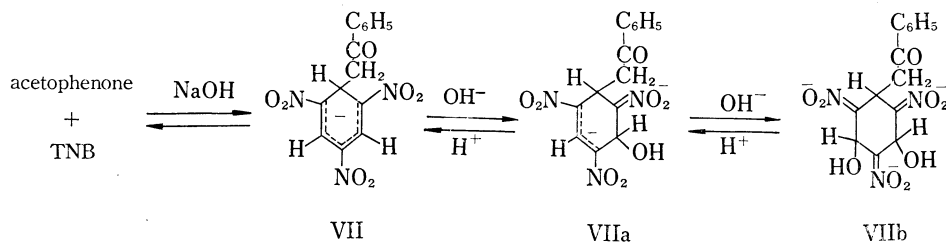


Chart 6

VIIa was ascribed to the spectrum with a maximum at 510 nm and VIIb to that with a weak absorption in the visible region (Fig. 7, b₂).

An aqueous solution of VII Na was fairly unstable and the intensity of the spectrum decreased with time keeping its band shape (*cf.* Fig. 7, a and b). Then, VIIa and VIIb were also considered to be unstable in the alkaline solutions. This probably caused the absorption intensities of the reproduced Meisenheimer bands to become lower (Fig. 7, b'₁ and b'₂).

On the other hand, according to the mechanism of the Zimmermann reaction⁹⁾ of acetophenone with *m*-dinitrobenzene,¹⁰⁾ it might be possible to consider that sodium salt of the conjugate base of 2,4,6-trinitrobenzyl phenyl ketone,^{4b,11)} sodium salt of VIII (Chart 7), was also one of the main coloring matters produced in the reaction of acetophenone with TNB.

- 9) W. Zimmermann, *Z. Physiol. Chem.*, **233**, 257 (1935); *idem, ibid.*, **245**, 47 (1937); O. Neunhoeffer, K. Thewalt, and W. Zimmermann, *ibid.*, **323**, 116 (1961). For reviews, see T. Nambara, *Bunseki Kagaku*, **13**, 184 (1964); E. Bunzel, A.R. Norris, and K.E. Russell, *Quart. Rev.*, **22**, 123 (1968).
- 10) T.J. King and C.E. Newall, *J. Chem. Soc.*, 367 (1962); R. Foster and R.K. Mackie, *Tetrahedron*, **18**, 1131 (1962).
- 11) M. Kimura, *Yakugaku Zasshi*, **73**, 1216 (1953).

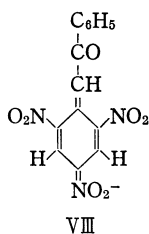


Chart 7

However, such a compound as sodium salt of VIII is not a main coloring matter under the present conditions of the spot test procedure. This is quite evident from the following facts: When the alkaline reaction mixture was neutralized by sodium dihydrogen phosphate, the solution showed the color due to only the Meisenheimer type anion (*cf.* Fig. 5), whereas, the alkaline color of 2,4,6-trinitrobenzyl phenyl ketone, which showed a spectrum with a maximum at 510 nm under the same solvent system, disappeared. The change of the Meisenheimer band to another in the absence of TNB in sodium hydroxide solution proceeded in the virtually same mode as those in the presence of TNB as shown in Fig. 6. It might thus be considered that TNB did not play an important role in the change of VII to another as well as in the case of the cyclization of IV to V.

From the above results, the color reaction of acetophenone with TNB under the conditions of the spot test procedure was explained by the scheme as shown in Chart 6, successfully.

Experimental¹²⁾

Isolation of IV Na—To a solution of 2.0 g of cyclohexanone and 1.0 g of TNB in 100 ml of MeOH, 1.0 g of NaOH powder was added with stirring at room temperature (20°). After 25 min, NaOH was filtered off with glass filter. The filtrate was evaporated to dryness *in vacuo*.

The residue was dissolved in a small amount of acetone and filtered. When benzene was added to the acetone solution, black violet precipitates were produced. Recrystallization from acetone-benzene gave black violet needles. Yield, 0.7 g. The crystals showed no melting point and exploded when ignited or heated rapidly. *Anal.* Calcd. for C₁₂H₁₂O₇N₃Na: C, 43.25; H, 3.63; N, 12.61; Na, 6.90. Found: C, 43.00; H, 3.88; N, 12.75; Na, 7.20. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2940, 2875, 1470 (CH₂), 1693 (CO), 1550, 1345, 1250—1210, 745—735 (NO₂, NO₂⁻ in 1,3,5-trinitrocyclohexadienate). UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm (ϵ): 245 (23000), 475 (11200), 550 (5500).

Isolation of V Na—The procedure was carried out in the same way as in the case of I, II or III as previously described^{1,4)} by using 0.5 g of cyclohexanone, 3.0 g of TNB, 300 ml of DMF, 100 ml of aqueous 1.8% NaOH and 100 ml of aqueous 18% NaH₂PO₄·2H₂O. Recrystallization from MeOH-ether gave purple red needles. Yield, 0.3 g. The crystals showed no melting point and exploded when ignited or heated rapidly. *Anal.* Calcd. for C₁₂H₁₂O₇N₃Na: C, 43.25; H, 3.63; N, 12.61; Na, 6.90. Found: C, 43.53; H, 3.82; N, 12.55; Na, 7.00. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2975, 2850, 1460 (CH₂), 1710 (CO), 1534 (NO₂), 1350—1336 (NO₂ and NO₂⁻), 1250—1215, 760—740 (NO₂⁻). NMR (in acetone-*d*₆) δ ppm: 8.37 (1H, Ha), 6.18 (1H, triplet, *J* = 3.0 Hz, H_b), 4.40 (2H, poorly resolved triplet, *J* = 3.0 Hz, H_c and H_{c'}), 2.8—2.2 (8H, multiplet, protons belong to original cyclohexanone). A configuration of this compound could not be determined, because it was considered to have a number of stereoisomers. UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ nm (ϵ): 262 (6000), 480 (13800).

Preparation of VII Na—It was prepared by Kimura's method.^{4b)}

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12) Absorption spectra were measured by a Hitachi 124 Spectrophotometer, equipped with Hitachi 056 Recorder, in a cell of 10 mm optical length. IR spectra were measured by a Nihonbunko DS 701-G Infrared Spectrophotometer in KBr pellet. NMR spectra were measured by a JEOL C-60H NMR Spectrometer with tetramethylsilane (TMS) as an internal standard.