KINETICS OF REACTION OF 1-SUBSTITUTED 3,5-DINITROBENZENES WITH CYCLOHEXANONE

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Kinetics of formation and decomposition have been studied of the Meisenheimer complexes formed by reaction of cyclohexanone anion with piperidide, methyl ester and nitrile of 3,5-dinitrobenzoic acid. The reactions were carried out in mixtures cyclohexanone–methanol in the presence of methoxide ions at 25°C. In all the cases the addition of the carbanion to 2(6)-position was faster and the complex formed was more stable than that at 4-position.

The 1-substituted 3,5-dinitrobenzenes react with anions of C-acids to give two isomeric Meisenheimer complexes[1] (Scheme 1). The symmetrical complexes *II* are less stable thermodynamically and are converted into complexes *III* (ref.[1,2]). The isomerization reactions of the complexes formed by reaction of anions of weak C-acids (*e.g.* acetone) are relatively slow[2], which make it possible to determine structures of the both isomers[1-3] from NMR spectra of the reaction products. Kinetics of formation, reverse reactions and isomerization reaction were studied with the complexes of 3,5-dinitrobenzoic acid piperidide and acetone[2].

In the present paper the kinetics have been studied of the methoxide ion-catalyzed reactions of cyclohexanone with 3,5-dinitrobenzoic acid piperidide, nitrile and methyl ester in methanol–cyclohexanone mixtures. The aim of the present work is the determination of polar and eventually also steric effects of 1-substituents on the rate constants of formation and decomposition of isomeric Meisenheimer complexes and comparison with similar reactions of acetone.

EXPERIMENTAL

Reagents

Methyl 3,5-dinitrobenzoate and 3,5-dinitrobenzoic piperidide were prepared from 3,5-dinitrobenzoyl chloride in usual way[4]. Purity of the compounds was checked by NMR spectroscopy. 3,5-Dinitrobenzonitrile, m.p. 128—129°C (ref.[5] 127°C) was prepared by dehydratation of 3,5-dinitrobenzamide with phosphorus pentoxide and purified by crystallization from n-butanol.

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Commercial cyclohexanone was distilled, and the fraction boiling within 152—154°C was taken, shaken several times with about 10% aqueous K_2CO_3 and redistilled. The middle fraction was used for kinetic measurements. Dimethyl sulphoxide was dried with CaO, distilled *in vacuo* and kept over molecular sieves. The other chemicals used were commercial products of *p.a.* purity grade. The substrates were used as 0·01M methanolic solutions. The samples of the Meisenheimer complexes for NMR measurements were prepared in similar way as the complexes with acetone[1,2]. The complexes from 3,5-dinitrobenzoic acid piperidide and nitrile were isolated as solids, that from methyl ester in the form of viscous oil. Their saturated solutions in dimethyl sulphoxide were used for the measurements. The spectra were measured with the use of a Tesla BS 487 B apparatus at 80 MHz at the room temperature.

Kinetic Measurements

Preliminary informative kinetic measurements were carried out with a Unicam SP 800 spectrophotometer at 25°C by measuring the spectra of the reaction solutions within 350—700 nm at regular time intervals. The proper kinetic measurements were carried out with a VSU-2P spectrophotometer (Zeiss, Jena) at 25°C. In the case of measurements of the reaction rate of isomerization $II \rightarrow III$ the chosen amounts of cyclohexanone, methanol and sodium methoxide solution were pipetted into the 1 cm quartz cell. The final volume was 2 ml. After temperation 40 µl of 0·01M substrate solution was injected into the cell which was then closed and the content thoroughly shaken. The absorbance decreases were measured at 650, 625 and 640 nm for amide, ester and nitrile of 3,5-dinitrobenzoic acid, respectively. The procedure of measurements of the reverse reaction rate $(II \rightarrow I)$ was the same until mixing except for the methanol amount added which was smaller by 0·1 ml. The cell was then opened and 0·1 ml methanolic acetic or hydrochloric acid of the chosen concentration was injected therein. After closing and shaking the absorbance decreases were measured at the abovementioned wavelengths. The reaction mixture for measuring the reverse reaction of the unsymmetrical complex $(III \rightarrow I)$ was prepared in the same way as that for the reverse reaction of the symmetrical complex except for that (a) only 20 µl of the substrate was added, and b) the solution of acid was added only after a time of about 5 half-lives of the isomerization reaction. In the case of the amide and nitrile the absorbance decrease was measured at λ_{max} of the respective unsymmetrical complex (550 and 540 nm), whereas in the case of the ester (λ_{max} 540 nm) it was measured at 510 nm where the symmetrical isomer does not practically absorb. The rates of formation of the complexes $(I \rightarrow II + III)$ were measured at λ_{max} 650 nm of the unsymmetrical complex and at the isosbestic point of the both complexes (560 nm) in the case of the amide and ester, respectively. Again the reaction solutions were prepared by mixing cyclohexanone, methanol, and CH_3ONa solution (overall 2 ml) and injecting 20 µl substrate solutions. The rate constants were calculated from the time dependence of $\log(A_t - A_\infty)$ resp. $\log(A_\infty - A_t)$.

Formation of the complexes from the nitrile was very fast, and therefore, it was followed with the use of a Durrum Gibson Stopped Flow Spectrophotometer at 580 nm. The reaction was carried out by mixing equal amounts of 10^{-4}M solution of 3,5-dinitrobenzonitrile in 1 : 1 mixture methanol–cyclohexanone with 0·02 to 0·04M-CH_3ONa in the same solvent. The reaction half-life was read from the screen of the oscilloscope, and the rate constant was calculated from the relation $k = 0·693/t_{1/2}$. Besides the absorbance change at 580 nm the absorbance increase at 460 nm (corresponding to formation of the nitrile–methoxide complex) was measured at similar conditions, too.

Acid catalysis of the reverse reaction of unsymmetrical complex from 3,5-dinitrobenzonitrile was studied as it follows: solution of this complex was prepared by mixing 1 ml cyclohexanone, 0·2 ml 0·1M sodium methoxide and 0·8 ml 10^{-2}M nitrile in methanol. After 10 minutes 0·1 ml

of this solution was injected into 3·9 ml acetate resp. chloroacetate buffer in methanol. The ionic strength was adjusted at 0·02 by addition of 0·5M methanolic lithium chloride. A part of the solution thus prepared was placed into a cell, and the absorbance decrease at 640 nm was measured by means of a VSU-2P spectrophotometer (Zeiss).

RESULTS AND DISCUSSION

Complexes of the both types *II* and *III* can be formed in reaction of 1-X-3,5-dinitro-benzenes with cyclohexanone anion (Scheme 1). Analysis of NMR spectra of the complexes prepared (Table I) and comparison of the chemical shifts with those of complexes of *Ia,b* with acetone[2] showed that the complexes prepared from *Ib* and *Ic* are mixtures of the isomers *II* and *III*. The unsymmetrical complex *III* predominates in the both cases. In the case of the substrate *Ia* the presence of the symmetrical complex *IIa* was not detected by NMR. The spectra were interpreted according to the rules of systems of the 1. order and by comparison with the spectra of the complexes of the same substrates with acetone[2,3].

The non-equivalence of the protons H2 and H6 of the symmetrical complexes *II* is probably due to hindered rotation around the bond connecting the both rings[6]. In the case of the unsymmetrical complexes *III* the protons H4 and H6 are located between different substituents, and, therefore, their chemical shifts are fundamentally different from each other (Table I). As it is the case with the symmetrical complexes, again in these cases there exist two rotamers, and, therefore, there are two multiplets for each of the protons H4 and H6. The both rotamers are not equivalent energetically in these cases (in contrast to the complexes *II*), and, therefore, their population is not the same either — the two multiplets for H4 resp. H6 have different intensities.

TABLE I
Values of Chemical Shifts (τ) and Coupling Constants J (Hz) in Complexes *II* and *III* in Dimethyl Sulphoxide

Complex	H_2	H_4	H_6	$J_{2,4}$	$J_{2,6}$	$J_{4,6}$	$J_{2,\alpha}$	$J_{4,\alpha}$
IIb	2·04	4·71	1·96	∼1	∼1	∼1	—	6·5
IIc	2·45	4·60	2·36	—[a]	—[a]	—[a]	—	7·0
IIIa[b]	5·22	1·74	3·34	1·0	0	2·0	2·0	—
IIIb[c]	5·18	1·71	2·28	1·2	0	1·8	6·0	—
IIIc[d]	5·18	1·71	2·58	—[a]	0	1·9	1·5	—

[a] Due to lower quality of spectra it was not possible to determine the coupling constants values.
[b] H_2 5·43τ, H_4 1·75τ, H_6 3·31τ, $J_{2,\alpha}$ 6·0 Hz. [c] H_4 1·77τ, H_6 2·23τ. [d] H_2 5·50τ, H_4 1·71τ, H_6 2·65τ, $J_{2,\alpha}$ 5·5 Hz.

The reaction of 1-X-3,5-dinitrobenzenes with cyclohexanone catalyzed by methoxide ion takes a two-step course (Scheme 1). The first reaction is much faster than the subsequent one so that the concentration ratio of methoxide and cyclohexanone anions is constant in the whole reaction course, and it is given by the value of the equilibrium constant K defined by Eq. (1). The rate of the formation of the complex II (v_2) can be expressed as in Eq. (2). The rate v_3 of formation of the complex III can be defined analogously.

$$K = [CH_3OH][C_6H_9O^-]/[CH_3O^-][C_6H_{10}O] = K'[CH_3OH], \qquad (1)$$

$$v_2 = k_2[C_6H_9O^-][I] = k_2K'[CH_3O^-][C_6H_{10}O][I]. \qquad (2)$$

Besides the reactions given in Scheme 1 some subsequent reactions, such as base--catalyzed cyclization of the complexes II and III, take place at higher methoxide ion and cyclohexanone concentrations[7]. At the same time it is advantageous for determination of the rate constants k_2K' and k_3K' and isomerization constant k_{iso} to work at relatively higher concentrations of methoxide ion and cyclohexanone
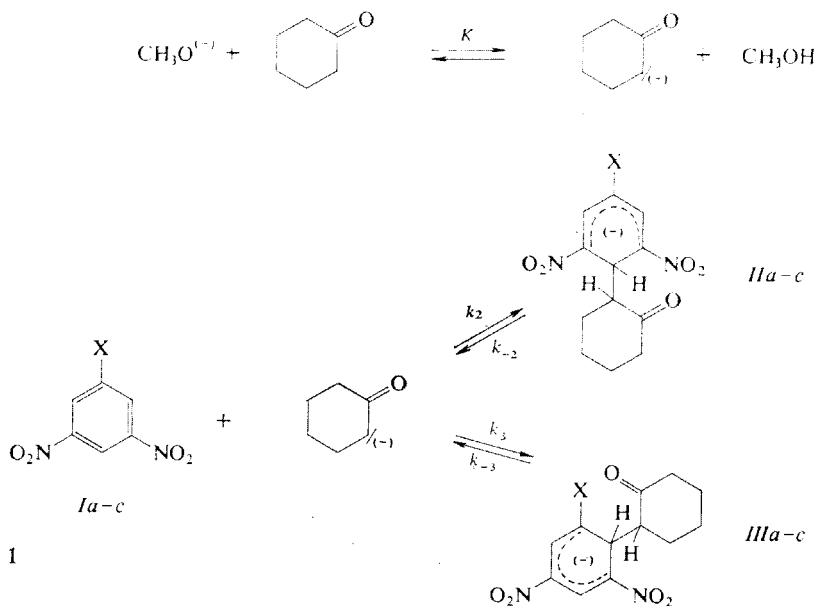
SCHEME 1

Ia—$IIIa$, X = CONC$_5$H$_{10}$
Ib—$IIIb$, X = COOCH$_3$
Ic—$IIIc$, X = CN

when the rates of formation of Meisenheimer complexes are much higher than those of their decomposition. Under these conditions it is possible to use simplified kinetic equations. It is necessary to choose individually such conditions for each substrate that the rates of formation are much higher than those of the reverse and isomerization reactions, and the decomposition reactions are still negligible compared with the reaction studied. It was quite easy to fulfil these conditions when following the rate of formation of the complexes which is relatively large, but difficulties were encountered with the much slower isomerization reactions. In addition to it, it was desirable to work in the same media with all the substrates used (cyclohexanone–methanol ratios 1 : 1, 3 : 1, 9 : 1 (by vol.), so that the influence of X on the individual reaction steps might be compared).

The measurements of the reverse reactions were not complicated by any side reactions, but increasing acid concentration resulted in reverse reaction rate increase. The rate constants obtained with small excess of acetic acid (up to max. 50% excess, where the catalytic influence of acetic acid was still insignificant) were taken as the constants k_{-2} and k_{-3}. The constants thus obtained are given in Table II.

In the solvent used it would have been difficult to determine whether specific or general acid catalysis was operating. Therefore, a series of measurements was carried out of the rate of reverse reaction of the complex *IIIc* in methanolic acetate and chloroacetate buffers. The values 9·52 and 7·96 given in ref.[8] were used for pK_a of acetic and chloroacetic acids in methanol, respectively. Besides the non-catalyzed reaction the catalysis by acetic and chloroacetic acids was observed, too; *i.e.* the reaction is subject to general acid catalysis. The rate constant is given by Eq. (3). Values of the individual catalytic rate constants obtained by the known method[9] are: $k_0 =$

$$k_{exp} = k_0 + k_{H^+}[H^+] + k_{HA}[HA] \tag{3}$$

$= 6 . 10^{-5} \text{ s}^{-1}$; $k_{H^+} = 8\cdot2 . 10^2 \text{ l mol}^{-1} \text{ s}^{-1}$; $k_{CH_3COOH} = 2\cdot4 . 10^{-5} \text{ l mol}^{-1} \text{ s}^{-1}$; $k_{ClCH_2COOH} = 1\cdot2 . 10^{-4} \text{ l mol}^{-1} \text{ s}^{-1}$. The influence of ionic strength on pK_a and the proton activity coefficient was not considered in calculation of k_{H^+}. The estimated value of the Brönsted coefficient is about 0·5.

In determination of the isomerization rate constants k_{iso} under the abovementioned conditions, the concentration of the starting substrates I was negligible as compared with that of complexes II and III, so that it was possible to determine k_{iso} on the basis of the Bodenstein steady state treatment (4), where $\overrightarrow{k}$ and $\overleftarrow{k}$ are the rate constants of the reactions $II \rightleftharpoons III$.

$$k_{iso} = \overrightarrow{k} + \overleftarrow{k} = (k_{-2}k_3 + k_{-3}k_2)/(k_2 + k_3), \tag{4}$$

$$k_2/k_3 = (k_{-2} - k_{iso})/(k_{iso} - k_{-3}) \tag{5}$$

Eq. (4) can be modified to give Eq. (5). By introducing the measured values for k_{-2}, k_{-3} and k_{iso} into Eq. (5) it was possible to obtain the rate constants ratios k_2/k_3 of formation of the both complexes (Table II).

The rate constants of formation of the isomeric complexes *II* and *III* were measured in cyclo-hexanone–methanol (1 : 1 by vol) medium for all the substrates. In the case of the amide *Ia* the equilibrium constant of formation of the complex *II* is very low in this medium. Therefore, we have used lower methoxide concentrations for this substrate to make the concentration of the complex *IIa* negligible as compared with *IIIa* in the whole reaction course. The experimental rate constant reflects here the formation of the complex *IIIa* (under the conditions used the reverse reaction is negligible compared with the rate of formation of *IIIa*). The experimental rate constant thus obtained increases linearly with increasing methoxide concentration; if it was divided by methoxide and cyclohexanone concentrations, the $k_3 K'$ constant was obtained.

The other substrates were studied in the same medium (methanol–cyclohexanone 1 : 1 by vol.) using such methoxide concentrations to make the reverse reactions practically insignificant. The experimental rate constant found concerns simultaneous formation of the both isomers. In the case of ester *Ib* again the dependence of this experimental rate constant on the methoxide concentration was linear, so that through dividing it by methoxide and cyclohexanone concentrations the sum of constants $(k_2 + k_3) K'$ was obtained.

In the case of the nitrile *Ic* the increase of the experimental rate constant with increasing methoxide concentration was gradually slower. The reason consists in that increasing methoxide concentration causes a gradually increasing formation of the Meisenheimer complex *IV* of the nitrile *Ic* with methoxide ion. This conclusion was confirmed by measuring the absorbance at 460 nm, when a rapid increase corresponding to formation of the complex *IV* was followed by a slower decrease due to gradual transformation of the complex *IV* into complexes *IIc* and *IIIc*. The half-life of formation of *IV* is about 20 times smaller than that of the reactions leading to the complexes *II* and *III*. Therefore, the reaction of *Ic* with CH_3O^- can be envisaged as an antecedent equilibrium, and the equilibrium constant K_4 can be used for calculation of the effective concentration I_{eff} of the substrate from Eq. (6). Eq. (7) holds for the simultaneos formation of the complexes *IIc* and *IIIc*; it can be converted into the form (8). The dependence $1/k_{exp}$ *vs.* $1/[CH_3O^-]$ was linear; its angular coefficient and intercept at the Y axis were used for calculation of $(k_2 + k_3) K'$ and $K_4 = (35 \pm 5) \, 1 \, mol^{-1}$, respectively.

$$I_{eff} = [I]/(1 + K_4[CH_3O^-]) \qquad (6)$$

$$v = k_{exp}[I] = ((k_2 + k_3) \, K'[C_6H_{10}O][CH_3O^-] \, [I])/(1 + K_4[CH_3O^-]) \qquad (7)$$

$$1/k_{exp} = \frac{1}{K'(k_2 + k_3) [C_6H_{10}O][CH_3O^-]} + \frac{K_4}{K'(k_2 + k_3) [C_6H_{10}O]} . \qquad (8)$$

The rate constants given in Table II point to several conclusions. Decreasing methanol concentration in the reaction medium causes the reaction constants $k_2 K'$ and $k_3 K'$ to increase and k_{-2} and k_{-3} to decrease (to a smaller extent). The increase in the both $k_2 K'$ and $k_3 K'$ is due probably to a) increasing concentration of cyclohexanone anion and b) its increasing reactivity resulting from lowered solvation. The decrease of the constants k_{-2} and k_{-3} is due to lowered solvation by methanol molecules of the cyclohexanone anion being split off in the activated complex. The ratio k_2/k_3 is independent of medium (within experimental error), its value being smaller than unity for all the three substrates, whereas in all the cases studied so far it was greater than unity[1,2,10-12].

TABLE II

Rate Constants of Formation ($k_2 K'$ and $k_3 K'$ in l^2 mol^{-2} s^{-1}), Reverse Decomposition (k_{-2} and k_{-3} in s^{-1}) and Isomerization (k_{iso} in s^{-1}) of Meisenheimer Complexes from Piperidide (Ia), Methyl Ester (Ib) and Nitrile of 3,5-Dinitrobenzoic Acid (Ic) with Cyclohexanone in Cyclohexanone–Methanol Mixtures at 25°C

A 10% (by vol.) methanol in cyclohexanone, B 25% (by vol.) methanol, C 50% (by vol.) methanol.

Constant	Ia			Ib		Ic^a
	A	B	C	B	C	
$k_{iso} \cdot 10^3$	7·2 ± 0·2	13·5 ± 0·5	—	2·25 ± 0·05	4·05 ± 0·15	1·46 ± 0·03
$k_{-2} \cdot 10^3$	12·7 ± 0·4	25·0 ± 5·0	—	3·38 ± 0·02	5·75 ± 0·05	2·0 ± 0·2
$k_{-3} \cdot 10^4$	—	1·30 ± 0·10	1·70 ± 0·05	9·5 ± 0·4	20·7 ± 0·6	0·18 ± 0·02
K'/k_2	—	$0·12^b$	$0·034^b$	—	$0·34^b$	$5·2^b$
K'/k_3	—	0·16 ± 0·03	0·045 ± 0·001	—	$0·39^b$	$13·6^b$
k_2/k_3	0·76 ± 0·05	0·85 ± 0·20	—	0·87 ± 0·03	0·86 ± 0·05	0·37 ± 0·04
$K'(k_2 + k_3)^c$	—	—	—	—	0·73 ± 0·04	18·8 ± 2·0

^{a} In 50% (by vol.) methanol. ^{b} Calculated values (see the text). ^{c} In l^2 mol^{-2} s^{-1}.

When evaluating the influence of substituent X on the rate constant of both formation of the complexes and their decomposition it is advantageous to consider separately those reactions in which the complexes *II* are formed resp. decomposed (the substituent X is in the *para* position, and only its polar effects are significant) from those reactions in which the complexes *III* are formed resp. decomposed (the substituent X is in *ortho* position). Values of the rate constants k_2K' strongly increase with increasing electron-withdrawing ability of the substituent X, whereas the constants k_{-2} decrease, but here the effect of the substituent is smaller. The constants k_3K' show a similar tendency as k_2K', however, the difference between the values of the nitrile and ester is much greater. This is probably due to the reactions of amide and ester being rather slowed down by steric hindrance of the bulkier groups. Dependence of k_{-3} on the character of X is anomalous. By far the fastest reaction is that of the complex *IIIb*, whereas the complex *IIIa* is very stable; this high stability can be explained by an energetically favourable hydrophobic interaction of piperidine ring with cyclohexane ring. Thereby the overall energy of the complex *IIIa* is lowered and the approach of methanol molecules (during splitting off of cyclohexanone anion) is made more difficult. This explanation can also be supported by comparison of the reaction of *Ia* with cyclohexanone to that of *Ia* with acetone[2] in comparable media (25% by vol. methanol, 75% by vol. ketone). The formation of the complex type *II* by reaction with cyclohexanone is 50 times faster than that with acetone, whereas the reverse reaction is 5 × slower. The fiftyfold faster formation of the complex with cyclohexanone is due, first of all, to that cyclohexanone is a stronger acid than acetone[13], the difference being three orders of magnitude, so that the concentration of its anion is greater by 3 orders of magnitude. Lower nucleophility and higher steric requirements of cyclohexanone anion have the reverse effect. The latter two factors cause the reverse reaction of the complex *IIa* to be faster. Addition to 2-position in the reaction with cyclohexanone is only 3·2 times faster than that with acetone, the reason being obviously steric — cyclohexanone is bulkier than acetone. The same reason should make the reverse reaction of the complex *IIIa* easier than that of the corresponding complex with acetone, and the ratio of the rate constants k_{-3} should be greater than 5. In fact, its value is only 1·3, which again indicates that formation of the complex *IIIa* involves an energetically favourable interaction between piperidine and cyclohexanone residues. Formation of the complex with acetone is not (or it is less) accompanied by such interactions.

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