

MECHANISM OF ACETOACETYLATION OF SUBSTITUTED ANILINES

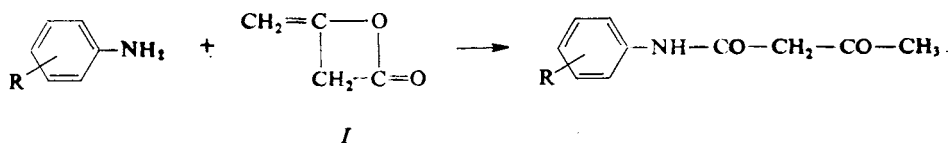
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Received June 2nd, 1984

Kinetics have been studied of the reaction of diketene with substituted anilines, and the reaction rate has been found to depend on relative permittivity of the system. The rate and equilibrium constants have been calculated by combination of rate and equilibrium relations with the relation by Amis; the constants correlate with the Hammett substituent constants. The reaction does not proceed as a simple bimolecular process. A reaction mechanism has been suggested.

Acetoacetanilides belong to an important group of dyestuff and pharmaceutical intermediates. The most effective way of their preparation consists in the acetoacetylation of anilines with diketene. Although this reaction has been used industrially for a long time, its kinetics has not been studied yet. The present communication deals with the course of this reaction carried out in excess diketene, 4-methylene-2-oxoetane (*I*), which contains a markedly polarized carbonyl double bond¹⁻³. Its reaction with substituted anilines was studied by Ljashchenko and Sokolova⁴ who found a linear dependence between logarithms of the bimolecular rate constants and the *pK*_a values of the anilines.

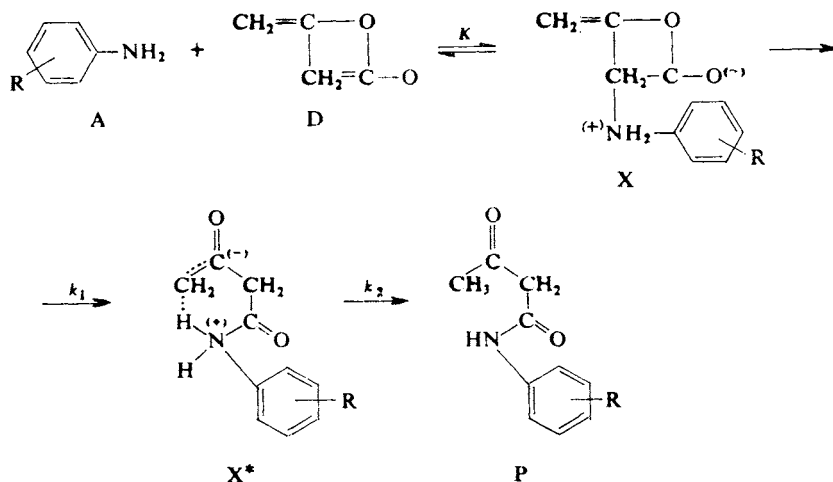


SCHEME A

The stoichiometric equation (Scheme A) indicates that the addition must be followed by the proton transfer from amino group to the methyl group of acetoacetanilide being formed. In aprotic medium and at low diketene concentrations, this transfer is most probably realized by an intramolecular mechanism. Another possibility consists in the proton transfer by a further diketene molecule. In this case the role of diketene concentration is interesting.

In the first approximation, we can consider a mechanism according to (Scheme B). The rate-limiting step consists probably in the transformation $\text{X} \rightarrow \text{X}^*$ which is

supported by formation of a hydrogen bond in the activated complex X^* . Its transformation into products, $X^* \rightarrow P$, is kinetically insignificant, because it represents



SCHEME B

a very rapid shift of electrons ($k_2 \gg k_1$). Furthermore it can be presumed that there exists a rapid pre-equilibrium between D, A, and X. Mathematically such a scheme can be described by the following equations:

$$K = [X]/[D][A] \quad (1)$$

$$d\Sigma[P]/dt = k_2[X] \quad (2)$$

$$d[X]/dt = k_1[X] - k_2[X] \quad (3)$$

With respect to the X^* being a relatively unstable intermediate, the Bodenstein steady-state treatment can be applied to obtain the expression of the unknown concentration of the activated complex X^* . If the reaction is carried out as a pseudo-monomolecular process (in excess diketene), then Eq. (4) results.

$$d[P]/dt = k_{\text{obs}}([A_0] - [P]), \quad (4)$$

where

$$k_{\text{obs}} = k_1 K [D_0] / (1 + K [D_0]) \quad (5)$$

means the experimental value of the rate constant of the pseudomonomolecular reaction. Investigation of time dependences of the product concentrations $[P]$ at various initial diketene concentrations $[D_0]$ allows thus determination of the dependence k_{obs} vs $[D_0]$. A successful solution of the problem needs a linear dependence of relative permittivity on the diketene concentration:

$$\varepsilon = a[D_0] + b. \quad (6)$$

The relation by Amis^{5,6} was used for expressing the dependence of the reaction rate of the dipolar molecules on the relative permittivity of medium

$$k = k_{\infty} \exp((1/\varepsilon) A_1) \quad (7)$$

with

$$A_1 = -2\mu_A\mu_B/(kT)(r_A + r_B)^3, \quad (8)$$

where k means the rate constant of the reaction taking place in a medium of relative permittivity ε , k_{∞} stands for the rate constant in a medium of infinitely large relative permittivity, k is the Boltzmann constant, T is absolute temperature, μ_A , μ_B and r_A , r_B are dipole moments and radii of the reacting particles, respectively. Mathematical transformations lead to Eqs (9), (10), and (11)

$$[\partial \ln k / \partial (1/\varepsilon)]_{p,T} = A_1, \quad (9)$$

$$k = k^* \exp \{[(1/\varepsilon) - (1/\varepsilon_0)] A_1\}, \quad (10)$$

$$K = K^* \exp \{[(1/\varepsilon) - (1/\varepsilon_0)] A_2\} \quad (11)$$

in which the integration constant was chosen in such way that k represents the rate constant extrapolated to the relative permittivity of the medium with zero concentration of the reacting components (pure solvent). Combination of Eqs (5), (10), and (11) gives the final explicit dependence of k_{obs} on $[D_0]$ (12) where A_2 is a relation analogous to Eq. (13) and valid for the equilibrium constant.

$$k_{\text{obs}} = k^* K^* \exp \{[(1/\varepsilon) - (1/\varepsilon_0)] (A_1 + A_2)\} [D_0] / \\ / (1 + K^* \{[(1/\varepsilon) - (1/\varepsilon_0)] A_2\} [D_0]), \quad (12)$$

where Eq. (6) is valid for ε and ε_0 .

On the whole, three regions of values of relative permittivity and/or diketene concentration can be differentiated. At high $[D_0]$ values, when $K^* \{ \exp [(1/\varepsilon) - (1/\varepsilon_0)] \}$.

. $A_2\} [D_0] \gg 1$, the equation (11) can be simplified and, by taking the logarithms, modified to the linear relation (13)

$$\ln k_{\text{obs}} = \ln k^* + [(1/\varepsilon) - (1/\varepsilon_0)] A_1. \quad (13)$$

Similarly Eq. (14) can be obtained for relatively low diketene concentrations (but high enough for the relation $K^*\{\exp [(1/\varepsilon) - (1/\varepsilon_0)] A_2\} [D_0] \ll 1$ to be valid):

$$\ln (k_{\text{obs}}/[D_0]) = \ln k^*K^* + [(1/\varepsilon) - (1/\varepsilon_0)] (A_1 + A_2) \quad (14)$$

The last three relations make it possible to calculate values of the constants k , K , A_1 , and A_2 .

EXPERIMENTAL AND RESULTS

Reagents: Cyclohexane for UV spectroscopy was dried with sodium and redistilled before use. Diketene was vacuum distilled (59–61°C, 6.7 kPa) before each daily series of measurements to reach the value n_D^{20} 1.4380 (ref.⁴). The substituted anilines prepared by known procedures were either recrystallized or vacuum distilled with addition of zinc powder to obtain the physical constants given in ref.⁷.

Relative permittivity was measured with a DK-meter 600 RL (Küstner, Wissenschaftliche Apparate, Dresden) according to Oehme. The apparatus was calibrated with the use of a capacity standard in a Q-meter Tesla BM 311 E. The measurements were carried out with solutions of 0.05 to 1.2 mol l⁻¹ diketene in cyclohexane. The results were treated by linear regression to give Eq. (15):

$$\varepsilon = (1.0585 \pm 0.0002) [D_0] + (2.0009 \pm 0.0001) \quad (15)$$

Kinetic measurements: The rate constants were measured at the conditions of pseudomonomolecular reaction using a Unicam SP 800 B spectrophotometer at the wavelength of the absorption maximum of the products (Table I). Eight to eleven initial diketene concentrations were used for each substituted derivative studied, and each measurement was carried out three times in 4.00 cm cells at $25 \pm 0.1^\circ\text{C}$. The initial concentrations of the anilines were $2.0 \cdot 10^{-4}$ mol l⁻¹. The k_{obs} values were obtained from the absorbance–time dependences by the Fibonacci optimization method⁸, and their values are given in Table I. A typical shape of the dependences of rate constants on relative permittivity of medium is given in Fig. 1.

Treatment of the measurement results: The primary data were treated by linear regression on the basis of Eqs (13) and (14) into which the values were separately introduced which corresponded to the both sections of the dependences. The fitting of the regression could be determined in advance with respect to the character of the dependences (a perfect fitting could not be obtained, due to shape of the curves — see Fig. 1). The calculation results are summarized in Table II.

The bimolecular rate constants and equilibrium constants obtained correlated with the Hammett σ_m and σ_p constants⁹. Logarithms of the rate constants gave the straight line (16) (Fig. 2).

$$\log k^* = (2.15 \pm 0.03) - (1.84 \pm 0.09) \sigma, \quad r = 0.989, \quad n = 11. \quad (16)$$

TABLE I

Values of rate constants k_{obs} (s^{-1}) of pseudomonomolecular reaction of diketene with substituted anilines in cyclohexane at $25 \pm 0.1^\circ\text{C}$

$[\text{D}_0]$ mol l^{-1}	Aniline ^b		3-Methoxyaniline ^b		4-Chloroaniline ^c	
	$10^3 k$	$\pm 10^4 s_k^a$	$10^3 k$	$\pm 10^4 s_k^a$	$10^3 k$	$\pm 10^5 s_k^a$
0.05	0.706	0.119	0.899	0.106	0.186	0.033
0.10	2.655	0.398	2.940	0.349	0.529	1.306
0.15	5.127	0.853	4.982	0.253	1.171	1.540
0.20	7.993	1.075	6.437	0.815	1.716	1.964
0.25	10.540	1.418	8.730	1.515	3.003	4.359
0.30	14.260	1.666	10.530	1.919	3.277	7.296
0.35	15.910	1.594	—	—	—	—
0.40	18.760	2.350	14.590	2.252	4.825	9.472
0.50	25.440	5.312	17.930	0.961	6.226	14.550
0.60	26.390	7.420	—	—	6.300	13.440
0.80	—	—	—	—	7.388	9.390

$[\text{D}_0]$ mol l^{-1}	4-Methoxyaniline ^b		4-Methylaniline ^b		4-Bromoaniline ^b	
	$10^3 k$	$\pm 10^4 s_k^a$	$10^3 k$	$\pm 10^4 s_k^a$	$10^3 k$	$\pm 10^4 s_k^a$
0.02	1.125	0.466	0.333	0.073	—	—
0.03	2.829	0.285	—	—	—	—
0.04	4.565	0.466	0.991	0.251	—	—
0.05	6.358	0.941	—	—	0.196	0.277
0.06	9.190	1.442	2.028	0.277	—	—
0.07	12.330	1.412	—	—	—	—
0.08	16.200	1.159	3.105	0.875	—	—
0.10	29.720	3.886	4.038	1.471	0.750	0.782
0.15	58.180	3.451	8.687	1.303	1.549	2.098
0.20	63.410	6.612	10.470	1.227	2.208	2.172
0.25	76.380	13.860	12.070	1.632	3.000	2.619
0.30	—	—	13.550	1.638	3.300	6.817
0.40	—	—	17.070	1.092	4.600	10.610
0.50	—	—	18.380	3.647	6.304	4.301
0.60	—	—	—	—	7.152	10.140
0.80	—	—	—	—	9.107	9.249

TABLE I
(Continued)

[D ₀] mol l ⁻¹	3-Methylaniline ^b		3-Chloroaniline ^b		3-Bromoaniline ^b	
	10 ³ k	± 10 ⁴ s _k ^a	10 ³ k	± 10 ⁵ s _k ^a	10 ³ k	± 10 ⁵ s _k ^a
0.03	0.521	0.106	—	—	—	—
0.05	1.345	0.291	0.090	0.333	0.109	0.495
0.10	3.615	0.595	0.322	0.669	0.317	0.478
0.15	5.021	0.895	0.524	1.264	0.488	0.877
0.20	6.209	3.252	0.945	0.758	0.781	0.874
0.25	8.980	3.233	—	—	—	—
0.30	10.330	2.214	1.641	2.472	1.760	1.248
0.40	10.910	2.898	2.482	4.802	1.891	4.318
0.50	13.80	3.372	3.310	7.341	2.742	6.137
0.60	17.530	1.933	4.008	7.378	3.529	7.049
0.80	—	—	4.715	7.800	4.492	8.276

[D ₀] mol l ⁻¹	3-Cyanoaniline ^b		3-Nitroaniline ^d	
	10 ³ k	± 10 ⁵ s _k ^a	10 ³ k	± 10 ⁵ s _k ^a
0.05	0.230	0.562	—	—
0.10	1.017	0.916	0.453	0.445
0.15	1.886	2.607	0.820	0.592
0.20	2.631	2.862	1.243	0.515
0.30	4.677	3.081	2.164	1.630
0.40	6.598	4.411	3.161	3.590
0.50	8.499	8.054	4.406	4.076
0.60	10.590	10.140	5.393	5.982
0.80	13.040	15.700	7.149	2.808

^a The standard deviation of k_{obs} ; ^b analytical wavelength 275 nm; ^c 280 nm; ^d 290 nm.

The dependence of logarithms of the equilibrium constants K on the substituent constants exhibits a large scattering, which is mainly due to inaccuracy of extrapolation in the steep decreasing sections of the dependences of $\ln k_{\text{obs}}$ on $((1/\epsilon) - (1/\epsilon_0))$. Roughly the dependence shows, however, a trend of lowering equilibrium constant with increasing σ value. The largest deviations are encountered with the equilibrium constants of the both methoxy derivatives (Fig. 3). When

these derivatives are excluded, the correlation equation has the form (17):

$$\log K = (0.01 \pm 0.04) - (0.56 \pm 0.11) \sigma, \quad r = 0.890, \quad n = 9 \quad (17)$$

TABLE II

Values of parameters of Eqs (12) and (13) obtained by linear regressions from individual sections of the dependences of $\log k_{\text{obs}}$ vs $((1/\epsilon) - (1/\epsilon_0))$

No	R	$k^* \cdot 10^3$	K^*	A_1	A_2	σ^a
1	4-OCH ₃	27.413	0.730	-17.54	-181.18	-0.28
2	4-CH ₃	11.730	0.953	-4.45	-76.52	-0.14
3	3-CH ₃	5.970	1.487	-8.02	-77.94	-0.06
4	H	7.630	0.949	-10.30	-41.48	0
5	3-OCH ₃	5.130	2.088	-11.98	-28.26	0.10
6	4-Cl	3.190	0.807	-5.64	-22.88	0.22
7	4-Br	2.635	0.747	-8.30	-45.00	0.22
8	3-Cl	1.997	0.489	-5.78	-31.80	0.37
9	3-Br	1.256	0.832	-8.56	-45.30	0.37
10	3-CN	0.435	0.458	-7.38	-57.65	0.62
11	3-NO ₂	0.355	0.384	-8.00	-40.00	0.71

^a Ref. ⁹.

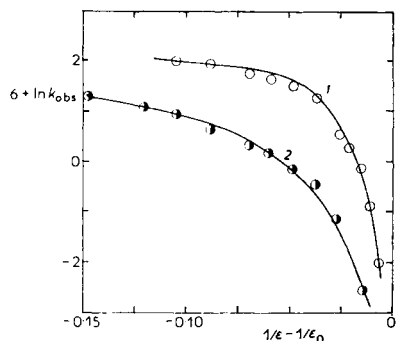


FIG. 1

Dependence of experimental values of rate constants on dielectric properties of the reaction mixture in the reaction of diketene with 4-toluidine 1 and 4-bromoaniline 2 in cyclohexane at 25.0°C. The calculated course (—)

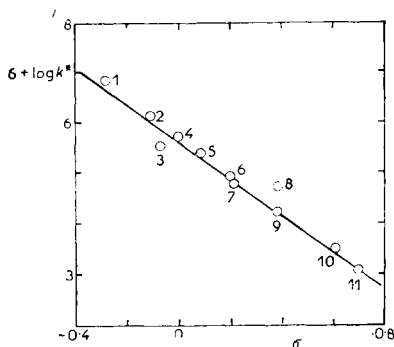


FIG. 2

The Hammett correlation of bimolecular rate constants of the reaction of diketene with substituted anilines in cyclohexane at 25.0°C. For numbers see Table II

DISCUSSION

Results of the single available study of kinetics of acetoacetylation of substituted anilines with diketene⁴ indicate that the reaction is bimolecular, and the reaction intermediate is formed the more easily the easier is the transfer of free electron pair of nitrogen atom in aniline to the diketene molecule. Hence it follows that the mechanism suggested by Lyashchenko and Sokolova is generally correct. Our study showed, however, that the system does not behave in the expected way during increasing diketene concentration. The reaction takes the pseudomonomolecular course at relatively low diketene excess already, but the reaction rate constant does not stop increasing even at its 4 000 fold excess. This phenomenon is due to the change in dielectric constant of the reaction mixture depending on the diketene concentration.

The determination of the reaction order with respect to diketene gave Eq. (18) for the reaction of aniline with diketene:

$$\ln k_{\text{obs}} = (-2.62 \pm 0.11) + (1.47 \pm 0.07) \ln [D_0], \quad (18)$$

which disproves a simple bimolecular reaction. The pre-equilibrium is established in accordance with theory, and stability of the intermediate X^* decreases with increasing electron-acceptor character of the substituent in the aniline molecule.

The negative slope value in the dependence of $\log k$ vs σ indicates that the rate-limiting step does not consist in the proton transfer from nitrogen atom, but consists in splitting of C—O bond in the primary intermediate X and in rearrangement of the four-membered ring into six-membered ring. Electron-acceptor substituents decrease the electron density at the nitrogen atom, wherefrom the effect is transferred by inductive effect to the carbonyl carbon atom of diketene. Thereby the electron shift from the C—O bond to the heterocyclic oxygen atom is made difficult. Moreover the proton transfer from nitrogen to oxygen atom will be more probable, being

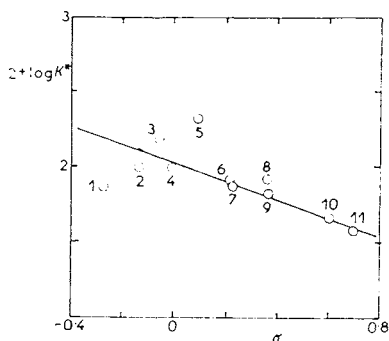
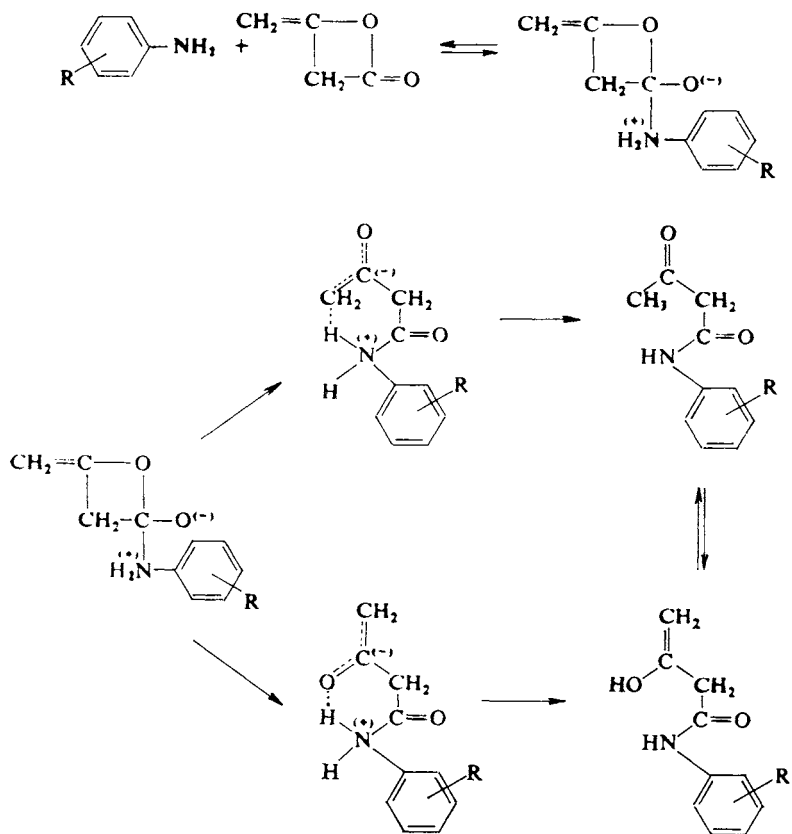


FIG. 3

The Hammett correlation of equilibrium constants of the pre-equilibrium of the reaction of diketene with substituted anilines in cyclohexane at 25.0°C. For numbers see Table II

a reaction of two hard centres. The transfer to methylene group would involve interaction of a hard with a soft centre. Thus Scheme *B* must be extended to give Scheme *C*.



SCHEME C

Obviously, the transformation of the enol form into keto form is responsible for the fraction in the reaction order, the rate constant k being a complex constant.

Values of the A_1 , A_2 parameters of Eq. (12) are functions of dipole moments and active radii of the reacting particles. As the reaction takes place between a single reagent (diketene) and various substrates (substituted anilines), the contribution of the reagent can be considered constant within the whole series, and the changes can be considered to be due to relative action of physical properties of the reacting substrates, which, however, cannot be described by any simple dependence.

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Translated by J. Panchartek.