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## KINETICS AND MECHANISM OF METHANOLYSIS OF BENZOYL DERIVATIVES OF SUBSTITUTED PHENYLUREAS AND PHENYLTHIOUREAS

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The methanolysis rate constants and dissociation constants have been measured of benzoyl derivatives of substituted phenylureas and phenylthioureas. The dissociation constants of the thio derivatives are higher by 1 order of magnitude and the rate constants are higher by 2 orders of magnitude than the respective values of the oxygen analogues. Logarithms of the rate and dissociation constants have been correlated with the Hammett  $\sigma$  constant; the  $\rho$  constant of the methanolysis of the oxygen derivatives is almost  $2\times$  higher than that of the thio derivatives, which is explained by a change in the rate-limiting step. Methylation of the phenyl nitrogen atom increases the acidity by almost 2 orders of magnitude. This effect is due obviously to steric hindrance to the conjugation with the adjacent carbonyl or thiocarbonyl group.

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Some substituted phenylureas and phenylthioureas and their N-benzoyl derivatives are used as selective herbicides. A typical representative is 1-benzoyl-1-(4-chlorophenyl)-3,3-dimethylurea which is produced under the trade name Benzomark as a selective herbicide for corn<sup>1</sup>.

The aim of the present work was to find the substituent effects in 1-aryl-3-benzoylureas and -thioureas (aryl = substituted phenyl) on values of their dissociation constants and methanolysis rate constants, and to determine quantitatively the effect of substitution of the carbonyl group by thiocarbonyl group. The hydrolysis rate constants could not be determined due to the negligible solubility of the starting benzoyl derivatives and the non-reproducibility of electronic spectra of their aqueous solutions even at the concentrations below  $10^{-4}$  mol l<sup>-1</sup>.

### EXPERIMENTAL

#### Reagents

The benzoyl isothiocyanate *I* was prepared by reaction of benzoyl chloride with ammonium thiocyanate in acetone<sup>2</sup>. The benzoyl isocyanate *II* was prepared by reaction of oxalyl chloride with benzamide<sup>3</sup>.

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1-Benzoyl-1-(4-chlorophenyl)-3,3-dimethylurea (III). Solution of 0.55 g (12 mmol) dimethylamine in 10 ml chlorobenzene was added to solution of 1.7 g (10 mmol) 4-chlorophenyl isocyanate in 20 ml chlorobenzene. The separated 1-(4-chlorophenyl)-3,3-dimethylurea was collected by filtration and washed with ether. Yield 1.96 g (99%), m.p. 175–177°C. A mixture of 10 mmol of the urea prepared with the same amounts of benzoyl chloride and pyridine was boiled in a flask on oil bath. After cooling, the resulting mixture was mixed with 5 ml water, and the solid product was collected and recrystallized from ethanol. Yield 1.1 g (37%), m.p. 197–199°C in accordance with ref.<sup>1</sup>.

Substituted 1-phenyl-3-benzoylureas IV–IX. A solution of 20 mmol *II* in 3 ml benzene was mixed with a solution of 20 mmol substituted aniline in 5 ml benzene. After the exothermic reaction ceased, the mixture was cooled, and the separated crystals were purified by crystallization from ethyl acetate, acetone, or a benzene–cyclohexane mixture.

Substituted 1-phenyl-3-benzoylthioureas X–XIV. A solution of 20 mmol *I* in 3 ml dry acetone was mixed with a solution of 20 mmol substituted aniline in 5 ml acetone. After 15 min, the mixture was cooled, and the product was collected by filtration and purified by crystallization from ethanol, acetone, or a 5 : 1 benzene–cyclohexane mixture.

The melting points of compounds IV–XIV are given in Table I. They agree with the literature data except for the compound VII (ref.<sup>4</sup> gives m.p. 250°C). Therefore, this compound as well as the not yet described compounds IX, XIII, XIV were submitted to elemental analysis. Compound VII: for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub> (285.1) calculated: 58.97% C, 3.86% H; found: 59.19% C, 4.00% H. Compound IX: for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (254.2) calculated: 70.87% C, 5.51% H; found: 71.10% C, 5.60% H. Compounds XIII and XIV: for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S (301.2) calculated: 55.82% C, 3.65% H; found for XIII: 55.58% C, 3.75% H; found for XIV: 56.05% C, 3.50% H.

TABLE I

Melting points of the ureas IV–XIV, values of their dissociation constants  $K_A$  in methanol and values of the rate constants  $k$  (l mol<sup>-1</sup> s<sup>-1</sup>) of their methanolyses at 25°C and at  $I = 0.05$

Compound <sup>ref.</sup>	M.p., °C	$\lambda_{\text{anal}}$ , nm		$k^a$	$pK_A^b$
		$k$	$K_A$		
IV <sup>11</sup>	208–210	275	300	$2.60 \cdot 10^{-2}$	15.24
V <sup>4</sup>	207–209	275	300	$10.6 \cdot 10^{-2}$	14.83
VI <sup>4</sup>	236–237.5	275	300	$5.64 \cdot 10^{-2}$	14.98
VII <sup>4</sup>	230–231	280	300	$40.6 \cdot 10^{-2}$	14.40
VIII <sup>12</sup>	212–213	275	300	$1.52 \cdot 10^{-2}$	15.43
IX	135–137	320	320	$2.72 \cdot 10^{-2}$	13.90
X <sup>13</sup>	130–132	320	340	0.51	12.96
XI <sup>14</sup>	160–161	315	—	2.17	14.80
XII <sup>15</sup>	148–149	342	—	4.92	14.15
XIII	160–162	324	—	9.17	13.50
XIV	183–184	350	—	10.0	13.28

<sup>a</sup> ± 5%; <sup>b</sup> ± 0.04.

1-Benzoyl-3-diethylurea (XV) was prepared by reaction of diethylamine with benzoyl isocyanate (II) in benzene. Yield 72%, m.p. 98–100°C in accordance with ref.<sup>15</sup>.

*Kinetic measurements:* The methanolysis of the benzoyl derivatives III–XV was followed spectrophotometrically. Methanolic solution of the benzoyl derivative (0.05 ml;  $3 \cdot 10^{-3}$  mol  $\cdot$  l<sup>-1</sup>) was added to 1.95 ml solution of methoxide or bromophenolate buffer (in the methanolyses of the thio derivatives) in a 0.5 or 1 cm quartz cell placed in the tempered cell compartment of the spectrophotometer. The experiments carried out in the bromophenoxide buffer or in methoxide of concentrations below 0.05 mol l<sup>-1</sup> required an adjustment of ionic strength ( $I = 0.05$ , KBr). The absorbance decrease was followed at 25°C with a Zeiss VSU-2P apparatus at the analytical wavelengths given in Table I. The rate constants were calculated from the relation  $\tau_{1/2} \cdot k_{\text{obs}} = 0.69$ , where  $\tau_{1/2}$  is the reaction half-life determined graphically from the time dependence of  $\log(A_t - A_\infty)$ .

*Measurement of dissociation constants:* The dissociation constants of all the compounds except for the thio derivative X were determined kinetically from the dependence of  $k_{\text{obs}}$  on methoxide ion concentration and the corresponding kinetic equation. The dissociation constants of the urea derivatives (except for the nitro derivative VII) were also determined spectrophotometrically in methanolic solutions using the Zeiss VSU-2P apparatus at the wavelengths 300 nm (for the ureas IV–VI and VIII) and 320 nm (for compound IX). The dissociation constant values were calculated from Eq. (1)

$$pK_A = pK_S + \log [\text{CH}_3\text{O}^{(-)}] - \log R, \quad (1)$$

where  $K_A$  is the dissociation constant measured,  $pK_S$  stands for negative logarithm of the ionic product of methanol (16.916 taken from ref.<sup>5</sup>), and  $R$  means the ratio of concentrations of the conjugated base and acid ( $[\text{S}^{(-)}]/[\text{HS}]$ ) of the substrate measured. The  $R$  value was calculated from the extrapolation of the absorbance values measured to the zero time according to Eq. (2)

$$R = [\text{S}^{(-)}]/[\text{HS}] = (A - A_{\text{HS}})/(A_{\text{S}^-} - A), \quad (2)$$

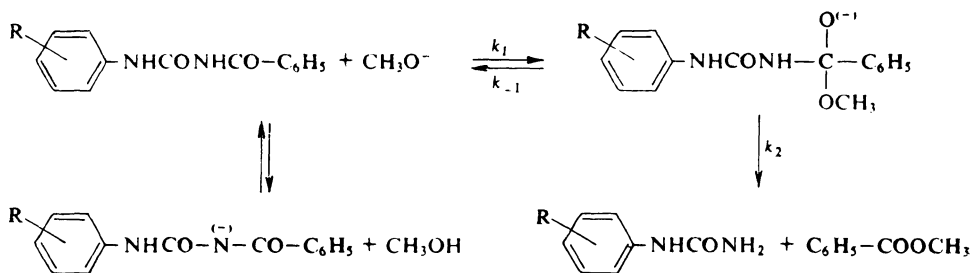
where  $A_{\text{HS}}$ ,  $A_{\text{S}^-}$ , and  $A$  are the absorbances of substrate, its conjugated base, and the measured solution, respectively. The dissociation constant of compound X was measured in bromophenoxide buffers at 340 nm and calculated from the relation  $pK_A = \text{pH}_{\text{buffer}} - \log R$ . The  $\text{pH}_{\text{buffer}}$  value was calculated from Eq. (3)

$$\text{pH}_{\text{buffer}} = pK_{A, \text{bromophenol}} - \log (c_{\text{bromophenol}}/c_{\text{bromophenoxide}}), \quad (3)$$

where it is  $pK_A = 13.61$  for 4-bromophenol in methanol<sup>6</sup>. The calculated values of dissociation constants are given in Table I.

## RESULTS AND DISCUSSION

The methanolysis kinetics of 1-substituted phenyl-3-benzoylureas and -thioureas were followed in methanol at various concentrations of sodium methoxide or in bromophenoxide buffers. The solvolyses were 1. order in the benzoyl derivative in all the cases. The overall reaction course is represented in Scheme 1.



SCHEME 1

The observed rate constant is defined by Eq. (4)

$$k_{\text{obs}} = \frac{k[\text{CH}_3\text{O}^{(-)}]}{K_A/K_S[\text{CH}_3\text{O}^{(-)}] + 1}, \quad (4)$$

where  $k = k_1 k_2 / (k_{-1} + k_2)$ . At the lowest methoxide concentrations  $k_{\text{obs}}$  increases linearly with increasing methoxide concentration (Fig. 1). When most of the benzoyl derivative is transformed into anion, the solvolysis rate becomes independent of methoxide concentration (until  $[\text{CH}_3\text{O}^{(-)}] < 0.2 \text{ mol l}^{-1}$ ), because concentration of the undissociated benzoyl derivative is inversely proportional to the methoxide concentration, so that the product of their concentrations remains constant. At the highest methoxide concentrations the observed rate constant shows a decrease again (Fig. 1). This phenomenon is not due to a change in mechanism, but it is a consequence of the fact that in these relatively concentrated solutions the activity coefficients of the reacting components are significantly affected, the effects on the

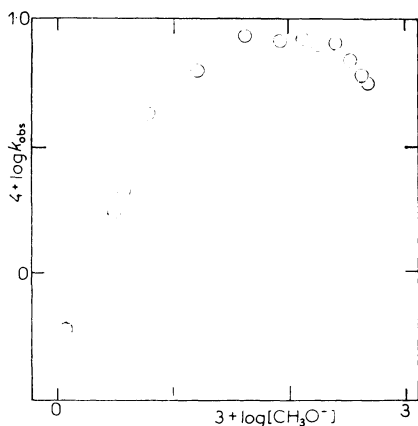
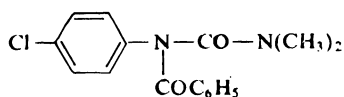


FIG. 1

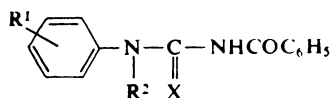
The dependence of the observed rate constant ( $k_{\text{obs}}, \text{s}^{-1}$ ) of methanolysis of benzoyl derivative *V* on methoxide concentration at 25°C

individual components being different. The activity coefficient of the substrate anion increases more slowly than that of the activated complex (Scheme 1). Consequently, the increasing methoxide concentration prefers the anion formation to the solvolytic reaction proper. The rate and equilibrium constants were calculated from Eq. (4) at lower methoxide concentrations (below  $10^{-1} \text{ mol l}^{-1}$ ) where the effect of methoxide on the activity coefficients of the reacting species is still insignificant.

In case of the slowly reacting compounds, the equilibrium constants were also determined spectrophotometrically. These constants were – within experimental error – the same as those calculated from the kinetic experiments. The results are given in Table I, wherefrom it follows that the sulphur analogues are by 1 order of magnitude more acidic than the oxygen derivatives and react faster with methoxide by 2 orders of magnitude. The facts found can be explained as follows. The C=S group attracts more strongly the electrons of the adjacent NH group, hence the sulphur derivatives are stronger N-acids. The dissociation constants of substituted phenylthioureas are by about 4 orders of magnitude higher than those of the analogues<sup>7</sup>. The same effect also is responsible for the fact that the anion of the substituted phenylthiourea is more stable and is split off more easily than the anion derived from the oxygen analogue. Therefore, the rate constants of the sulphur derivatives are substantially higher, too. Logarithms of the rate constants and the equilibrium constants of the substituted phenyl derivatives correlate with the Hammett  $\sigma$  constants. The  $\rho$  constant values are 1.53 and 0.70 for the acid-base equilibria and methanolyses, resp., of the benzoylthio derivatives XI–XIV, and 1.17 and 1.50, resp., for the oxygen analogues IV–VIII. At low methoxide concentrations, the substrates XI–XIV are present predominantly in their neutral forms, and the



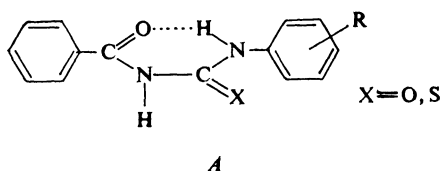
III



- IV,  $R^1 = R^2 = \text{H}$ ,  $X = \text{O}$   
 V,  $R^1 = 3\text{-Cl}$ ,  $R^2 = \text{H}$ ,  $X = \text{O}$   
 VI,  $R^1 = 4\text{-Cl}$ ,  $R^2 = \text{H}$ ,  $X = \text{O}$   
 VII,  $R^1 = 3\text{-NO}_2$ ,  $R^2 = \text{H}$ ,  $X = \text{O}$   
 VIII,  $R^1 = 4\text{-CH}_3$ ,  $R^2 = \text{H}$ ,  $X = \text{O}$   
 IX,  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_3$ ,  $X = \text{O}$

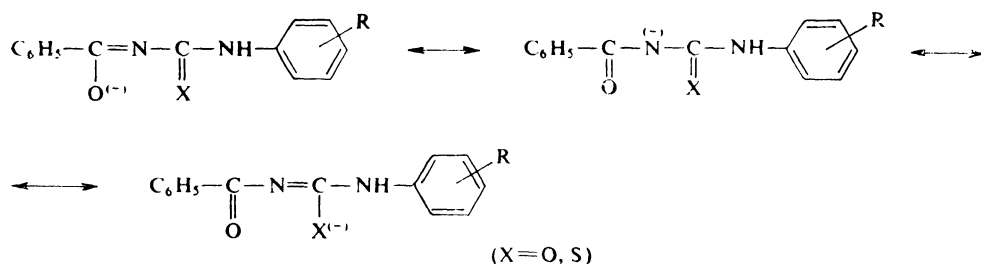
- X,  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_3$ ,  $X = \text{S}$   
 XI,  $R^1 = 4\text{-CH}_3$ ,  $R^2 = \text{H}$ ,  $X = \text{S}$   
 XII,  $R^1 = 4\text{-Br}$ ,  $R^2 = \text{H}$ ,  $X = \text{S}$   
 XIII,  $R^1 = 3\text{-NO}_2$ ,  $R^2 = \text{H}$ ,  $X = \text{S}$   
 XIV,  $R^1 = 4\text{-NO}_2$ ,  $R^2 = \text{H}$ ,  $X = \text{S}$

methanolysis rate is determined by the rate of attack of the carbonyl group by methoxide anion. At these conditions the fastest reacting derivative is the nitro derivative *XIV* and the slowest is the methyl derivative *XI*. At the highest alkoxide concentrations, the most of the substrate is present in the form of anion, and the rate depends on both the rate and the dissociation constants, which affect  $k_{\text{obs}}$  in opposite directions. The substituent effects on the dissociation constants of the thio derivatives are greater than those on the rate constants and, therefore, the reactivity order is inverted at higher methoxide concentrations (the nitro derivative *XIV* reacts most slowly, and the methyl derivative *XI* is the fastest to react). In case of the oxygen derivatives *IV–VII* the substituent effects on the rate constants are greater than those on the dissociation constants, hence the reactivity order remains unchanged within the whole range measured. The  $\rho$  constants of the acid-base equilibria have relatively high values, which can be explained by the substituent effect being also transferred through the hydrogen bond (*A*).



The other possibility, that the hydrogen atom is split off from the nitrogen atom adjacent to phenyl group, is less probable.

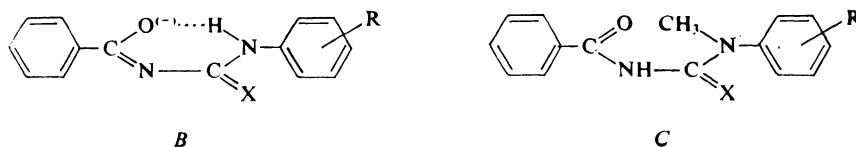
The  $\rho$  constant of the methanolysis rate of the oxygen derivatives is more than  $2\times$  greater than that of the sulphur analogues. It is even greater than that of the dissociation constants. A possible explanation is that, after the proton is split off, the negative charge is delocalized from the nitrogen atom to both the rest of the substituted phenylurea and the adjacent benzoyl group which is more distant from the R substituent, so that the effect of R is not so large (Scheme 2).



SCHEME 2

The first step of the methanolysis produces a tetrahedral intermediate (Scheme 1). As the methoxide anion splits off more easily than the phenylurea anion the subsequent step only is rate-limiting, *viz.* the splitting off of the substituted phenylurea. At the same time, there takes place a considerable negative charge transfer to the urea residue, so that the substituent effect can make itself felt to a considerably greater extent than that in the dissociation. The lower value of  $\rho$  constant of the methanolysis of the sulphur analogues can be explained by easier splitting off of thio-urea, hence the activated complex is formed sooner, and the substituent effects (of R) are less significant. It cannot be excluded that, in this case, the phenylthiourea anion is split off from the tetrahedral intermediate more rapidly than methoxide anion, hence the attack of carbonyl group by methoxide anion becomes rate-limiting. Acidity of  $\text{NH}_2$  group in the substituted phenylthiourea cannot be expected much lower than that of methanol, and in a number of cases<sup>8-10</sup> amines are split off from the tetrahedral intermediate by several orders of magnitude faster than the alkoxide ions of the same basicity.

The substituted phenylbenzoylureas in methanolic solutions have the structure (A) with strong hydrogen bond between the carbonyl oxygen and hydrogen of the amino group. Still more favourable conditions for formation of hydrogen bond are encountered in case of the anion B. Therefore, it was interesting to investigate the influence of the substitution of the hydrogen atom of the  $\text{PhNH}$  grouping by methyl group (Structure C). For this purpose we prepared the methyl derivatives IX and X.



$\text{X} = \text{O}, \text{S}$

It was surprising to find that the two methyl derivatives are much stronger N-acids than their non-methylated analogues. In case of the thio derivative X the acidity was so high that the dissociation constant could not at all be measured in methanol solutions. The considerable acidity increase due to methylation at nitrogen can be explained as follows. The methylated molecule cannot assume the coplanar arrangement represented in structure (A) due to strong steric interactions between the carbonyl of benzoyl group and the methyl group. This unfavourable interaction is eliminated, if the phenylamino group is partially rotated around the N-C bond, which restricts to considerable extent the conjugation between the free electron pair at the methylated nitrogen and  $\pi$  electrons of the  $\text{C}=\text{X}$  bond. Then the conjugation becomes more significant between the electron pair of the other nitrogen atom and the  $\pi$  electrons of the  $\text{C}=\text{X}$  bond, which is just the reason of the acidity increase observed.

One of the aims of this communication was also to follow the solvolysis rate of the commercial herbicide *III*. As this compound contains no dissociable proton, its solvolysis rate should increase with increasing methoxide concentration. But no solvolysis was observed even after several days boiling in 1M methoxide. Such a reactivity decrease can be due either to the presence of two alkyl groups at nitrogen (predominant polar effect) or to the presence of 4-chlorophenyl group in the neighbourhood of benzoyl group (steric effect). Therefore we measured the solvolysis ( $k = 2.5 \cdot 10^{-5} \text{ l mol}^{-1} \text{ s}^{-1}$ ) along with the dissociation constant ( $\text{p}K_{\text{A}} = 14.75$ ) of 1-benzoyl-3,3-diethylurea (*XV*). In  $0.1 \text{ mol l}^{-1}$  methoxide at  $25^{\circ}\text{C}$ , the methanolysis of compound *XV* has a half-life of about 100 h, although less than 10% of the substrate is present in its reactive neutral form at this methoxide concentration. This means that the decisive factor of the negligible reactivity of compound *III* is probably the steric effect of the chlorophenyl group which prevents the attack of the benzoyl group by methoxide anion.

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