THE METHANOLYSIS KINETICS AND DISSOCIATION CONSTANTS OF 1-(SUBST. BENZOYL)-3-PHENYLTHIOUREAS

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A series of seven 1-(subst. benzoyl)-3-phenylthioureas have been prepared and their dissociation constants and solvolysis rate constants have been measured in methanol at 25°C. The reaction constants found show that the solvolysis rate is limited by the attack of methoxide ion on the benzoyl carbonyl group of the non-dissociated substrate. The polar effect of substituents in benzoyl group is extensively transferred also by the intramolecular hydrogen bond.

Earlier we studied[1] the methanolysis kinetics of 1-benzoyl-3-(subst. phenyl)ureas *I* and 1-benzoyl-3-(subst. phenyl)thioureas *II*. From the values found for the ϱ reaction constants of the methanolysis and dissociation of compounds *I* and *II* conclusions could be made about structures of the activated complexes of the rate-limiting step of the methanolysis and those of the conjugated bases of compounds *I* and *II*. The aim of this present communication is a study of solvolysis of 1-(subst. benzoyl)-3-phenylthioureas *III*. In contrast to the series *I* and *II*, in the reaction series of compounds *III* there is a substituent affecting the dissociation of the starting compound and its solvolysis rate in the benzoyl group.

EXPERIMENTAL

Preparation of 1-(*subst. benzoyl*)-3-*phenylthioureas, procedure* A: A solution of 15 mmol (2·9 g) 1-acetyl-3-phenylthiourea[2] in 100 ml dry acetone was treated with 15 mmol substituted benzoyl chloride and the mixture was boiled on an oil bath in a flask with a condenser. A mixture of acetone and the acetyl chloride being formed was slowly distilled off, and the volume in the flask was kept constant by addition of acetone. After 3 h, the reaction mixture was concentrated to the volume of 50 ml, cooled, and treated with 150 ml ether or petroleum ether. The separated crystals were collected by suction and washed with 20 ml ether. For kinetic experiments the substances were purified by crystallization from acetone. The yields, melting points, elemental analyses, and ^{1}H chemical shifts are given in Table I. Acetone was dried with calcium chloride and distilled.

Procedure B: A solution of 15 mmol substituted benzoyl chloride in 20 ml acetone was treated with a solution of 15 mmol (1·1 g) ammonium thiocyanate in 20 ml acetone. The mixture was boiled 5 min and cooled below 15°C. The separated ammonium chloride was collected by suction, and the filtrate was treated with 15 mmol aniline, which was accompanied by a spontaneous

temperature increase. The product separated after cooling was collected and recrystallized from acetone. The physical constants are given in Table I.

The ^{1}H NMR *spectra* of the compounds prepared were measured in 5% solutions in hexadeuteriodimethyl sulphoxide with a JNM FX-100 (JEOL) spectrometer at 99·602 MHz at 25°C. The values of chemical shifts are related to the solvent signal (δ 2·55).

The methanolysis kinetics was followed spectrophotometrically with a Specord UV-VIS apparatus (Zeiss, Jena) at 25°C. A thermostated cell was charged with 1·95 ml sodium methoxide or methanolic 4-bromophenol – sodium 4-bromophenoxide buffer (the concentration of 4-BrC_6H_4ONa was 0·01 mol l^{-1}), 0·05 ml 3 . 10^{-3} mol l^{-1} methanolic solution of benzoylthiourea *IIIa*—*IIIg* was added thereto, and the absorbance decrease was followed at the wavelength given in Table II. The k_{obs} rate constants were calculated from the relation $k_{obs}t = -2{\cdot}3 \log (A_t - A_\infty) + \text{const.}$ and are given in Table III.

RESULTS AND DISCUSSION

The solvolysis kinetics of the benzoylthioureas *IIIa*—*IIIg* was studied in solutions of sodium methoxide and methanolic 4-bromophenol – sodium 4-bromophenoxide

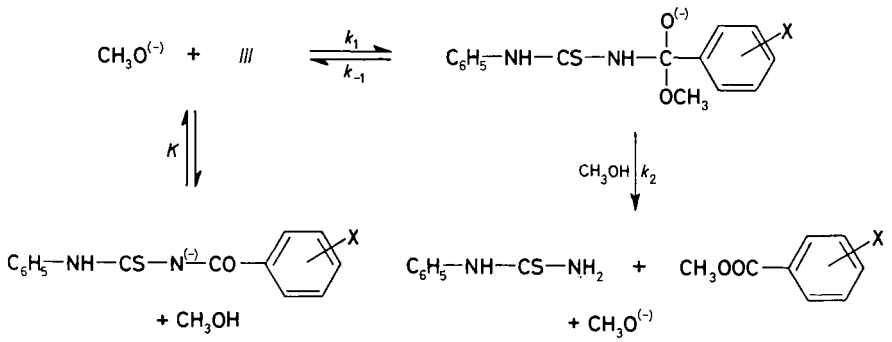
TABLE I

The benzoylthioureas *III* prepared and chemical shifts of the protons of NH groups

Compound (X)	Preparation procedure	Yield, % (m.p., °C)	Calculated/found % C	Calculated/found % H	$\delta(NHC_6H_5)$	δ(NHCO)
IIIa	*A*	86	—	—	12·66	11·66
(H)		(147—148)[a]	—	—		
IIIb	*B*	56	66·64	5·22	12·74	11·56
(3-CH_3)		(113—114·5)	66·82	5·12		
IIIc	*A*	46	66·64	5·22	12·73	11·51
(4-CH_3)		135—136	66·41	5·30		
IIId	*A*	12	—	—	12·55	11·68
(4-Cl)		142—143[b]	—	—		
IIIe	*B*	67	61·13	4·40	12·56	11·83
(4-CO_2CH_3)		128—130	61·35	4·54		
IIIf	*A*	52	55·81	3·72	12·48	12·06
(3-NO_2)		154—156	56·02	3·72		
IIIg	*A*	83	—	—	12·39	12·03
(4-NO_2)		171—173[c]	—	—		

[a] Ref.[3] gives m.p. 147—148°C; [b] ref.[4] gives m.p. 142—143°C; [c] ref.[5] gives m.p. 171—173°C.

buffers. In all the cases the reaction was first order in the substrate. The solvolysis course is represented in Scheme 1. The observed rate constant k_{obs} is defined by



SCHEME 1

Eq. (*1*) at $[CH_3O^{(-)}] < 0{\cdot}1$, and the rate constant k is defined by Eq. (*2*). K_a means the dissociation constant of the substrate *III*, and $K_S = 10^{-16.92}$ is the autoprotolytic constant of methanol[6]. The expression $1/(1 + [CH_3O^{(-)}]K_a/K_S)$ means the molar fraction of benzoylthiourea in the mixture with its conjugated base

$$k_{obs} = \frac{k[CH_3O^{(-)}]}{1 + K[CH_3O^{(-)}]} = \frac{k[CH_3O^{(-)}]}{1 + [CH_3O^{(-)}]K_a/K_S} \qquad (1)$$

$$k = k_1k_2/(k_{-1} + k_2)\,. \qquad (2)$$

TABLE II

The methanolysis rate constants (k, $l\,mol^{-1}\,s^{-1}$) and dissociation constants of compounds *IIIa*—*IIIg* in methanol at 25°C and the analytical wavelengths (λ, nm)

Compound	pK_a	k	λ
IIIa	14·40	4·5	350
IIIb	14·56	3·3	305
IIIc	14·61	2·2	305
IIId	13·92	11	345
IIIe	13·69	25	352
IIIf	13·22	56	312
IIIg	13·05	104	333

TABLE III

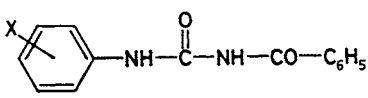
The values of observed rate constants k_{obs} (s^{-1}) corresponding to the respective methoxide concentrations c (mol l^{-1}) for the compounds *IIIa*—*IIIg* at 25°C

IIIa		*IIIb*		*IIIc*		*IIId*		*IIIe*		*IIIf*		*IIIg*	
$c \cdot 10^3$	$k_{obs} \cdot 10^3$	$c \cdot 10^3$	$k_{obs} \cdot 10^3$	$c \cdot 10^3$	$k_{obs} \cdot 10^3$	$c \cdot 10^3$	$k_{obs} \cdot 10^3$	$c \cdot 10^4$	$k_{obs} \cdot 10^3$	$c \cdot 10^4$	$k_{obs} \cdot 10^3$	$c \cdot 10^4$	$k_{obs} \cdot 10^3$
1·78	5·01	0·79	2·24	1·78	2·82	0·36	2·95	0·87	1·74	0·87	2·82	0·87	5·50
2·24	5·75	1·32	3·31	2·19	3·31	1·00	5·62	1·70	3·35	1·70	4·47	1·70	8·04
3·24	6·92	2·29	5·01	2·75	3·89	1·51	6·61	3·39	5·25	3·39	6·61	3·39	10·00
4·79	8·32	3·31	6·03	4·79	5·37	2·00	7·50	7·94	8·32	7·94	8·71	7·94	11·22
7·24	9·44	4·79	7·76	5·89	6·68	2·51	8·04	18·62	11·75	23·44	10·00	19·50	13·49
10·03	10·47	7·41	9·55	10·00	6·92	3·98	8·91	28·18	12·59	48·98	10·00	24·58	13·49
15·85	11·48	10·00	10·47	14·13	6·92	6·31	9·55	39·81	13·49	58·84	10·23	49·89	13·49
25·71	12·02	25·12	12·02	21·38	8·91	7·24	10·00	100·00	14·125	100·00	10·72	77·62	12·88
50·12	12·59	34·67	12·02	52·48	9·55	10·00	12·59	199·63	14·12	199·63	10·47	338·84	12·88
—	—	50·12	12·30	125·89	8·91	15·85	10·00	316·23	14·12	—	—	501·19	12·88
—	—	75·86	12·59	—	—	—	—	—	—	—	—	—	—

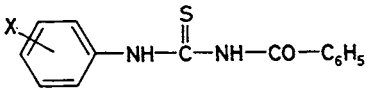
At $[CH_3O^{(-)}] > 0{\cdot}1$ mol l^{-1} the rate constants k_{obs} have lower values than those calculated from Eq. (*1*), which is caused by the decreased ability of medium to solvate the substrate anion and the activated complex of the rate-limiting step at increasing methoxide concentration. The solvation requirements of the substrate anion are (due to the charge delocalization possibility therein) smaller than those of the activated complex, and hence also the activity coefficient of the activated complex of the solvolysis rate-limiting step increases with increasing methoxide concentration more rapidly than the activity coefficient of the conjugated base of substrate *III* (refs[1,7]). This statement follows from the activated complex theory and can be expressed[8] by Eq. (*3*), where γ_{S^-} and $\gamma^{\ddagger}$ are the activity coefficients of the substrate anion and the activated complex, respectively, and k_0 is the rate constant of the reaction in a solution of infinite dilution

$$k_{obs} = k_0 \gamma_{S^-} / \gamma^{\ddagger} \,. \qquad (3)$$

In the methanolyses of the benzoylthioureas *III* in methanolic bromophenoxide buffers, the methoxide anion only acts as the nucleophilic agent, the bromophenoxide anion being insignificant as a nucleophile. The methoxide ion concentration in the bromophenoxide buffers was determined in the following way: A series of measurements of the solvolyses of derivatives *IIId* and *IIIe* were carried out in methoxide solutions and in bromophenoxide buffers. The dependence of k_{obs} on $[CH_3O^{(-)}]$ found for the methoxide solutions was then used for determination of the methoxide concentration in the bromophenoxide buffers. This procedure proved to be more reliable than a calculation of $[CH_3O^{(-)}]$ from the pK_a values given for 4-bromophenol in literature. The buffers for which the methoxide concentration was determined in the above-described way were then used for determination of the solvolysis of the benzoylthioureas *IIIf* and *IIIg*.



I



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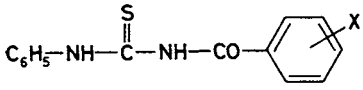


III

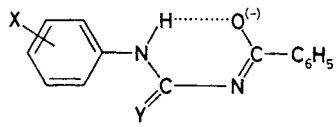
The rate constants k and the dissociation constants K_a (Table II) calculated by optimization from the k_{obs} values and methoxide concentration by Eq. (*1*) were

correlated with the Hammett σ constants (Eqs (*4*) and (*5*)). The values found for the reaction constant ϱ were compared with the reaction constants of methanolysis and dissociation of compounds *I* and *II* (ref.[1], Table IV).

$$\log k = (1{\cdot}68 \pm 0{\cdot}05)\,\sigma + (0{\cdot}64 \pm 0{\cdot}024)\,; \qquad (4)$$
$$r = 0{\cdot}998,\ s = 0{\cdot}049,\ n = 7$$

$$\log K_a = (1{\cdot}66 \pm 0{\cdot}06)\,\sigma - (14{\cdot}38 \pm 0{\cdot}03)\,; \qquad (5)$$
$$r = 0{\cdot}995,\ s = 0{\cdot}060,\ n = 7$$

The reaction constant ϱ found for the dissociation of benzoylthioureas *III* is only by about 40% higher than that for the dissociation of benzoylureas *I*, being very close to that of the dissociation of benzoylthioureas *II*, although the compounds *III* have their dissociable proton by one bond closer to the substituent *X*. An acceptable explanation is represented by the presumption that the polar effect of the substituent *X* is transferred also via the intramolecular hydrogen bond in compounds *I* and *II*; this presumption for the conjugated base is presented in structure *IV*.



IV, Y = O, S

Still more significant is the comparison of the reaction constants ϱ for the methanolyses of benzoylureas *I* and benzoylthioureas *III*. Although in compounds *I* the substituent X is by 3 bonds more distant from the reaction centre than in com-

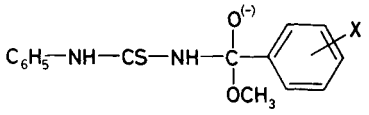
TABLE IV

The reaction constants ϱ of the Hammett correlation of the methanolysis rate constants k and dissociation constants K of the benzoylureas *I* and benzoylthioureas *II* and *III*

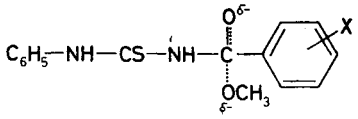
Reaction series	I^a	II^a	*III*
ϱk	1·50	0·70	1·68
ϱK	1·17	1·53	1·66

[a] Ref.[1].

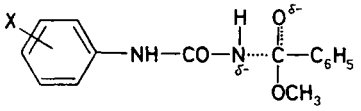
pounds *III*, the values of the methanolysis reaction constants are almost the same for both series (Table IV). Thereform it is obvious that the distributions of charges in the reaction centre of the activated complexes of the rate-limiting steps of the solvolyses of both substrates must be very different, and hence it is highly probable that the two activated complexes belong to two different rate-limiting steps. The NH groups of thioureas are known to be more acidic than those of ureas by several orders of magnitude[9]. In accordance therewith, thioureide group is split off more easily than ureide group in nucleophilic substitutions[1,10,11]. In the benzoylthioureas *III* the thioureide group is split off from the intermediate *V* more easily than methoxy group, and hence the methanolysis rate-limiting step consists in the attack of the substrate carbonyl group by methoxide ion. The activated complex of the rate--limiting step of this reaction could have structure *VI*. In the case of methanolysis of benzoylureas *I*, the splitting off of methoxy group from the intermediate *V* is faster than that of the ureide group. Hence the rate-limiting step consists in the transformation of the intermediate into the product, and the activated complex is presumed to have structure *VII*.



V



VI



VII

The methanolyses of the benzoylthioureas *II* and *III* have the same rate-limiting steps. The reaction constant of the methanolysis of compounds *III* has more than two times higher value than that of compounds *II* in accordance with the reaction centre in compounds *III* being by 3 bonds closer to the substituent X as compared with compounds *II* (Table IV). With regard to the difference in the distance of the substituent and the reaction centre, the reaction constant of methanolysis of compounds *II* should be still smaller than 0·7. The value 0·7 found for the reaction constant ϱ of the methanolysis of compounds *II* can be explained by the facilitating effect of the intramolecular hydrogen bond between the proton at N-3 nitrogen atom and acyl oxygen atom[12] exerted on the attack of the carbonyl group of acylthioureas by methoxide ion. The greater is the σ constant of substituent X in compounds *II*, the stronger is the intramolecular hydrogen bond and the easier is the attack of the

acyl carbonyl group by methoxide. The transfer of polar effects of the substituent X through the hydrogen bond is also significant in the benzoylureas *I*, but this effect cannot be great enough for the reaction constant ϱ of the methanolysis to reach the value of 1·5, if the rate-limiting step were the attack of acyl carbonyl group by methoxide.

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