

AN ANOMALOUS EFFECT OF METHYL GROUP ON ACIDITY OF ACYLTHIOUREAS

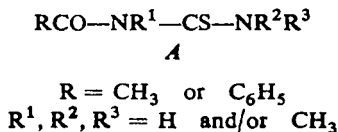
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Dissociation constants and methanolysis rate constants have been measured of 1-acetyl- and 1-benzoylthioureas and their N-methyl derivatives. Replacement of hydrogen atom at N(1) (next to the acyl group) by methyl group increases the acidity of the benzoyl derivative by one order, that of the acetyl derivative by as much as two orders of magnitude. Replacement of both hydrogens at N(3) by methyl groups lowers the methanolysis rate constant by more than two orders, whereas the replacement of hydrogen atom at N(1) by methyl group increases the methanolysis rate by the factor of 30.

In our earlier research we dealt with methanolysis of 1-acyl-3-phenylthioureas. In this context we arrived at a surprising conclusion that replacement of hydrogen atom at N(1) (next to the acyl group) increased the acidity by several orders of magnitude¹, although according to the accepted conception the hydrogen atom at N(1) is more acidic, hence the substitution should lead to a substantial decrease of acidity. In order to find whether this anomaly has any more general validity, we have concentrated this present paper on measurements of the dissociation constants and methanolysis rate constants of 1-acetyl- and 1-benzoylthioureas whose hydrogen atoms at nitrogen are gradually replaced by methyl groups (structure A).



EXPERIMENTAL

Reagents

1-Acetyl-3-methylthiourea (I) was prepared either by acetylation of methylthiourea² or by reaction of methylamine with methyl-N-acetyldithiocarbamate according to the procedure described³ for compound II (yield 85%, m.p. 170–172°C in accord with ref.², sublimed at 110°C at 400 Pa).

1-Acetyl-3,3-dimethylthiourea (II) was prepared in 90% yield by reaction of methyl-*N*-acetyl-dithiocarbamate with dimethylamine in ethanol. M.p. 99–100°C (benzene–heptane 1:1; in accordance with ref.³).

1-Acetyl-1,3-dimethylthiourea (III): A solution of 2.1 g (20 mmol) 1,3-dimethylthiourea in 10 ml acetic anhydride was treated with one drop of sulphuric acid. The mixture was heated at 90°C 1 h and then evaporated under reduced pressure. The solid residue was digested with boiling ether. Yield 1.6 g (53%), m.p. 85–87°C. For C₅H₁₀N₂OS (146.1) calculated: 41.10% C, 6.84% H, 19.17% N; found: 41.35% C, 7.00% H, 18.95% N. ¹H NMR spectrum: δ(CH₃CO) = 2.19, δ(NCH₃) = 3.32, δ(NHCH₃) = 3.05, δ(NH) = 10.63. ¹³C NMR spectrum: δ(CS) = 186.33, δ(CH₃CO) = 171.00, δ(NCH₃) = 36.28, δ(NHCH₃) = 32.99, δ(CH₃CO) = 24.02.

1-Acetyl-1,3,3-trimethylthiourea (IV): A mixture of 7.5 ml acetic anhydride and 1.8 g (15 mmol) 1,1,3-trimethylthiourea was boiled 5 min, whereupon 4 ml of the solvent was distilled off under reduced pressure. The viscous liquid residue crystallized on being left in a refrigerator overnight. The crystalline solid obtained was digested with boiling ether. Yield 1.3 g (54%), m.p. 68.5–70°C (ref.⁴ gives m.p. 154°C). For C₆H₁₂N₂OS (160.1) calculated: 45.00% C, 7.50% H, 17.50% N; found: 45.22% C, 7.58% H, 17.24% N. ¹H NMR spectrum: δ(NCH₃) = 3.41, δ(N(CH₃)₂) = 2.82; 3.10, δ(CH₂CO) = 2.06. ¹³C NMR spectrum: δ(CS) = 186.67, δ(CO) = 167.54, δ(COCH₃) = 21.60, δ(N(CH₃)₂) = 41.36; 43.17, δ(NCH₃) = 41.36.

1-Benzoyl-3-methylthiourea (V): A solution of 1.3 g (10 mmol) acetyl derivative II and 1.4 g (10 mmol) benzoyl chloride in 30 ml anhydrous acetone was heated on a boiling water bath 2.5 h with simultaneous addition of acetone to make up for that distilled off with the acetyl chloride being formed. Then the mixture was concentrated to the volume of 15 ml, cooled, and diluted with 40 ml ether. The separated crystals were collected by filtration and washed with ether. Yield 1.7 g (87%), m.p. 146–147°C (ref.⁵ gives m.p. 151–152°C).

1-Benzoyl-3,3-dimethylthiourea (VI): A solution of 5.3 g (70 mmol) ammonium rhodanide and 10 ml (71 mmol) benzoyl chloride in 70 ml anhydrous acetone was heated to boiling 5 min. After cooling, ammonium chloride was removed by filtration, and the filtrate was further cooled to –18°C, whereupon 3.2 g (71 mmol) dimethylamine (cooled to –60°C) was added. The separated crystals were collected and recrystallized from ethanol. Yield 5 g (34%), m.p. 140–142°C (ref.⁶ gives m.p. 117°C). For C₁₀H₁₂N₂OS (208.2) calculated: 57.69% C, 5.76% H, 13.46% N; found: 57.78% C, 5.79% H, 13.57% N. ¹H NMR spectrum: δ(CH₃) = 3.19; 3.44, δ(NH) = 10.75. ¹³C NMR spectrum: δ(CH₃) = 41.94; 43.46, δ(CS) = 180.83, δ(CO) = 163.98, δ(C₆H₅) = 132.79; 128.48; 133.44.

1-Benzoyl-1,3-dimethylthiourea (VII): A saturated solution of 1.04 g (10 mmol) 1,3-dimethylthiourea in anhydrous acetone was treated with a solution of 1.4 g (10 mmol) benzoyl chloride in 5 ml acetone while boiling. The separated white crystalline *S*-benzoyl-1,3-dimethylisothiuronium chloride was filtered off after cooling. Yield 2.3 g (94%), m.p. 103–107°C (decomposition; in a preheated Kofler block). The above-mentioned isothiuronium salt (0.5 g; 2 mmol) was dissolved in 10 ml methanol, and this solution was added to a hot saturated methanolic solution of 0.16 g anhydrous sodium acetate. The mixture was heated to boiling 1 min, diluted with 20 ml water, and rapidly cooled. The separated crystalline solid was collected by filtration and washed with cold methanol. Yield 0.2 g (50%), m.p. 79–79.5°C. For C₁₀H₁₂N₂OS (208.2) calculated: 57.69% C, 5.76% H, 13.43% N; found: 57.80% C, 5.91% H, 13.20% N. ¹H NMR spectrum: δ(NH) = 10.07, δ(C₆H₅) = 7.40–7.68, δ(NCH₃) = 3.40, δ(NHCH₃) = 2.75. ¹³C NMR spectrum: δ(CS) = 186.79, δ(CO) = 169.53, δ(C–CO) = 135.60, δ(C₆H₅) = 127.35; 128.06; 130.81, δ(NCH₃) = 36.90, δ(NHCH₃) = 32.46.

Measurements

The electronic spectra were measured with a Zeiss Specord UV-VIS. The ^1H and ^{13}C NMR spectra were measured at 99.602 and 25.047 MHz, resp., by means of a JNM-FX 100 JEOL apparatus in hexadeuteriodimethyl sulphoxide at 25°C. The chemical shifts are related to the solvent signal ($\delta(^1\text{H}) = 2.55$, $\delta(^{13}\text{C}) = 39.6$).

Kinetics and Dissociation Constants

The kinetic measurements of methanolysis of compounds *I–V* and *VII* were carried out photometrically in solutions of sodium methoxide in closed quartz cells ($d = 1$ cm) kept at 25°C: 2 ml $8 \cdot 10^{-4}$ to 1.0 mol l^{-1} sodium methoxide was placed in the cell, and 20 μl fresh solution of compound *I–V* or *VII* ($10^{-2} \text{ mol l}^{-1}$) in methanol was injected therein, whereupon the absorbance decrease was followed at a suitable wavelength (Table I). The rate constants k_{exp} (s^{-1}) were calculated from the relation $k_{\text{exp}}t = -2.3 \log(A_t - A_\infty) + \text{const.}$, where A_t and A_∞ mean the absorbances at a time t and after at least six half-lives, respectively. The differences between the k_{exp} values obtained from three independent experiments were less than 5%.

The dissociation constants of compounds *I–III* and *V* were calculated from the dependence of $\log k_{\text{exp}}$ on $\log [\text{CH}_3\text{O}^{(-)}$] according to Eq. (3) (see Results and Discussion). The dissociation constant of compound *III* was calculated from the concentration ratio of the dissociated and undissociated forms according to Eq. (1), where K_A is the dissociation constant measured, $\text{p}K_S$ is negative logarithm of ionic product of methanol⁸ (16.916), and R means the concentration ratio of the conjugated base $\text{S}^{(-)}$ and acid SH of the substrate *III* measured.

$$\text{p}K_A = \text{p}K_S + \log [\text{CH}_3\text{O}^{(-)}] - \log R \quad (1)$$

The R value was calculated from the absorbances measured at 270 nm and extrapolated to the zero time according to the relation $R = [\text{S}^{(-)}]/[\text{SH}] = (A - A(\text{SH}))/A(\text{S}^{(-)} - A)$, where $A(\text{SH})$, $A(\text{S}^{(-)})$, and A stand for the absorbances of the substrate, its conjugated base, and the solution measured, respectively. For the measurement proper, a cell was charged with 0.4 ml solution of $10^{-3} \text{ mol l}^{-1}$ *III* and with 1.6 ml methoxide solution to make its resultant concentration $1 \cdot 10^{-3}$ to $10^{-1} \text{ mol l}^{-1}$, whereupon the absorbance decrease was followed 2 min. The absorbances of the undissociated and dissociated forms were measured in pure methanol and in $5 \cdot 10^{-1} \text{ mol l}^{-1}$ methoxide, respectively.

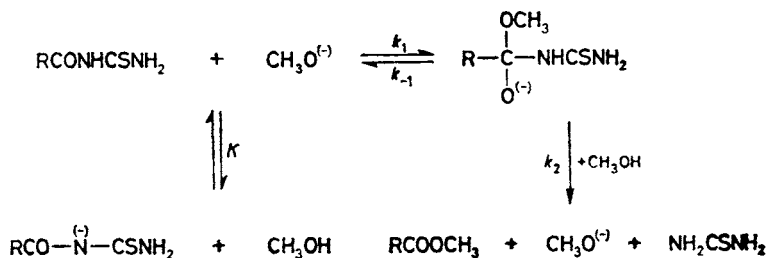
The dissociation constant of the benzoyl derivative *VI* was calculated from Eq. (2)

$$\text{p}K_A = \log((c_{VI} - c_m)/c_m) + \log((A_{\text{exp}} - A(\text{HA}))/A(\text{A}^-) - A_{\text{exp}}) + 12.44, \quad (2)$$

where c_{VI} and c_m are analytical concentrations of compound *VI* and methoxide, respectively (the latter being equal to analytical concentration of the anion of compound *VI*); the expression $(c_{VI} - c_m)$ is the concentration of the neutral compound *VI*; the value 12.44 is $\text{p}K_A$ of 3-nitrophenol in methanol⁹; $A(\text{HA})$, $A(\text{A}^-)$, and A_{exp} are absorbances of 3-nitrophenol, its conjugated base, and the mixture of the two forms in the given buffer formed by the compound *VI*. The concentration ratio of the dissociated and undissociated forms of compound *VI* was determined from the absorbance of 3-nitrophenol in the following way: 1 ml methanolic solution containing $2 \cdot 10^{-4} \text{ mol l}^{-1}$ 3-nitrophenol and $5 \cdot 10^{-2} \text{ mol l}^{-1}$ compound *VI* was placed into a cell and 0.1 to 1.0 ml $10^{-2} \text{ mol l}^{-1}$ methoxide solution was added, whereupon methanol was added to make the final volume of 2 ml, and the absorbance was measured at 420 nm. The spectra of undissociated and dissociated forms were determined in pure methanol and $5 \cdot 10^{-2} \text{ mol l}^{-1}$ sodium methoxide, respectively.

RESULTS AND DISCUSSION

The methanolysis of acylthioureas was kinetically the first order reaction in all the cases. Except for the compound *IV*, the reaction course is represented in Scheme 1.



The observed rate constant k_{exp} is defined by Eq. (3) where $k_m = k_1 k_2 / (k_{-1} + k_2)$ and $K_A = KK_S$ means the dissociation constant of the acylthiourea. The expression $(1 + K[\text{CH}_3\text{O}^{(-)}])^{-1}$ gives the ratio of the real and analytical concentrations of the

$$k_{\text{exp}} = \frac{k_m[\text{CH}_3\text{O}^{(-)}]}{1 + K[\text{CH}_3\text{O}^{(-)}]} = \frac{k_m[\text{CH}_3\text{O}^{(-)}]}{1 + [\text{CH}_3\text{O}^{(-)}]K_A/K_S} \quad (3)$$

substrate. For acetyltrimethylthiourea (*IV*), which has no dissociable proton, the rate constant is defined by Eq. (4).

$$k_{\text{exp}} = k_m[\text{CH}_3\text{O}^{(-)}] \quad (4)$$

Curve 1 in Fig. 1 represents the dependence of the k_{exp} (calculated from Eq. (3)) of the reaction of compound *V* on methoxide concentration. When the substrate

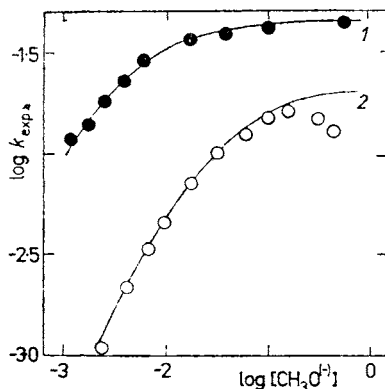


FIG. 1

The dependence of the experimental constants k_{exp} (s^{-1}) of methanolysis of compound *III* (●) and *V* (○) on sodium methoxide concentration. The curves 1 and 2 represent the k_{exp} values calculated from Eq. (3) for $K = 260$, $k_m = 12 \text{ l mol}^{-1} \text{ s}^{-1}$ and $K = 26$, $k_m = 0.56 \text{ l mol}^{-1} \text{ s}^{-1}$, respectively

is mostly present in the form of the anion ($[\text{CH}_3\text{O}^{(-)}] > 0.4 \text{ mol l}^{-1}$), the k_{exp} value should become practically independent of the methoxide concentration, as the concentration of the undissociated benzoyl derivative V is inversely proportional to the methoxide concentration. In fact, however, the k_{exp} value experimentally found at $[\text{CH}_3\text{O}^{(-)}] > 0.2 \text{ mol l}^{-1}$ decreases, and the decrease is progressively steeper with increasing alkoxide concentration. The decrease is due to the fact that the activity coefficient of the anion increases more slowly than that of the activated complex, which results in a decrease in the ratio of the concentration of the activated complex to that of the anion with increasing methoxide concentration¹⁰. This difference between the measured and calculated k_{exp} values (Fig. 1) is characteristic for all those acylthioureas which have a dissociable proton at the N(1) (acylated) atom. Curve 2 in Fig. 1 represents the dependence of the methanolysis rate constants of compound *III* on methoxide concentration. In this case, the calculated rate constant values (the curve calculated from Eq. (3)) agree with the experimental values (points) even at the highest methoxide concentrations (1 mol l^{-1}). The same applies to compound *VII*, too. This finding could indicate that if the proton is dissociated from N(3) the ratio of activity coefficients of the anion and the activated complex is independent of the methoxide concentration.

Table I presents the rate and equilibrium constants calculated from Eqs (3) and (1), respectively, and the rate constant of compound *IV* calculated from Eq. (4) for

TABLE I

The $\text{p}K_{\text{A}}$ values (in methanol) of acylthioureas type $\text{RCONR}^1\text{CSNR}^2\text{R}^3$ and the rate constants k_{m} ($\text{l mol}^{-1} \text{ s}^{-1}$) of their methanolysis defined by Eq. (3)

Compound	R	R ¹	R ²	R ³	$\text{p}K_{\text{A}}$	k_{m}	λ^{a} , nm
<i>I</i>	CH ₃	H	CH ₃	H	16.60 ± 0.1	0.46	270
<i>II</i>	CH ₃	H	CH ₃	CH ₃	14.30 ± 0.04	$1.2 \cdot 10^{-2}$	273
<i>III</i>	CH ₃	CH ₃	CH ₃	H	$14.50 \pm 0.04^{\text{b}}$	12	270
<i>IV</i>	CH ₃	CH ₃	CH ₃	CH ₃	—	$7 \cdot 10^{-4}$	278
<i>V</i>	C ₆ H ₅	H	CH ₃	H	15.50 ± 0.05	0.56	278
<i>VI</i>	C ₆ H ₅	H	CH ₃	CH ₃	13.00 ± 0.02	small ^c	420
<i>VII</i>	C ₆ H ₅	CH ₃	CH ₃	H	14.66 ± 0.03	17	270
—	C ₆ H ₅	H	H	H	$15.20 \pm 0.05^{\text{d}}$	1.4^{d}	—
—	CH ₃	H	H	H	$16.27 \pm 0.06^{\text{d}}$	5.3^{d}	—

^a The wavelength at which the measurements were carried out; ^b the kinetically and spectrophotometrically determined values are 14.47 and 14.52, respectively; ^c the half-life of about 4 days; ^d the values from ref.⁷.

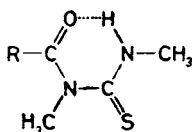
$[\text{CH}_3\text{O}^{(-)}] < 0.2 \text{ mol l}^{-1}$ (the region of linear dependence between $\log k_{\text{exp}}$ and $\log [\text{CH}_3\text{O}^{(-)}]$ with the slope 1). At higher methoxide concentrations, k_{exp} increases more steeply than it corresponds to the alkoxide concentration.

With compound *VI* the methanolysis was so slow (the assessed $\tau_{1/2}$ value was 4 days) that it could not be reliably measured. Therefore, we only measured its dissociation constant (spectroscopically — see Experimental). In order to verify, in an independent way, the correctness of the calculation of K_A from kinetical data, we also estimated the dissociation constant of compound *III* by spectrophotometric method from concentration ratio of SH and $\text{S}^{(-)}$.

A replacement of one hydrogen atom at N(3) by methyl group will bring about a two fold acidity decreases with both the acetyl and the benzoyl derivatives. Introduction of the second methyl group at N(3) results in an acidity increase by about 2.5 orders of magnitude as compared with the monomethyl derivative. A similar acidity increase was observed¹⁰ (also in methanol) in the case of replacement of a hydrogen atom by methyl group at N(3) atom of 1-benzoyl-3-phenylthiourea¹⁰ as well as in the case of the replacement by butyl group at N(3) of 1-benzoyl-3-butylthiourea (in 70% aqueous dioxane)¹¹. A still greater change (by 4 orders of magnitude) was observed in the case of the replacement of hydrogen atom by ethyl group in 1-furoyl-3-ethylthiourea in the medium of dimethylformamide¹². A decrease in conjugation possibilities of the electron pair at N(3) with π electrons of C=S group due to steric effect of the two alkyl groups is given as a possible reason of the increased acidity at the N(1) atom¹⁰. The same acidity increase of 1-acetylthioureas, however, takes place if methyl replaces the hydrogen atom at N(1) which is generally considered to be the most acidic and, therefore, is split off preferably in the process of formation of the anion. In this case the acidity of both the acetyl and the benzoyl derivatives (compounds *III* and *VII* in Table I) is practically the same, whereas in other cases the benzoyl derivative was more acidic than the acetyl derivative by more than one order of magnitude. Hence, again a marked acidity increase is observed as it is the case with 1-acetyl-3-phenylthiourea¹, but in this case the anomaly is still greater. With 1-acetyl-3-phenylthiourea the acidity of hydrogen atom at N(3) is strongly increased already by the presence of the phenyl group, hence in the 1-(subst.phenyl)-thioureas alone the acidity of hydrogen atom at N(1) is already so high that its dissociation takes place in sodium methoxide solutions¹³.

The gradual substitutions of hydrogen atoms by methyl groups in acylthioureas not only affect their dissociation constants but also affect the rate constants of their solvolyses. When replacing the first hydrogen atom at N(3) by a methyl group (compound *V*), the methanolysis rate of the benzoyl derivative decreases by the factor of three and that of the acetyl derivative (compound *I*) by more than one order of magnitude. Introduction of the second methyl group at N(3) again causes a decrease (forty fold) of the solvolysis rate of the acetyl derivative *II*. With the benzoyl derivative *VI* the solvolysis rate already was so low that it was impossible to measure

it under usual conditions. The compound *VI* does not undergo solvolysis even at enhanced temperatures⁶. On the other hand, the replacement of the hydrogen atom at N(1) by methyl group in compounds *I* and *V* results in a thirty fold increase in the solvolysis rate constant (k_m of compounds *III* and *VII* in Table I). The lowest k_m value was found with the trimethyl derivative *IV* (by about four orders of magnitude lower than that of the N(1)- and N(3)-monomethyl derivatives *III* and *VII*). The measurement was enabled only by the fact that the compound *IV* possesses no dissociable proton, so the solvolysis rate continually increases with increasing methoxide concentration. The main reason of decreased reactivity of the N(3)-dimethyl derivatives obviously lies in that no hydrogen bond can be formed between the carbonyl oxygen atom and hydrogen atom at N(3) which would strongly increase the reactivity of the carbonyl carbon atom to nucleophiles. The highest k_m values with compounds *III* and *VII* are explained by the steric effect of N(1)-methyl group which supports the formation of cyclic structure *B* with the hydrogen bond.

*B*

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