The rate of acid-catalyzed solvolysis and tuberculostatic activity of thioamides

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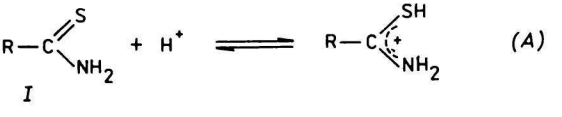
The dependence of rate constant of acid-catalyzed solvolytic reaction of thioamides on concentration of the acid as well as the entropy of activation and positive value of the ϱ constant in the Hammett equation has confirmed in accordance with literature the suggested S_N2 mechanism of this reaction for the whole investigated group of substances. The uniformity of reaction mechanism made possible a correlation of the determined rate constants with microbial activity of these substances.

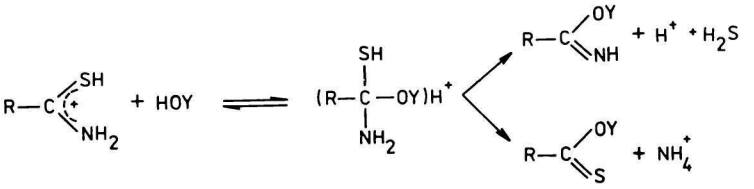
Зависимость константы скорости кислотно катализируемой реакции сольволиза тиоамидов от концентрации кислоты, энтропии активации реакции и положительные значения величин Гамметтовских констант ϱ подтвердили предлагаемый в литературе S_N2 механизм этой реакции для всей изученной группы веществ. Универсальность реакционного механизма позволила проведение корреляции найденных констант скоростей с микробиальной активностью данных соединений.

On the basis of spectral methods [1—5] and structural analysis [6, 7], it has been ascertained that thioamides exhibit structure *I* and in acid solutions protonize on the sulfur atom [8—11] according to scheme (*A*).



I (*A*)

In the medium of prototropic solvents the arising cation is subjected to solvolysis and splits off hydrogen sulfide or ammonia according to scheme (*B*)



(B)

with possible tautomeric reactions of the forming products. The S_N2 mechanism is attributed to this reaction [12—14]. The solvolytic reaction was kinetically investigated only for thioacetamide and thiobenzamide. Therefore it appears useful to extend the experimental material for a greater number of substances. The present therapeutic use of thioamide of 2-ethylisonicotinic acid suggests the possibility of a correlation between the rate constants of solvolytic reaction and microbial activity of the investigated group of substances.

Experimental

Chemicals

Thioamides of nicotinic acid (*I*) [15] and isonicotinic acid (*II*) [16] were prepared according to literature. Thioamide of 2-ethylisonicotinic acid (*III*) was a commercial preparate (Léčiva, Prague). *p*-Methylthiobenzamide (*IV*) [17], thiobenzamide (*V*) [18], *p*-chloro- (*VI*) [19], *m*-chloro- (*VII*) [11], *o*-chlorothiobenzamide (*VIII*) [20], *N*--diphenylthiobenzamide (*IX*) [21] as well as *N*-methyl- (*X*), *N*-ethyl- (*XI*), *N*-phenyl- (*XII*), *N*-dimethyl- (*XIII*), *N*-phenylmethyl- (*XIV*), and *N*-diphenyl-*p*-chlorothiobenzamide (*XV*) [22] were prepared according to literature. *N*-Benzyl- (*XVI*), *N*-(*p*-methoxyphenyl)- (*XVII*), *N*-(*p*-tolyl)- (*XVIII*), *N*-(*p*-chlorophenyl)- (*XIX*), and *N*-(*m*-chlorophenyl)-*p*-chlorothiobenzamide (*XX*) were prepared by customary method [23]. The results of analyses and melting points of the prepared substances are summarized in Table 1.

Kinetic measurements

Except slightly soluble substance *XV*, the preparations were used for producing 5×10^{-4} M solutions in water or aqueous solution of ethanol ($\phi = 50$ volume %) containing convenient concentration of sulfuric acid. The concentration of acid was checked by titration and the H_0 values of solutions were taken from literature [24, 25]. The solutions were sealed into ampoules and heated to the temperatures θ/°C = 49.5, 59.5, 68.5, 80, and 90 which were held constant accurate to ±0.1 °C. After a certain time, the solutions were taken from the bath and polarographically analyzed. It was the concentration of thioamide that was determined. The solutions containing 50 % or more of sulfuric acid were diluted before analysis with a known quantity of water owing to which the waves were more distinct. The

Table 1

Characterization of the synthesized substances

No.	Substance	Formula	M_r	M. p./°C	w_i (calc.)/% w_i(found)/%		
					C	H	N
XVI	*N*-Benzyl-*p*-chlorothiobenzamide	$C_{14}H_{12}ClNS$	261.79	47—50	64.22	4.63	5.35
					64.35	4.57	5.42
XVII	*N*-(*p*-Methoxyphenyl)-*p*-chlorothiobenzamide	$C_{14}H_{12}ClNOS$	277.79	168—172	60.53	4.35	5.04
					60.72	4.22	5.13
XVIII	*N*-(*p*-Tolyl)-*p*-chlorothiobenzamide	$C_{14}H_{12}ClNS$	261.79	178—182	64.22	4.63	5.35
					64.12	4.81	5.53
XIX	*N*-(*p*-*Chlorophenyl*)-*p*-chlorothiobenzamide	$C_{13}H_{11}Cl_2NS$	282.21	208—209	55.32	3.93	4.96
					55.45	4.25	4.83
XX	*N*-(*m*-Chlorophenyl)-*p*-chlorothiobenzamide	$C_{13}H_{11}Cl_2NS$	282.21	137—142	55.32	3.93	4.96
					55.13	3.82	5.12

analysis was based on the use of the limiting current which was proportional to concentration in accordance with literature [26—28]. The rate constants were always calculated from two independent measurements by using the equation $\ln \{i_t\} = kt + q$, where i_t is the limiting current in the time moment t, k is the rate constant and q is a constant of experiment. The current was recorded with a polarograph E 7 (Laboratorní přístroje, Prague), the drop time was 2.9 s and the flow rate of mercury was 4.4 mg s^{-1}.

Microbiological tests

Antimycobacterial effectiveness of thioamides was determined by the diluting method, *i.e.* by determining the minimum inhibitory concentration necessary against pathogenic strain *Mycobacterium tuberculosis* $H_{37}R_v$ from the collection of the department of mycobacterial infection of the Research Institute of Preventive Medicine. Two liquid media were used, *i.e.* the semisynthetic protein substrate according to Šula and the synthetic substrate according to Sauton. The substances were added into substrates in a constant volume of solvent (DMSO 1 %). Their resulting concentrations in substrates were $c/(\text{mol dm}^{-3}) = 0.075$, 0.15, 0.30, 0.62, 1.25, 2.5, 5.0, 10, and 20×10^{-4}. The results of antimycobacterial effectiveness were valuated after 14 days' incubation performed at 37 °C.

Results and discussion

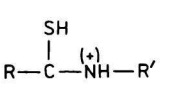
As for acid-catalyzed solvolyses, we frequently observed changes in reaction mechanism from addition (bimolecul) mechanism to elimination (monomolecular) mechanism due to the variation in the concentration of acid [29—35]. For this reason, the solvolysis of substances *V*, *IX*, and *XII* selected as model substances was investigated in a wide region of the concentration of sulfuric acid. The ascertained relationships between $\log \{k\}$ and H_0 are presented in Fig. 1. In comparison with esters [29], it appears that, even in solutions with the highest concentration of sulfuric acid, the E-1 mechanism could not be unambiguously proved. In agreement with literature, these experiments confirm the idea [12—14] that the slowest step of solvolysis is the addition of nucleophile HOY to the protonized form of thioamide (Scheme 2). It results from Fig. 1 that the reaction proceeds most rapidly in the region of H_0 near to -4.5 and moreover the reaction rate in this region changes only little with the concentration of acid. Therefore we used for other experiments $H_0 = -4.85$ in aqueous solution of ethanol (50 volume %) which is a medium where the reaction was adequately rapid with respect to polarographic method and the substances were sufficiently soluble. In this medium the rate constants of the reaction were measured at different temperatures. The results found at 68.5 °C and the activation parameters calculated from the temperature dependence of rate constants are summarized in Table 2. The determined entropies of activation correspond to the S_N2 mechanism of the investigated reaction in agreement with literature [35].

Table 2

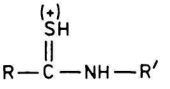
Rate constants and activation parameters of solvolysis of thioamides in 50 volume % ethanol at $H_0 = -4.85$ and $\theta = 68.5$ °C and their minimum inhibitory concentration at $\theta = 37$ °C

Substance	k $10^5/s^{-1}$	$\Delta H^{\neq}$/kJ mol^{-1}	$-\Delta S^{\neq}$/J mol^{-1} K^{-1}	c_{mi} 10^4/(mol dm^{-3})	
				Šula substrate	Sauton substrate
I	30.3	62	130	1.25	0.62
II	18.3	—	—	—	—
III	34.4	53	157	0.15	0.07
IV	1.82	6.03	300	5.0	1.25
V	4.62	96.7	43	5.0	1.25
VI	8.84	92.2	53	2.5	1.25
VII	11.9	102	21	2.5	1.25
VIII	9.04	95.3	40	—	—
IX	2.99	87.1	78	0.62	0.62
X	1.31	92.5	69	10	2.5
XI	1.07	88.8	81	10	5.0
XII	17.5	90.2	54	1.25	0.31
XIII	1.65	88.5	78	20	10
XIV	7.76	101	29	—	—
XVI	3.0	—	—	0.62	0.31
XVII	4.85	50.8	179	0.62	0.31
XVIII	7.75	30.0	244	0.62	0.15
XIX	20.1	49.6	175	0.31	0.15
XX	36.4	90.8	43	0.31	0.15

Furthermore, the reaction mechanism was corroborated by observing the influence of substitution on rate constant. The dependence of log $\{k\}$ (Table 2) on the σ constant in the Hammett equation [36] gave the value 1.5 for the ϱ constant of substances *IV*—*VII*, and the value $\varrho = 1.25$ for substances *XII*, *XVII*—*XX*. It is obvious that both constants are not too different, which means that the influence of the electron density on the thiocarbonyl carbon atom due to a substituent ought to be only little different in both cases. Thus we assume that formula *II* is more suited to protonized thioanilides than formula *III*



II



III

At last, the influence of substitution on the rate constant of solvolysis was investigated in the region of the Taft equation. The dependence of log $\{k\}$ of substances *X*—*XII* and *XVI* on the σ^* constants of the Taft equation [37] gave the value +1.0 for the ϱ^* constant. The positive value of this constant as well as the positive value of the constant in the Hammett equation confirms the S_N2 mechanism of the investigated reaction in the rate-determining step in conformity with literature [38].

All the methods used unambiguously have confirmed that the mechanism of solvolytic reaction suggested in literature [12—14] is valid under above conditions for the whole investigated group of substances and thus we may correlate the rate constants with the microbial activity the measure of which was the minimum inhibitory concentration found for action of these substances on *Mycobacterium tuberculosis*. The results of these tests are given in Table 2. They are near to literature data [39] provided these data are available. The correlation between the logarithms of numerical values of the rate constants and the logarithms of numerical values of the minimum inhibitory concentrations in the Sauton substrate is represented in Fig. 2. The position of the points corresponding to thioamides of pyridinecarboxylic acids has only orienting importance because the nitrogen atom in their pyridine ring is entirely protonized under the conditions of kinetic measurements whereas it is only to a minimum protonized under the conditions of microbial tests. It is evident from Fig. 2 that the correlation sought for gives two relations the first of which is inconspicuous and belongs to the thioamides nonsubstituted in the functional group (*IV*—*VII*), while the second one corresponds to the thioamides substituted in the functional group. The substitution in the functional group also changes the lipophile character of substance [40] and thus it is likely that the microbial activity is affected by lipophility. As for slightly active substances (*IX*—*XI*, *XIII*), the graphic dependence of microbial activity on rate constants is sharp. It seems that the microbial activity in this region is affected by

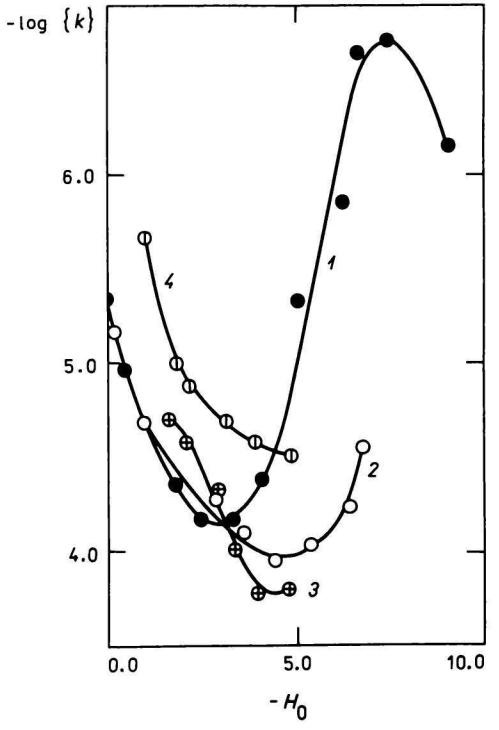


Fig. 1. Logarithm of numerical value of the rate constant of solvolysis of thioamides as a function of H_0 at 68.5 °C.
1. Thiobenzamide; *2.* thiobenzamide; *3.* *p*-chlorothiobenzamide; *4.* diphenylthiobenzamide. Substance *1* in water, substances *2*, *3*, and *4* in aqueous solution of ethanol ($\varrho = 50$ volume %).

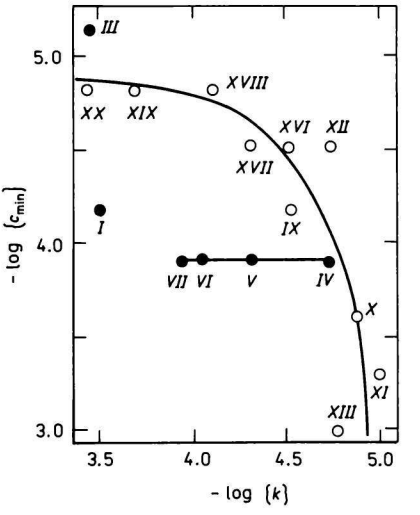


Fig. 2. Logarithm of numerical value of the minimum inhibitory concentration as a function of the logarithm of numerical value of the rate constant of the solvolytic reaction of thioamides in aqueous solution of ethanol ($\varrho = 50$ volume %) at 68.5 °C.

electron density in the functional group, *i.e.* mainly by chemical influence. As for highly active thioamides (*XVI—XX*), the microbial activity changes only little with rate constant. For this reason, we may assume that the microbial activity in this region is predominantly affected by nonchemical effects. It results from these facts that the microbially most active thioamides are to be found among lipophile thioamides substituted in such a manner that the rate of their acid-catalyzed solvolysis should be as much as the greatest.

References

1. Hantzch, A., *Ber. 64,* 661 (1931).
2. May, P., *J. Chem. Soc.* (London) *1913,* 2272.
3. Bacon, N., Boulton, A. J., Brownlee, R. T. C., Katritzky, R. A., and Tomson, R. D., *J. Chem. Soc.* (London) *1965,* 5230.
4. Sandström, J., *Acta Chem. Scand.* 18, 1059 (1964).
5. Shuvaev, A. T., Landyshev, A. V., Belousov, A. K., and Baida, G. S., *Izv. Akad. Nauk SSSR, Ser. Fiz.-Mat. Nauk 31,* 898 (1967).
6. Truler, M. R., *J. Chem. Soc.* (London) *1960,* 997.
7. Colleter, C. J. and Gadret, M., *Bull. Soc. Chim. Fr. 1967,* 3463.
8. Walter, W., Meyer, H. W., and Lehman, A., *Justus Liebigs Ann. Chem. 1974,* 765.
9. Hall, A. J. and Satchell, D. P. N., *J. Chem. Soc., Perkin Trans. II, 1974,* 1077.
10. Hall, A. J. and Satchell, D. P. N., *Chem. Ind.* (London) *1974,* 527.
11. Tissier, C. and Tissier, M., *Bull. Soc. Chim. Fr. 1972,* 2109.
12. Swift, E. H. and Buttler, E. A., *Anal. Chem. 28,* 146 (1956).
13. Butler, E. A., Peters, D. G., and Swift, E. H., *Anal. Chem. 30,* 1379 (1958).
14. Peeters, O. M. and de Ranter, C. J., *J. Chem. Soc., Perkin Trans. II, 1974,* 1832.
15. Fairfull, A. E. S., Lowe, J. L., and Peak, D. A., *J. Chem. Soc.* (London) *1952,* 742.
16. Gardner, T. S. and Lee, J., *J. Org. Chem. 19,* 753 (1954).
17. Kindler, K., *Justus Liebigs Ann. Chem. 431,* 204 (1923).
18. Gabriel, S. and Heyman, Ph., *Ber. Deut. Chem. Ges. 23,* 158 (1890).
19. Kindler, K., *Justus Liebigs Ann. Chem. 450,* 1 (1926).
20. Pappalardo, G., Tornetta, B., and Scapini, G., *Farmaco Ed. Sci. 21,* 740 (1966); *Chem. Abstr. 66,* 46363*m* (1967).
21. Bernthsen, A., *Justus Liebigs Ann. Chem. 192,* 1 (1878).
22. Kučerová T. and Mollin, J., *Chem. Zvesti 32,* 463 (1978).
23. Pravdić, N. and Hahn, V., *Croat. Chem. Acta 37,* 55 (1965).
24. Gillespie, R. J. and Peel, T. E., *Advan. Phys. Org. Chem. 9,* 1 (1971).
25. White, W. N., Vogelman, T., Morse, M., and White, H. S., *J. Org. Chem. 42,* 162 (1977).
26. Lund, H., *Collect. Czechoslov. Chem. Commun. 25,* 3313 (1960).
27. Kane, P. O., *Electroanal. Chem. 2,* 152 (1960).
28. Mollin, J. and Kučerová, T., *Acta Univ. Palacki. Olomuc., Fac. Rerum Natur. 57,* 37 (1978).
29. Yates, K. and McClelland, R. A., *J. Amer. Chem. Soc. 89,* 2686 (1967).
30. Vinnik, M. I., Medvetskaya, I. M., Andreeva, L. P., and Tiger, A. E., *Zh. Fiz. Khim. 41,* 252 (1967).
31. Vinnik, M. I. and Medvetskaya, I. M., *Zh. Fiz. Khim. 41,* 1775 (1967).
32. Medvetskaya, I. M. and Vinnik, M. I., *Zh. Fiz. Khim. 43,* 630 (1969).
33. Zakharini, N. A., Promyslov, V. M., Vinnik, M. I., and Yudin, L. G., *Zh. Fiz. Khim. 43,* 637 (1969).
34. Kučerová, T. and Mollin, J., *Collect. Czechoslov. Chem. Commun. 43,* 1571 (1978).
35. Schaleger, L. L. and Long, F. A., *Advan. Phys. Org. Chem. 1,* 1 (1963).
36. Jaffe, H. H., *Chem. Rev. 53,* 191 (1953).
37. Newman, M. S., *Steric Effects in Organic Chemistry.* (Russian translation.) P. 622. Izdatel'stvo inostrannoi literatury, Moscow, 1960.
38. Hammett, L. P., *Physical Organic Chemistry,* p. 188. McGraw-Hill, New York, 1940.
39. Waisser, K., Čeladník, M., Palát, K., and Odlerová, Ž., *Česk. Farm. 29,* 335 (1980).
40. Waisser, K., unpublished results.

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