Reports of the Academy of Sciences of the USSR

CHEMISTRY

1960

SovietRxiv

Abstract

Full Text

Reports of the Academy of Sciences of the USSR
1960. Volume 134, No. 3

CHEMISTRY

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ISOTOPIC EXCHANGE OF NITROGEN IN ACID AMIDES

In our previous communications ([1,2]), data were presented on a systematic study of nitrogen exchange between liquid ammonia and amino compounds as a function of the structure of the latter. It was found that such exchange is observed only in compounds in which the carbon atom bonded to the amino group acquires electrophilicity owing to the inductive effect of the groups attached to it and conjugation with them. The rate of exchange increases with increasing positive charge on this carbon atom. On the basis of these data, a mechanism of exchange was proposed, the essence of which is reduced to a nucleophilic attack by ammonia nitrogen on the carbonyl carbon, with transfer of a proton to the primary amino group and elimination of the latter. This exchange mechanism is consistent with the acceleration we found in the presence of NH_4Cl.

The same dependence of the rate of exchange on the electrophilicity of the carbonyl carbon was found for several acid amides studied at that time. It was also found by Haines and co-workers ([3]) in a paper published shortly after ours. In that work, the kinetics of exchange could be determined quantitatively only for *n*-nitrobenzamide in the presence of NH_4Cl, since the experiments, unlike ours, were carried out at low temperatures, where for most amides the exchange reached only a few percent of equilibrium in 3–7 days.

The study of the exchange of amino groups in acid amides is of special interest because of the similarity of this reaction to the reactions of hydrolysis of amides and ammonolysis of esters, whose mechanism was studied in a number of works ([4]), which, however, did not lead to final conclusions.

In the present communication, data are given on the influence of substituents and of the structure of the radical on the rate of exchange of amino groups in acid amides with ammonia, both without additives and in the presence of NH_4Cl as an acid catalyst.

The results of the kinetic measurements are presented in Table 1, where the mean values of the first-order rate constants and the half-exchange periods are

given. According to the rate of exchange, depending on the radical R, the amides $RCO \cdot NH_2$ form the series*:

$$CCl_3 > CHCl_2 > H > CH_2F > NH_2 > C_2H_5O > CH_3 \text{ and } X{-}C_6H_4.$$

In it the differences in rates are very large: from half-periods of 12 min at 25° for trichloroacetamide to 3.6–17 h at 180° for acetamide and benzamides, and absence of exchange in 20 h at 180° for *n*-methylbenzamide. Para substituents in benzamides have a considerably smaller effect, being arranged in the series:

$$NO_2 > OCH_3 > Br > H > Cl > CH_3.$$

In the meta position, the nitro group accelerates exchange more strongly than in the para position, while in the ortho position chlorine retards exchange more strongly than in the para position.

In the presence of NH_4^+, exchange is always accelerated, and with small rearrangements the same sequence of series is retained, but in substituted benzamides the influence of the substituents is expressed more weakly. For the para positions they form the series:

$$NO_2,\ Br > Cl > OCH_3 > H > CH_3.$$

* Data for $CCl_3CO \cdot NH_2$, NH_2CONH_2, $C_6H_5CONH_2$, and CH_3CONH_2 are taken from (2).

Table 1

Rate constants and half-periods of exchange in acid amides

Substance	Temp., °C	Moles of amine per 1 mole NH_3	k, h^{-1}	Half-period of exchange, h
Trichloroacetamide (2)	25	0.4–0.5	3.6	0.19
Same + NH_4Cl	25		complete in 2 min.	
o-Bromobenzamide + NH_4Cl	180	0.5	0.249	2.8
p-Chlorobenzamide	180		0.0418	16.6

Substance	Temp., °C	Moles of amine per 1 mole NH_3	k, h^{-1}	Half-period of exchange, h
Dichloroacetamide	22	0.6–0.7	0.493	1.41
Formamide	50	0.9–1.0	0.799	0.87
Fluoroacetamide	50	0.33	0.153	4.5
Acetamide (2)	180		0.13	5.3
Same + NH_4Cl	120	1.0	0.61	1.1
p-Nitrobenzamide	180		0.192	3.6
Same + NH_4Cl	180	0.2	1.51	0.46
m-Nitrobenzamide	180		0.118	5.9
Same + NH_4Cl	180	0.4	2.28	0.30
p-Bromobenzamide	180		0.096	7.3
Same + NH_4Cl	180	0.35	1.51	0.46
Same + NH_4Cl	180		1.25	0.55
o-Chlorobenzamide	180	0.5	0.0317	22
Same + NH_4Cl	180		0.285	2.4
p-Methoxybenzamide	180	0.5	0.151	4.6
Same + NH_4Cl	180		0.13	0.61
Benzamide	180		0.059	11.8
Same + NH_4Cl	180	0.9–1.0	0.94	0.74
Same + NH_4Cl	160		0.069	10.0
p-Methylbenzamide	180		no exchange	
Same + NH_4Cl	180	0.9–1.0	0.685	1.02

In the meta position the nitro group accelerates the exchange somewhat more strongly, whereas in the ortho position chlorine and bromine considerably retard the exchange.

Comparison of these data reveals that in the para and meta positions electron-donor radicals and substituents retard exchange, whereas acceptor substituents accelerate it, in agreement with the general accelerating action, for amino compounds, of a decrease in electron density on the carbon in the C–NH_2 bond.

The same influence of substituents is known for the rate of hydrolysis of esters [4,5], hydrolysis of amides* [7–9], and ammonolysis of esters [6]. The small effect of substituents in benzamide, compared with the effect of the nature of the radical, is explained by their remoteness from the reaction center. This permits the assumption that in para- and meta-substituted benzamides the inductive effect of substituents predominates over the conjugation effect. The anomalous position of the OCH_3 group and, in part, of chlorine should be attributed to the same cause: as is known, they act inductively as acceptors, and under conjugation as donors ($-J, +M$, in Ingold' s terminology). The predominant inductive action of the OCH_3 group during exchange, in contrast to amide hydrolysis, can be explained by the fact that, upon attack at the carbonyl carbon, the more basic nitrogen atom removes conjugation more strongly than the oxygen atom.

Fig. 1. Dependence of $\lg k$ in para-substituted benzamides on the inductive component σ_i of the Hammett equation.
1 –exchange in NH_3 (left ordinate);
2 –exchange in NH_3 + 1 N NH_4Cl

The predominant inductive influence of substituents during exchange in benzamides is confirmed by the fact that the Hammett equation $\lg k/k_0 = \rho\sigma$ is obeyed much better if one introduces into it not the total substituent constant –

* In the presence of sulfonic acid, introduction of a nitro group into the para position retards hydrolysis of benzamide [7].

substituents σ [10], but only its component σ_i, relating solely to the inductive effect [11] (Fig. 1). For this equation, for lack of other data, it was necessary to take the values of σ found for reactions at considerably lower temperatures than those at which the exchange rate was measured.

The retardation of exchange by ortho substituents is consistent with the well-known retardation, independent of their polarity, of hydrolysis by the acyl-oxygen mechanism, with the increase in the strength of benzoic acids and the decrease in the basicity of anilines; it has been explained by steric effects [4].

The presence of catalytic amounts ($0.1\,N$) of potassium amide does not affect the exchange rate in benzamide. This should be attributed to the fact that, owing to the reduced basicity of the amino group in the amide, the equilibrium
$NH_2^- + RCONH_2 = NH_3 + RCO \cdot NH^-$
is strongly shifted to the right, and the amide anion, because of the reduced electrophilicity of its carbonyl carbon, practically does not participate in the exchange.

Fig. 2. Dependence of the exchange rate in benzamide on the concentration of NH_4Cl at 150°

The regularities considered coincide completely with those indicated by Ingold [4] for the bimolecular hydrolysis of esters and amides by the $A_{Ac}2$ and $B_{Ac}2$

Fig. 2. Dependence of the exchange rate in benzamide on the concentration of NH_4Cl at 150°

Figure 1: Fig. 2. Dependence of the exchange rate in benzamide on the concentration of NH_4Cl at 150°

mechanisms. As applied to exchange in amides, they correspond to the equations:

$$N^{15}H_3 + R{-}C(=O){-}NH_2 \rightleftharpoons N^{15}\overset{+}{H}_3{-}C(\bar{O})(R){-}NH_2 \rightleftharpoons N^{15}H_2{-}C(=O)(R) + NH_3. \quad (1)$$

and in the presence of NH_4^+

$$N^{15}H_3 + R{-}C(=O){-}\overset{+}{N}H_3 \rightleftharpoons N^{15}\overset{+}{H}_3{-}C(\bar{O})(R){-}\overset{+}{N}H_3 \rightleftharpoons N^{15}H_3{-}C(=O)(R) + NH_3 \quad (2)$$

with formation of an intermediate complex or by a one-stage synchronous replacement of one amino group by another ([12]).

Mechanisms (1) and (2) are not the only possible ones. On energetic grounds some authors ([8,13]) suppose that in the acid conjugate with the amide the proton is attached to the carbonyl, $RC\overset{+}{O}HNH_2$, and not to the nitrogen $RCO \cdot \overset{+}{N}H_3$, or that both forms constitute an equilibrium system. Meloche and Laidler ([7]) propose the simultaneous participation of two attacking molecules: H_2O and OH^- in alkaline hydrolysis, or H_2O and H_3O^+ in acid hydrolysis. Syrkin and Moiseev ([14]) consider it probable that such an interaction of three particles occurs in a six-membered intermediate complex.

All these variants, however, correspond to the exchange regularities found and are a detailed elaboration of the mechanism proposed by us earlier ([2]) for nucleophilic substitution with proton transfer, which explains the features of amino-group exchange between various amino compounds and ammonia. These variants cannot be distinguished from one another without additional detailed kinetic and other physicochemical investigations.

The influence found for the concentration of NH_4Cl on the exchange rate in benzamide is presented in Fig. 2. Up to 4.5 N NH_4Cl the rate constant increases linearly, and with a further increase in acidity it decreases. A similar passage of the rate through a maximum at 3-5 N acid was found by Edward and Meacock ([8]) for the hydrolysis of benzamides in aqueous HCl and H_2SO_4, and by other authors ([4]). It is explained by the fact that at the maximum the whole amide is located

in the protonated form, so that a further increase in the acid concentration, without increasing the concentration of this form, decreases the activity of the solvent participating in the reaction.

We thank the members of our laboratory I. M. Protas, A. S. Knyazev, and T. N. Korbut for carrying out numerous isotopic analyses of nitrogen, and also G. I. Derkach for providing a number of amides.

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Received
13 VI 1960

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Note: Figure translations are in progress. See original paper for figures.