EFFECT OF ACIDITY AND SUBSTITUTION OF CARBOXYLIC ACIDS ON THE RATE AND EQUILIBRIUM OF ACIDOLYSIS OF N-BUTYLHEXANAMIDE IN NON-AQUEOUS MEDIUM

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The rate and equilibrium of transacylation of carboxylic acids with N-butylhexanamide were investigated in the absence of solvents by means of gas chromatography for equimolar mixtures at 200—260°C. The rate constants of acidolysis decrease with increasing acidity of the acids as follows: dodecanoic acid ≅ 2-phenylbutyric acid > 4-fluorobenzoic acid > 4-chlorobenzoic acid > 2,6-dichlorobenzoic acid. The equilibrium constants depend not only on the acidity of the acid but also on its structure and vary from 0·1 to 2·3.

The exchange of the acyl group between an amide and a carboxylic acid

$$R^1CONR^2R^3 + R^4COOH \underset{k'}{\overset{k}{\rightleftharpoons}} R^4CONR^2R^3 + R^1COOH \qquad (A)$$

(R^1, R^4 = alkyl, aryl; R^2, R^3 = H, alkyl; or R^1—R^2 = —$(CH_2)_m$—) may be classified as the transacylation of the amide or as its acidolytic cleavage. The reaction has predominantly been used for the synthesis of amides[1]. In the acidolysis of a cyclic amide (lactam) polymerization takes place giving rise to a linear polyamide

$$R^4COOH + n\,(CH_2)_m\begin{array}{l}CO\\|\\NR\end{array} \longrightarrow R^4CO[NR(CH_2)_mCO]_n—OH \qquad (B)$$

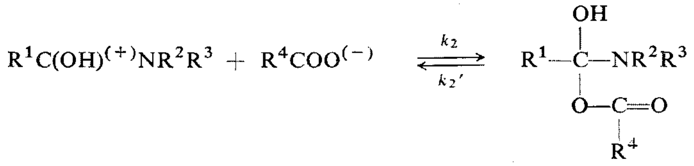
the degree of polymerization (n) is determined by the extent of reaction and by the concentration of the initiating acid[2–7]. Also on heating of a polymer containing carboxylic and amide groups the intra- and intermolecular transacylations can alter the polymer structure, molecular weight distribution, and in the case of copolyamides also the distribution of monomeric units.

In papers in which the transacylation mechanism of amides is mentioned the first step is seen in the activation of the amide group by protonation[2–5,8–10]. In earlier papers the protonation of nitrogen was assumed, because the latter is more basic than the carbonyl oxygen. More recent measurements and the reinterpretation of earlier data point out that the O-protonation is absolutely predominant in amide groups capable of resonance stabilization[11].

$$R^4COOH \underset{k_a'}{\overset{k_a}{\rightleftharpoons}} R^4COO^{(-)} + H^{(+)} \qquad (C)$$

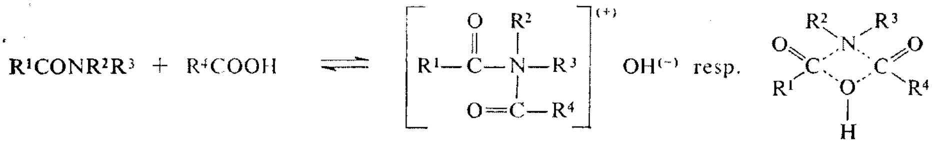
$$R^1CONR^2R^3 + H^{(+)} \underset{k_1'}{\overset{k_1}{\rightleftarrows}} R^1C(OH)^{(+)}NR^2R^3 \qquad (D)$$

Nucleophilic substitution[2-4] of the amide with the acid anion connected with a transitional formation of a tetraedric activated complex[8-10] is regarded as a further step:



(*E*)

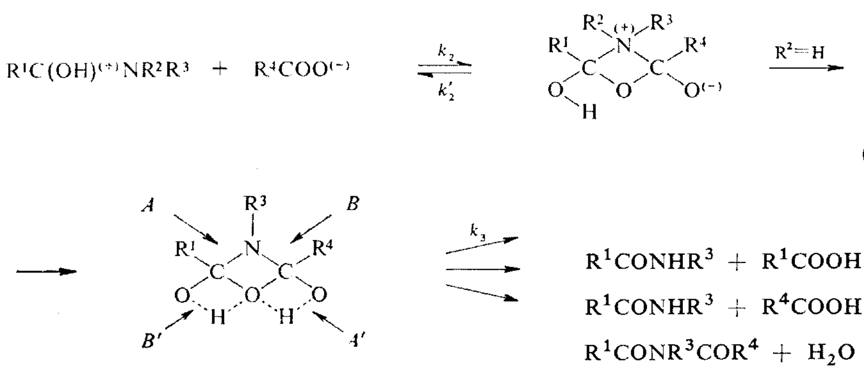
The occasional occurrence of diacyl amines in transacylation mixtures also led to the suggestion of a transition structure of the diacyl ammonium type[8]. The structure arises by a reaction of the amide nitrogen atom with the carbonyl carbon atom of an undissociated acid, that is, *via* a mechanism with exchanged donor–acceptor roles compared to the former case. Later on the scheme was modified to become a four-center transition state[12].



(*F*)

However, views concerning the decomposition of the activated complex (*E*) differ from each other. The suggested splitting-off of the amine with formation of anhydride which then acylates the amine[8] is less likely, because the presence of anhydride in such reaction has not been proved[10]. The view that the decomposition proceeds *via* a four-center transition state[9,10] directly to give final products given in (*A*) is more acceptable.

According to our hypothesis, the intermediate product could be a 1,3-oxazetidine ring arising *via* a coordinated, generally acid-base catalyzed mechanism:



(*G*)

Structures of the 1,3-oxazetidine type have been suggested for a number of reactions as activated complexes which cannot be isolated[13]. However, with suitable substitution they are stable[14]. In our case too it may be assumed that an abundant substitution with alkyl and hydroxyl groups supports formation of such a four-membered ring. Its decomposition to yield transacylation products can occur in the direction AA′ or to give the original amide and acid by cleavage in the direction BB′ or to give diacyl amine which is formed by the splitting-off of water in the direction B′A′. In the latter case, when water is formed in the system, one may also expect formation of hydrolytic products.

Although the acidolysis of amides plays an important role in the synthesis of amides and polyamides, the influence of pK_a and of the acid structure on the rate and equilibrium of transacylation of amides has not yet been examined. Neither could it be said that a detailed reaction mechanism of the acidolysis of amides had been confirmed. We therefore started this series of investigations by studying the kinetics and equilibria of reactions of N-substituted amide with acids of various acidity.

EXPERIMENTAL

Preparation and purification of N-butylhexanamide have been described earlier[15]. The acids used were purified by rectification *in vacuo* or crystallization, their purity was checked by GC. The reaction mixture was prepared from 0·5—2 g of compounds in an anhydrous medium under purified nitrogen. Using vacuum and nitrogen the mixture was transferred into glass ampoules

TABLE I

Rate and Equilibrium of Acidolysis of N-butylhexanamide

Acid	pK_a	T °C	K	k kg/mol h	
Dodecanoic	4·9	240	1·07	0·47	±0·02
		260	1·10	1·23	±0·03
2-Phenylbutyric	4·3[a]	200	2·28	0·047	±0·001
		240	2·16	0·49	±0·01
4-Fluorobenzoic	4·1	200	0·74[a]	0·031	±0·005
		220	0·82	0·095	
		240	0·96	0·30	±0·03
4-Chlorobenzoic	2·9	200	0·86[a]	0·033	±0·006
		220	0·92[a]	0·09[a]	
		240	0·92[a]	0·25[a]	
2,6-Dichlorobenzoic	1·8	200	0·15[a]	0·0062[a]	
		240	0·13[a]	0·078[a]	
		260	0·10[a]	0·27[a]	

[a] Approximate values.

which were predried at 150°/2 Torr for 15 h. The sealed ampoules (packed with 30—100 mg to 70—90% of their volume) were heated in a thermostat (±0·3°C) and cooled after the reaction. The transacylation mixture was analyzed directly or after diluting with tetrahydrofuran to c.10% solutions on a Perkin–Elmer F-11 gas chromatograph with a D-26 integrator; a flameionization detector, 1 m stainless column packed with 15% PEGA on 150—175 mesh Chromosorb W, T_c 175—180°C, T_i 230—250°C, N_2 stream 50 ml/min. Only in the case of transacylation with dodecanoic acid the results of the analyses of all four products were evaluated; for the other systems the determination of only one forming acid and the original amide were used. The content of acid groups in selected samples of the reaction products was determined by conductometric titration

RESULTS AND DISCUSSION

Main Products

The transacylation was carried out with an equimolar amount of amide and acid, without solvent. In all cases only two amides and two acids were found in the reaction mixture, in accord with (*A*). No traces of anhydride or imide were detected; no water was formed either.

Since the transacylation proceeds at a satisfactory rate only at temperatures above 200°C, it was difficult to find sufficiently stable carboxylic acids which would allow to follow the effects of acidity and steric effects. The aliphatic series offers only a limited choice of acids, since *e.g.* mono-, di-, and trichloroacetic acid or trifluoroacetic acid greatly decomposed under the above conditions. Partial decomposition was also observed with some of the chlorosubstituted benzoic acids used. During the relatively long heating of mixtures to high temperatures partial decarboxylation of 2,6-dichlorobenzoic acid cannot be ruled out, in agreement with the observed decrease in the concentration of carboxylic groups in the acidolyses of polyamides[16,17]. On the other hand, in the case of 4-chlorobenzoic acid the content of acid groups in the reaction products remained the same as in the starting mixture.

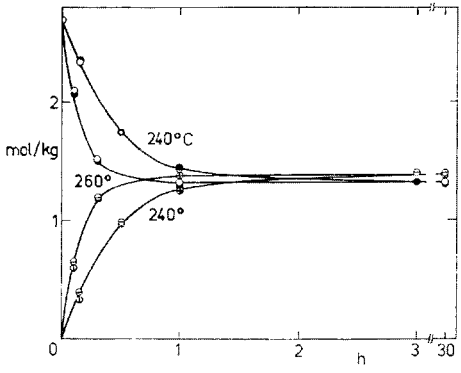


FIG. 1

Change in the Concentration of Components During the Acidolysis of N-butylhexanamide with Dodecanoic Acid

○ N-Butylhexanamide, ● dodecanoic acid, ⊖ hexanoic acid, ⊙ N-butyldodecanamide.

Equilibrium and Rate of Transacylation

The systems studied in this work and the data obtained are summarized in Table I. The process of establishment of the transacylation equilibria is shown in Figs 1–2.

The reaction of N-butylhexanamide with dodecanoic acid (Fig. 1) leads to an almost symmetrical equilibrium (equilibrium constant $K = k/k' = 1$). In this case R^1 of the acyl amide and R^4 of the acid are long n-alkyl groups, so that the reactivities of both acids are almost identical.

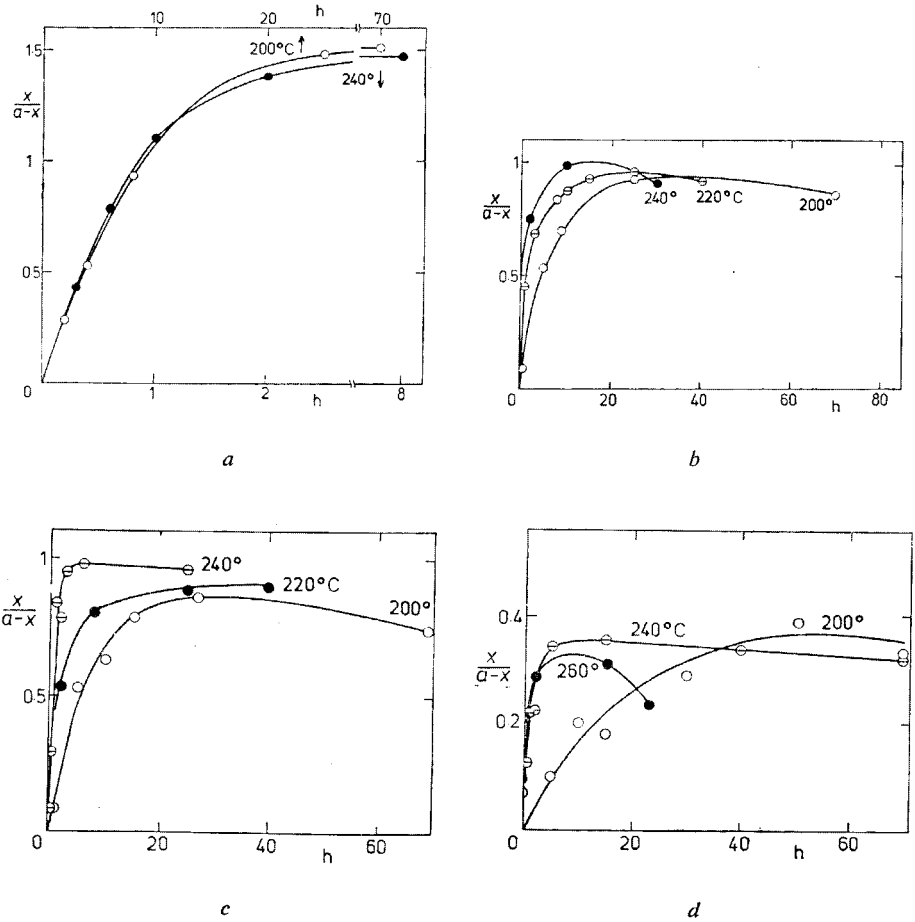


FIG. 2

Formation of Hexanoic Acid in the Acidolysis of N-butylhexanamide with Following Acids: 2-Phenylbutyric (*a*), 4-Chlorobenzoic (*b*), 4-Fluorobenzoic (*c*) and 2,6-Dichlorobenzoic (*d*)

Concentration of components (mol/kg): x hexanoic acid, $(a - x)$ N-butylhexanamide and also acidolyzing acid.

For thermally less stable systems (Figs 2*b*,*d*) the constants were calculated not from the equilibrium data, but from the maxima of conversions. In such cases the rate constants also somewhat depend on the extent of the reaction. As a result, both the equilibrium and rate constants thus calculated can be regarded only as approximative.

The dissociation of the acid, protonation of the amide and probably also the decomposition of the intermediate are very fast, so that the controlling process of the above sequence of consecutive reactions is bimolecular nucleophilic substitution ($k_2 \ll k_d, k_1, k_3$ from (*C*) to (*G*)). Consequently, the experimental rate constants determined in this work are only apparent ones, because they involve also contribution of all the other reactions, $k = (K_d K_1 K_3)\, k_2$, and also because they are based only on concentration (mol per kg of the mixture) and not on the activities.

The rate of transacylation with aromatic acids somewhat decreases with an increase in their acidity, which may be explained by the fact that the effect of increasing acidity of the acid (increase in K_d) is overcompensated with the decreasing nucleophilicity of its anion (decrease in k_2). The larger decrease in the reactivity of 2,6-dichlorobenzoic acid can be assigned both to the effect of acidity and to the steric hindrance of the carboxylate group.

Substitution of the acylating acid with a phenyl group in position 2 considerably raises the value of the equilibrium constant K without affecting the rate constant. This means that in the case of the reverse reaction the 2-phenyl substitution of the acyl amide slows down the transacylation with an unsubstituted acid. A strong influence of the substitution of acyl amide on the rate of transacylation has also been described for aromatic amides[12]. Hence it follows that in the formation of the primary tetraedric transition structure a bulky substituent at the acyl group of the amide is a larger obstacle than the same substituent at the same position in the acylating acid. Therefore the rate determining SN_2 attack is more likely to proceed according to the mechanism (*E*) than (*F*).

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