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Tertiary Amines in Acyl Transfer Reactions

E.M.Cherkasova, S.V.Bogatkov, and Z.P.Golovina

The mechanism and kinetics of acyl transfer reactions in the presence of tertiary amines are examined and the quantitative relations between the rate of reaction and the structure of the acylating agent, the acylated substrate, the amine, and the solvent, temperature, and the ratio of the efficiencies of intramolecular and intermolecular catalysis are discussed. A number of examples of the application of tertiary amines as accelerators of acyl transfer reactions, which are of practical importance, are presented.
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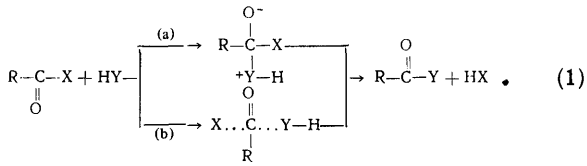
I. INTRODUCTION

The accelerating influence of tertiary amines (TA) on acyl transfer reactions has been known since the end of the past century, but fundamental studies have been made only in the last decades. In this review, an attempt is made to give a systematic and critical account of these data (using studies published up to 1975) mainly from the standpoint of the reaction mechanism and quantitative allowance for the influence of the structure of the reactants on the reaction rate. The problems of the structure of the products and the synthetic aspects are only briefly discussed, since a relevant review has been published recently [1].

II. THE REACTION MECHANISM. GENERAL KINETIC RELATIONS

1. General Consideration of the Mechanism. Type of Catalysis

Acyl transfer reactions can be described by mechanism (1), which has two main versions—the two-stage reaction (1a) with formation of a tetrahedral intermediate (TI) or the single-stage reaction (1b)†, the transition state of which resembles that of an S_N2 reaction:

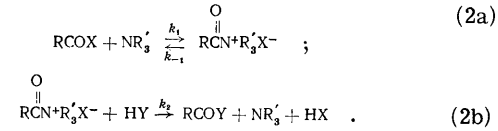


(1)

The compounds RCOX in this reaction are usually acid halides (X = F, Cl, Br, or I), anhydrides (X = OCOR), esters (X = OR′), and more rarely acids (X = OH), amides (X = NH_2 or NHR′), etc.; the nucleophiles HY are water, alcohols, phenols, and amines.

†A unimolecular mechanism with formation of the cations RCO^+ is fairly rarely encountered and is not considered in this review.

The hypothesis of the nucleophilic catalysis‡ of acyl transfer reactions by tertiary amines [mechanisms (2a) and (2b)] was first put forward at the beginning of the 1950s [2-5]:



(2a)

(2b)

Koshland [2] used it to account for the acceleration of the hydrolysis of acetyl phosphate after the addition of pyridine; he regarded the isolation of solid acetyl-pyridinium chloride as evidence demonstrating the proposed mechanism. However, a direct comparison of the rates of formation and decomposition of the chloride with the overall reaction rate was not made and only the half-reaction times were compared. The same mechanism was proposed [3-5] for the hydrolysis of acetic anhydride (AA) on the basis of the significant influence of steric hindrance in the amine on the reaction rate. This influence was observed also in many other instances (see Section III) and the breakdown of the Brønsted and Hammett–Taft relations was observed when amines with variable steric characteristics were used, which was usually regarded by the authors as evidence for the nucleophilic nature of the catalysis. However, this conclusion cannot be regarded as fully rigorous, since the equilibrium in the formation of a hydrogen bond has been shown recently [6-8] to depend also on the steric structure of the amine, which can therefore influence the rate of reaction also in general base catalysis.

‡We employ the term "catalysis", although in certain cases tertiary amines are removed from the reaction as a result of their interaction with the products HX and this term does not therefore correspond to the strict definition of the concept of the "catalyst". However, the identity of the mechanism and characteristics of these reactions with those of others where tertiary amines are not removed from the reaction sphere justify the use of all cases of the single term "catalysis", the interaction of tertiary amines with HX being regarded as stoichiometric poisoning of the catalyst.

On the other hand, during the last 15 years new facts have been obtained, which can be regarded as evidence in support of nucleophilic catalysis.

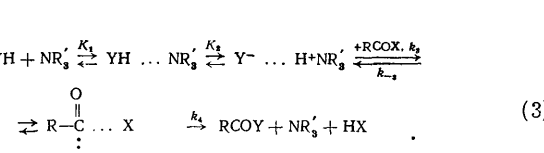
1. The formation in the esterification of racemic alcohols RR'CHOH in the presence of optically active tertiary amines of esters having a single preferred configuration, *S* or *R*, depending on the alcohol and the amine[9]. This is apparently due to the preferential existence of the acylammonium salt (AAS) and the tetrahedral intermediate arising when it interacts with the alcohol in the least hindered conformation. Similar results were obtained for the reaction of phenylmethyl keten with alcohols in the presence of optically active tertiary amines[10].

2. Anomalies in the temperature variation involving either a very slight increase of k_{cat} or even its decrease as the temperature rises, i.e. the apparent activation energy is $E_{act}^{app} \leqslant 0$.[11-13] This is satisfactorily consistent with the hypothesis of the reversible formation of an acylammonium salt, which is highly exothermic in the case of reactive amines. Since $E_{act}^{app} = \Delta H + E_2$ for mechanism (2a, b), where E_2 is the activation energy for the second stage (2b), it follows that, when $\Delta H \ll 0$, E_{act}^{app} can also become less than zero. The increase of steric hindrance and decrease of the resonance stabilisation of the acylammonium salt hinder its formation, which leads to a general retardation of the reaction and to an increase of E_{act}^{app}. In general base catalysis, the reversible formation of a hydrogen bond is weakly exothermic and $E_{act}^{app} \leqslant 0$ is unlikely.

3. Kinetic relations: the hydrolysis of acetic anhydride is faster by several orders of magnitude in the presence of pyridine than in the presence of CH_3COO^-, despite their approximately equal basicities, which indicates different reaction mechanisms[3,4,14].

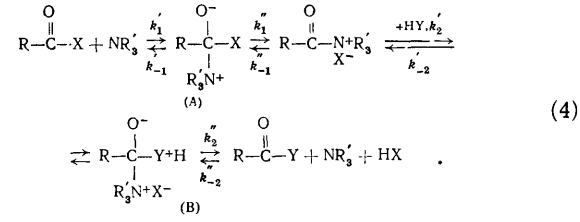
The most detailed and convincing evidence for a nucleophilic mechanism of catalysis by tertiary amines in aqueous solutions was obtained by Fersht and Jencks[14,15], who confirmed experimentally the possibility of the accumulation of analytically measurable concentrations of the acetylpyridinium ion (API), which had been predicted beforehand from an estimate of the free energy of its hydrolysis[16]. In water, which stabilises polar acylammonium salts, it was possible to detect the spectrum of the acetylpyridinium ion (λ_{max} = 225 and 272 nm, $\epsilon \simeq$ 7000 and 4400) by the stopped flow method and also by employing the retardation of the hydrolysis of the acetylpyridinium ion by three orders of magnitude compared with its formaton in 9 M $NaClO_4$ solution; the two spectra proved to be identical[14]. It was also found that the rate of hydrolysis of the acetylpyridinium ion synthesised by the method of Sheinkman et al.[17] is equal to the rate measured by the stopped flow method in the direct interaction of acetic anhydride with pyridine in water. This implies that in this reaction (and probably in many analogous reactions) pyridine and other tertiary amines behave as nucleophilic catalysts.

On the other hand, a number of workers noted also the possibility of the operation of general base catalysis via the following mechanism:



(3)

This version will be examined in greater detail in Section III, but, as regards the problem as a whole, one must emphasise that the possibility of nucleophilic catalysi is determined primarily by the comparative basicity (in the general sense—nucleophilicity) of the leaving group and the attacking nucleophile. If the reaction is formulated in the general form (4), taking into account the intermediate tetrahedral intermediates (A) and (B), one may note that the dominant mode of their decomposition involves the elimination of the less basic ("easily removed") group[18]



(4)

Thus, when the leaving group X in RCOX is less basic than the tertiary amine, i.e. $pK_a^{HX} < pK_a^{HN^+R'_3}$, then (A) is converted preferentially into the acylammonium salt. As a result of this, nucleophilic catalysis is of decisive importance in the reactions of acyl derivatives with easily removed groups[19,20] and its efficiency decreases in the sequence of the following groups X: I > Br > Cl > F > RCOO. The specific situation depends on solvent; for example, the hydrolysis of acid fluorides and anhydrides in water is catalysed by tertiary amines[3,5,14,21,22] and the aminolysis of benzoyl fluoride[23] and of the majority of anhydrides in benzene is inhibited by tertiary amines[24,25]. In this medium, F^- and $RCOO^-$ are probably stronger bases than NR'_3, which prevents the conversion of (A) into an acylammonium salt. However, for anhydrides of stronger acids, tertiary amines do exhibit catalytic properties[25,26]. Similarly, in the acylation of phenols in CCl_4 by acetyltrifluoroacetate in the presence of pyridine and its analogues, the rate of acetylation does not change, while the rate of trifluoroacetylation increases sharply and the latter process becomes of decisive importance[27,28].

On the other hand, the probability of general base catalysis increases in the reactions of substrates with groups which are difficult to remove[15,19,29] and which are more basic than the tertiary amine. For example k_{cat}/k_0 for aminolysis in the presence of carboxylic acids[30,31] or 2-hydroxypyridine[32] increases in the following sequence of groups X in ArCOX: Br < Cl < F < OAr.

On the other hand[33], the tetrahedral intermediates (B) will decompose preferentially with formation of the final products if the attacking nucleophile is a weaker acid than the ammonium ion, i.e. $pK_a^{HY} > pK_a^{HN^+R'_3}$. The validity of this condition also depends on the solvent in the general case. For example, in water carboxylic acids do not undergo acylation catalysed by tertiary amines (even in an undissociated form). However, in certain non-aqueous media we may have $pK_a^{RCOOH} > pK_a^{HN^+R'_3}$ and reaction (5),[34] leading to the formation of anhydrides and used for a long time as a method for their synthesis[35], becomes possible:

$$RCOOH + RCO^+NR'_3Cl^- \rightarrow (RCO)_2O + R'_3N \cdot HCl \quad . \qquad (5)$$

Anhydrides do not react further under these conditions. In the acylation of phenols, the situation where $pK_a^{ArOH} < pK_a^{HN^+R'_3}$ is also possible as a function of the solvent; here $k'_{-2} \gg k''_2$ and nucleophilic catalysis does not occur, although general base catalysis via mechanism (3) is possible[27,33,36-39].

When HY = H_2O, ROH, or RNH_2, the condition $pK_a^{HY} > pK_a^{HN^+R'_3}$ holds always and nucleophilic catalysis of the acylation of these compounds is possible and probably takes place in water and other polar solvents. On the other hand, one should note that, in aprotic solvents with low dielectric constants, the formation of products with a considerable separation of the charges and their intense localisation is energetically unfavourable and such products (to which acylammonium salts and tetrahedral intermediates belong) are characterised by a high energy level. This can lead to their approach to the corresponding transition states and, in the limit, to the occurrence of the reaction via a synchronous mechanism [40].

2. The Ratio of the Rates of Individual Stages. Kinetic Relations

In those cases where tertiary amines behave as nucleophilic catalysts of acyl migration, the reaction is usually irreversible under the experimental conditions ($k''_{-2} = 0$) and is described by mechanism (2) if the stage involving the formation of a tetrahedral intermediate is omitted. The problem arises of the ratio of the rates of the stages of this reaction. It has been found [2-5] that the process proceeds via a pseudostationary mechanism (the acylammonium salt does not accumulate)§ and, in the presence of an excess of the nucleophile, the kinetic equation is

$$v = (k_0 + k_{cat}[B]) \cdot [RCOX],$$

where [B] is the concentration of the base form of the amine and k_0 and k_{cat} are the rate constants for the spontaneous reaction and the reaction catalysed by the tertiary amine respectively; here k_0 is negligibly small compared with $k_{cat}[B]$. The following equation then holds in a medium ensuring the complete dissociation of the acylammonium salt into ions:

$$k_{cat} = \frac{k_1 k_2 [HY]}{k_{-1}[X^-] + k_2 [HY]}$$

{the notation is the same as in mechanism (2), $k'_2 = k_2[H_2O]$ being used for hydrolysis in water}.

The ratio of the rates then depends on the concentrations of HY and the anion X and on their nucleophilic properties characterised by the constants k_{-1} and k_2: in water the slowest stage is usually the formation of the acylammonium salt ($v_2 > v_{-1}$, $k_{cat} = k_1$). [2-5] By comparing the influence of pyridine on the hydrolysis of acetic anhydride in water and on the isotope exchange in its reaction with $CH_3^{14}COO^-$ (0.5–1 M), $k_{-1}/k'_2 \simeq 50$ litre mol^{-1} was estimated [21]. A similar value (~80 litre mol^{-1}) was found for the hydrolysis of acetyl fluoride in water in the presence of pyridine [22]; here $k_1 = 15$ litre mol^{-1} s^{-1}. It follows from these data that the acylammonium salt is in equilibrium with the initial substance [21,42]. The equilibrium is displaced to the left after the addition of dioxan [42,43], probably as a result of the decrease of polarity; when $[H_2O] < 4$ M, pyridine proved to be a weaker nucleophile than the acetate ion [42]. For the acetylpyridinium ion in water¶, $k_1 = 84$ litre mol^{-1} s^{-1}, $k_{-1} = 910$ litre mol^{-1} s^{-1}, and $k'_2 = 6.9$ s^{-1}, so that $k_{-1}/k'_2 = 130$ litre mol^{-1}. [14] Thus the reactivity of the acetylpyridinium ion in relation to the acetate ion is almost 4 orders of magnitude greater than in relation to water, assuming that $[H_2O] = 55$ M, $k_2 = k'_2/[H_2O] = 0.125$ litre mol^{-1} s^{-1}, and $k_{-1}/k_2 = 7.3 \times 10^3$. Therefore, when the concentration of CH_3COO^- (and in general of the ion X^-) is sufficiently high, we have $k_{-1}[X^-] > k_2[HY]$ and

$$k_{cat} = \frac{k_1 k_2}{k_{-1}[X^-]},$$

which has been observed, for example, in acetate buffers [5,42-44]. On the other hand, when the concentration of X^- is extremely low, then, although $k_{-1} > k_2$, $v_{-1} = k_{-1}[X^-][AAS]$ may be smaller than $v_2 = k_2[HY][AAS]$ {in water $k'_2[AAS]$}. Indeed the rate of hydrolysis of acetic anhydride in water in the presence of pyridine is equal to the rate of acylation of anisidine and toluidine under these conditions ($k = 84 \pm 2$ litre mole^{-1} s^{-1}) and is independent of the concentration of the acylated amines [14]. Consequently, under the given conditions, the lowest rate is observed for the stage involving the formation of the acetylpyridinium ion, for example we have $v_{-1}/v_2 \simeq 0.1$ and $k_{cat} = k_1$ when $[CH_3COO^-] \leq 10^{-3}$ M.

Since the lyonium ion H_3O^+ is the strongest acid in water, other species HY are stronger bases than water and are characterised by higher values of k_2. *p*-Toluidine and *p*-anisidine therefore react with the acetylpyridinium ion faster than CH_3COO^- even at a concentration of 0.001 M.

On the other hand, in solvents of low polarity (benzene, dioxan, etc.) the reaction is usually of first order with respect to the acylated nucleophile over a wide range of its concentrations (see Section III, subsections 2 and 3). Within the framework of mechanism (2), this implies that the second stage determines the rate of reaction. This is probably associated with the absence of the dissociation of the AAs ion pair and hence the absence of the free X^- ion in such solvents. The decomposition of the acylammonium salt into the initial components can then be regarded as a unimolecular process [33] and the expression for the rate of reaction becomes

$$v = \frac{k_1 k_2 [RCOX] \cdot [NR'_3] \cdot [HY]}{k_{-1} + k_2 [HY]}.$$

The transition to a unimolecular reaction leads to a considerable gain of activation entropy, as a result of which the process becomes faster and $k_{-1} \gg k_2[HY]$. Then

$$v = \frac{k_1 k_2}{k_{-1}} [RCOX] \cdot [NR'_3] \cdot [HY],$$

which has been observed experimentally. Under these conditions, k_2 may be greater than k_{-1} but $v_2 < v_{-1}$ owing to the very low concentration of the acylammonium salt. In the limit, this version of the reaction can be converted into a synchronous process when the involvement of all the reactants in the transition state is responsible for the first order with respect to each.

An intermediate case has been described recently [41,45] involving a decrease of k_{cat} during the acylation of *p*-anisidine and *p*-chloroaniline by sulphonyl bromides in nitrobenzene in the presence of pyridine (or its *N*-oxide), which the authors explained by the occurrence under these conditions of the equilibrium

$$[ArSO_2N^+C_5H_5Br^-] \rightleftarrows ArSO_2NC_5H_5^+ + Br^-.$$

The accumulation of the Br^- ions displaced this equilibrium towards the less reactive ion pair, which decreases k_{cat}: the above relation disappears when the experiments

§ This conclusion has been confirmed [41] by the equality of the rates of consumption of the acylating and acylated components: the pre-stationary stage, involving the accumulation of the acylammonium salt, was observed only when the stopped flow method was used [14].

¶ The values for substituted pyridines are listed in Table 2.

are performed in tbe presence of an excess of added bromide[45]. Unfortunately, the authors were unable to calculate the equilibrium constant and the rate constants for the individual forms of the acylammonium salt.

On the other hand, for various stable acylammonium salts, such as acetylimidazolium halides, the relation $k_1 \gg k_2 \gg k_{-1}$ may hold even in non-polar solvents. The second stage is then slowest, but the acylammonium salt accumulates rapidly and irreversibly[46].

3. The Structure of the Intermediates

According to the data described above and also results obtained independently by conductimetric[47-49], potentiometric[50], infrared spectroscopic[17,51-66], NMR[57,58], and ultraviolet spectroscopic[14,59,60] measurements (see also Sheinkman et al.[1]), one can assume that acylammonium salts of the type $RCON^+R'_3X^-$ are the main intermediates in many acyl transfer reactions catalysed by tertiary amines†. On the other hand, by analogy with other acyl transfer reactions[65-71], one may assume that the reactions involving the formation and decomposition of acylammonium salts proceed via the tetrahedral intermediates (A) and (B) in Eqn.(4). However, these tetrahedral intermediates are probably fairly unstable, particularly in non-polar solvents, and a shallow minimum corresponds to them on the energy diagram, i.e. the transition states in the stages involving the formation and decomposition of the tetrahedral intermediate are similar to the intermediates themselves as regards energy and structure and in this sense the reaction is close to direct substitution of the S_N2 type[15,40]. One must emphasise that, according to some data[67,69-72], proton transfer in (B) is an important stage, since it is the only process which ensures the strengthening of the C–Y bond, i.e. the conversion of the readily removed group (a weak base) HY into a strongly basic group Y. This process is also particularly important in aprotic solvents, where it can occur spontaneously, and requires the cooperation of the base molecule[71]—in this sense one may speak of a combination of base and nucleophilic catalysis.

Table 1. Hydrolysis of the acid chlorides RCOCl in aqueous acetone (10.9 vol.% of water) in the presence of tertiary amines[87].

R	Temp., °C	10^4k_0, s^{-1}	10^4k_{cat}, s^{-1}			
			$(CH_3)_3N$	$(C_2H_5)_3N$	pyridine	2,4,6-trimethylpyridine
CH_3	−40	0.975	35 000	7000	$>10^5$	39
$(CH_3)_3C$	−40	0.027	770	1.2	6600	5.8
C_6H_5	−40	0.0047	$>10^5$	35 000	$>10^5$	30
$2,4,6\text{-}(CH_3)_3C_6H_2$	−40	1.22	1.2	1.2	1.79	1.1
$2,4,6\text{-}(CH_3)_3\text{-}3,5\text{-}(NO_2)_2C_6$	+20	0.056	2.5	7	93	0.17

Apart from tetrahedral intermediates, the formation of charge-transfer complexes has been demonstrated in a number of studies[53,73-82] in the first stage of the interaction of acylating agents with tertiary amines. It has come to be assumed that charge-transfer complexes can be converted into acylammonium salts (via a tetrahedral intermediate or via direct S_N2 substitution)[75-78], but one-electron transfer with formation of the acyl radical-ions $RCO^\cdot$ and amine radical-ions is more characteristic of these species. As a result of this, acid chloride–tertiary amine and acid anhydride—tertiary amine systems are capable (particularly for aromatic tertiary amines) of initiating effectively radical polymerisation[73,74,80-82].

On the whole, one should note that data for the structures and properties of acylammonium salts are still extremely incomplete, mainly because of their instability. However, stable polymeric acylammonium salts, obtained in the acylation of polyvinylpyridine partly alkylated by bulky groups, have been described recently[83]. The hydrophobic environment of the quaternary nitrogen atom probably prevents further reaction of these acylammonium salts. However, their properties were not investigated in detail.

III. THE INFLUENCE OF REACTANT STRUCTURE ON THE REACTION RATE

1. The Hydrolysis of the Halides and Anhydrides of Carboxylic and Sulphonic Acids

The hydrolysis of acid halides and anhydrides has been one of the first acyl transfer reactions in the presence of tertiary amines which were investigated in detail as regards kinetics, mechanism, and structural relations. A study has been made of the accelerating influence of pyridine on the hydrolysis of acetic anhydride[3,4,84-86] and acetyl phosphate[2]. It has been found that 2-methyl- and 2,6-dimethylpyridines and also quinoline accelerate the process less effectively than 3- and 4-substituted pyridines and isoquinoline, probably owing to steric hindrance. The Bronsted equation holds separately for unhindered and hindered amines with the same proportionality coefficients β (0.92) but different constant terms (10.36 and 9.42 respectively). According to Koskikallio[42], triethylamine is only 7 times more reactive in this reaction than pyridine despite a difference in pK_a of almost 6 units (apparently also mainly owing to steric hindrance).

The role of the steric accessibility of the tertiary amine is clearly seen from the data in Table 1, particularly for the chlorides of hindered acids of the type of trimethylacetic acid[87]. Mesitoyl chloride is apparently hydrolysed via an S_N1 mechanism and catalysis by tertiary amines is not observed.

If the steric factor in the reaction investigated is constant, it is possible to observe the validity of the Brønsted and Hammett–Taft equations. The influence of the structure of the tertiary amines on the elementary stages of the hydrolysis of acetic anhydride has been examined[14]. It is seen from the results (see Table 2) that both the rate constants (k_1) and the equilibrium constants (K_{eq}) for the formation of the acetylpyridinium ion vary linearly with the basicity of the tertiary amine and $\beta = 0.87$ and 1.6 respectively. Thus the nucleophilic properties of substituted pyridines in relation to the carbonyl carbon atom vary in parallel with their basicity, the equilibrium nucleophilic properties being much more sensitive to the influence of the substituents than the basicity.

According to Fersht and Jencks[14], this indicates a greater "effective electronegativity" of the acyl group compared with the proton. On the curve relating the

†Other types of reactions of acylammonium salts have also been examined[1,61-64].

reactivity to structure for reactions of nucleophiles with the carbonyl group, pyridines are located close to a breakpoint[15,88,89]. As a result, while still retaining virtually the maximum dependence of their reactivity on basicity, they form highly reactive and selectively acylating agents (for example $k_{AcO^-}/k_{H_2O} = 7300$ for the acetylpyridinium ion, while the corresponding ratio for the acetylimidazolium ion is 29).[43]

Table 2. The interaction of acetic anhydride with tertiary amines in water (25°C, $I = 1$).[14]

Amine	pK_a	k_1, litre mole^{-1} s^{-1}	k_{-1}, litre mole^{-1} s^{-1}	K_{eq}	k_2, s^{-1}
C_5H_5N	5.51	84	910	0.092	6.9
4-$CH_3C_5H_4N$	6.33	490	262	1.86	2.3
3,4-$(CH_3)_2C_5H_3N$	6.79	1160	120	9.67	1.5
4-$CH_3OC_5H_4N$	6.82	935	30	31.2	0.4

The rate of reaction of the acetylpyridinium ion with water decreases with increase of the basicity of the initial tertiary amine and $\beta = -0.5$, i.e. water is relatively unselective in relation to these electrophiles. The possibility of direct polar coupling of the substituent with the reaction centre has been demonstrated for the acetyl-4-methoxypyridinium ion[14] and acetyl-4-dialkylaminopyridinium ions[60]; this has also been confirmed by the correlation of lg k_2 and lg k_1 with σ^+. Here $\beta = -0.8$ and the sensitivity of the reaction to the basicity of the leaving group therefore increases with decrease of the reactivity of the electrophile[60]. On the other hand, in the hydrolysis of 3- and 2,3-substituted acetylimidazolium ions, which also exhibit an enhanced resistance to nucleophilic attack (the additional stabilisation corresponds to approximately 2.7 kcal mole^{-1})[14], we have $\beta = 0.55$. Thus the relation between reactivity and sensitivity to the influence of the structure of the reactants on the rates of these reactions is on the whole fairly complex.

The only reaction for which the influence of the simultaneous changes in the structures of the catalyst and the acylating agent on the rate has been investigated is the hydrolysis of arenesulphonyl chlorides in the presence of substituted pyridines (RPy).[90,91] It was found that the correlation with σ^0 for R (sensitivity coefficient $\rho = -2.68$) and the Brønsted equation ($\beta = 0.45$) hold for the hydrolysis of $C_6H_5SO_2Cl$; the 4-acetyl and 4-cyano-derivatives deviate from this relation, possibly owing to the direct resonance interaction of the substituents with the reaction centre. Analogous correlations have been obtained for different R'$C_6H_4SO_2Cl$ (Table 3), where the coefficients β vary linearly with σ for R' (the slope is 0.122 ± 0.002). The values of ρ, characterising the influence of R' (they have been calculated for R' = H, *p*-CH_3, or *p*-CH_3O; the *para*- and *meta*-nitro-derivatives deviate towards reduced reactivities) increase linearly in their turn with increase of pK_a for the amine (proportionality coefficient 0.114 ± 0.004). Thus, contrary to Hammond's postulate, in this series of reactions an increase of the reactivity of the reactants is accompanied by an increase of the coefficients β and ρ.

Treating these quantities as characteristics of the degree of dissociation and formation of the bond in the transition state‡, the author suggested that, by virtue of its greater polarisability, sulphur forms bonds over greater distances than does carbon and that electron-accepting substituents in the acid chloride and electron-donating substituents in the amine catalyst promote the formation of bonds between them. The transition state thus becomes more "dense", i.e. the sum of the orders of the formed and ruptured bonds increases. On the other hand, electron-donating substituents in the acid chloride facilitate the preferential rupture of the bond, which is faster than the formation of the new bond.

Table 3. The influence of the structure of the sulphonyl chloride R'$C_6H_4SO_2Cl$ and the catalyst RPy on the rate of hydrolysis (water; 0.05 M NaCl solution; 25°C).[91]

R	pK_a	ρ (with respect to R')	R'	σ	β (with respect to RPY)
3,4-$(CH_3)_2$	6.46	0.89	*p*-NO_2	0.78	0.557
4-CH_3	6.02	0.82	*m*-NO_2	0.71	0.545
3-CH_3	5.68	0.78	H	0	0.457
H	5.21	0.69	*p*-CH_3	−0.17	0.441
3-CH_3CO	3.18	0.52	*p*-CH_3O	−0.45	0.406
4-CN	1.90	0.34			
3-CN	1.39	0.30			

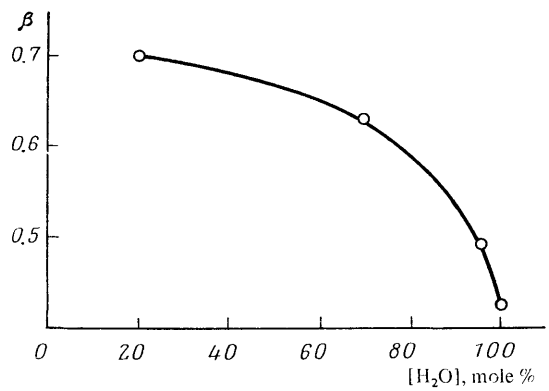


Figure 1. Variation of the Brønsted coefficient β with the water content in acetonitrile in the hydrolysis of benzenesulphonyl chloride in the presence of pyridine[92].

However, we believe that the direct correlation of the coefficients β with the orders of the formed and ruptured bonds is not always valid. For example, according to data[92] for the hydrolysis of benzenesulphonyl chloride in the presence of pyridine and 4-methylpyridine, β increases from 0.43 to 0.70 when the mole fraction of water in the mixture with acetonitrile is reduced from 1 to 0.2, while in 45% aqueous dioxan solution $\beta = 0.79$. Fig. 1 shows that the greatest change in β occurs in the presence of small amounts of added organic solvents, where significant changes in the structure of the transition state can hardly be expected.

‡Since the reaction was carried out in water, the acylammonium salt formation stage, regarded here as an elementary process, is probably rate-determining.

The difficulty of taking into account the steric accessibility of the nitrogen atom in the tertiary amine hindered for a long time a quantitative description of the dependence of the catalytic activities of aliphatic tertiary amines on their structure[13,93,94]. Such description has been based on a modified[95] Taft equation [Eqn.(6)], where the steric hindrance in the amines $R_1R_2R_3N$ was chaac: terised, on the basis of the isosteric principle, by the constants E_N which are equal to the Taft steric constants E_S for isosteric hydrocarbon substituents $R_1R_2R_3C$:

$$\lg k = \lg k_0 + \rho^* \sum \sigma^* + \delta E_N \quad . \qquad (6)$$

The applicability of this equation was tested in series where the amines (primary, secondary, and tertiary) behave as nucleophiles[95,96] and then in reactions where tertiary amines function as nucleophilic catalysts[97,98]. An equation relating quantitatively the catalytic activity of aliphatic tertiary amines to their inductive and steric characteristics was obtained for the first time for the hydrolysis of benzoyl chloride in 98% dioxan[97]:

$$\lg k = 2{,}80 - (2{,}0 \pm 0{,}2) \sum \sigma^* + (1{,}39 \pm 0{,}09) E_N .$$

Using this equation and also the analogous expressions for other reactions involving tertiary amines, the values of E_N have been calculated for a fairly large number of tertiary amines[97,98]. These data give rise to the prospect of a quantitative description of many other acyl transfer reactions catalysed by tertiary amines, some of which will be examined in subsequent Sections.

2. Alcoholysis of Carboxylic and Sulphonic Acid Halides and Anhydrides

It is surprising that there are almost no literature data on the quantitative characteristics of the influence of tertiary amines on the acylation of phenols and particularly alcohols, which are important processes. For example, the mechanism of the catalysis of the acylation of phenols is still obscure. Thus the greater catalytic effect of tertiary amines in the acylation of phenols compared with alcohols and thiophenol[27,28,37,38] and the increase of this difference between the catalytic effects with increasing basicity of the amine[38] as well as the acidity of the phenol[37] support, according to the authors, a general base catalytic mechanism.

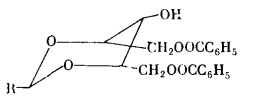
A detailed study of the reaction of RC_6H_4OH with acetic anhydride in carbon tetrachloride in the presence of pyridine bases R'Py showed[99] that there is a satisfactory linear correlation between $\lg k$ and σ^0 for R with a slope $\rho = +1.52$. On the basis of the observed rate constants and K_{ass} for the reactions of the same phenols with pyridine, the authors calculated the constants k_B, which were referred to the interaction of the complex ArOH...PyR' with acetic anhydride, and found that they too obey the Hammett equation with $\rho = +0.99$. The increase of the rate of reaction with enhancement of the electron-accepting properties of R confirms, according to the authors[99], the general base catalytic mechanism (for the non-catalytic reaction, $\rho = -0.82$).[27] $\rho = +0.6$ was also found for the reaction of phenols with benzoyl chloride in dioxan in the presence of triethylamine[39]. Later it was shown[100,101] that the introduction of strong electron-donating substituents R (for example, HO or CH_3O) likewise increases the reactivity of phenol, as a result of which the curve relating $\lg k$ to σ shows an inflection in the range $\sigma = 0$–0.1; a similar inflection has been observed for the relation between $\lg k$ and the pK_a for phenols (in dimethyl sulphoxide).[33] In catalysis by pyridine, the Hammett relation again had a descending branch with $\rho = -0.7$ and an ascending branch with $\rho = +0.4$.[39] According to the authors[33,39,100], these phenomena indicate a change in the mechanism of the catalytic reaction from nucleophilic for basic phenols ($\beta > 0$, $\rho < 0$) to the general base catalytic mechanism for acid phenols ($\beta < 0$, $\rho > 0$). The lower (by two orders of magnitude) catalytic activity of pyridine compared with that of triethylamine is also regarded as an argument in support of the above hypothesis[102]. However, one should note that the inflection in the Hammett or Brønsted plot can also be accounted for by the increased contribution of the direct polar coupling of electron-donating substituents of the type RO to the reaction centre[101]. We believe that one cannot fully rule out also the possibility of nucleophilic catalysis in the acylation of phenols—the inflection in the $\lg k$–σ or $\lg k$–pK_a curve can then be explained by a change in the relative rates of the stages [for example k_2' and k_2'' in mechanism (4)]. The ready acylation of phenols by an equimolar amount of RCOOH in the presence of pyridine and chlorocyclophosphazene $(PNCl_2)_3$ has been explained[103] from the standpoint of nucleophilic catalysis. The reaction probably proceeds via the formation of a cyclophosphazenylpyridinium salt followed by interaction with RCOOH and the formation of an acylammonium salt.

The available information about the influence of the structure of the acylating agent in catalytic alcoholyses is limited to the above comparison of acetic anhydride, trifluoroacetic anhydride, and acetyl trifluoroacetate and also data[99] showing a decrease of the rate of acylation of *m*-nitrophenol in the presence of 3- and 4-quinolines by the anhydrides $(RCO)_2O$ in the sequence $CH_3 > C_2H_5 >$ iso-$C_3H_7 >$ t-C_4H_9. The proportionality between $\lg k$ in this series and the values of E_S (or E_S^0) supports a steric type of effect although one cannot claim this with complete confidence in view of the relation between the values of σ^* and E_S for certain substituents R.[104]

Even less is known about the kinetics and structural characteristics of the acylation of alcohols. Since alcohols are weak acids and fairly strong nucleophiles, one may expect that tertiary amines will behave as nucleophilic catalysts in their acylation. This is confirmed by Bird's data[9], already mentioned, for the acylation of racemic alcohols RR'CHOH in the presence of optically active tertiary amines. It has been shown[105] that the methanolysis of a number of aliphatic acid halides in the presence of triethylamine proceeds via two competing mechanisms: via the formation of an acylammonium salt and via dehydrohalogenation with formation of a keten, which reacts further with methanol. Nucleophilic catalysis apparently also operates in the methanolysis of tetrachlorophthalic anhydride in the presence of pyridine[106]; by virtue of steric hindrance, dimethylaniline does not catalyse the process and actually gives rise to an inactive complex; because of this, the reaction is described by a kinetic equation of the Michaelis–Menten type.

The influence of the structure of tertiary amines and acylating agents has been investigated by Rogne[107] in the methanolysis of aromatic sulphonyl chlorides in the presence of pyridine and its methyl derivatives. As in hydrolysis (see Section III, subsection 1), electron-donating substituents in the tertiary amine and electron-accepting substituents in $RC_6H_4SO_2Cl$ increase the rate of reaction, the influence of R being more effectively described by the Hammett equation when σ^+ constants are used ($\rho^+ = 0.63$).

Similarly the rate of acylation of 5-hydroxy-1,3-dioxan derivatives of the type



where R = H or C_6H_5, by the chlorides of *para*-substituted benzoic acids and benzenesulphonic acid in pyridine is similarly correlated with the values of σ^+ ($\rho^+ = 0.83-0.95$ and 0.85 respectively)[108]. This indicates an appreciable contribution of the conjugation of the substituent with the reaction centre in the transition state. It was shown in the same study[108] that, in contrast to the majority of cyclic compounds where the equatorial hydroxy-group is more reactive than the axial group[108,109], in this case the axial epimers are more reactive; the authors explained this by the influence of the electronegative oxygen atoms in the ring.

Until very recently, there were no literature data for the influence of the structure of aliphatic alcohols on the rate of their catalytic acylation. We were able to show only recently[110,111] that this influence can be described by the extended Taft equation. The equation for the alcoholysis of benzoyl chloride in tetrachloroethylene is§

$$\lg (k/k_0) = (2.1 \pm 0.3)\,\sigma^* + (1.4 \pm 0.3)\,E_{S\,(RCH_2)}\ , \qquad (7)$$

the coefficients of sensitivity to inductive (ρ^*) and steric (δ) influences being independent of the structure of the amine catalyst[111]. This shows that the electron density at the oxygen atom of the nucleophile increases during activation. Consequently the rate-determining stage of the process under the given conditions is attack by the alcohol on the carbonyl carbon accompanied by the transfer of a proton, the degree of dissociation of the O–H bond predominating over the degree of formation of the C–O bond[110]. The importance of the proton transfer xtage, which has been demonstrated theoretically[71] (see Section II, subsection 3), was also confirmed by studies of the isotope effect. In contrast to reactions in water, where the first stage is rate-determining and $k_H/k_D = 1.1 \pm 0.1$,[90,112] an isotope effect is observed in alcoholysis in a non-aqueous medium, indicating the involvement of proton transfer in the rate-determining stage[113]. One should note that similar considerations are applicable also to the acylation of phenols and the observed sign of ρ^* in relation to the nucleophile cannot thus be regarded as a criterion of the type of catalysis.

The influence of the structure of tertiary amines on their catalytic effectiveness in the acylation of alcohols and phenols obeys the same relations as in the hydrolytic reactions. Thus the Brønsted equation holds for 3- and 4-substituted pyridines, high values of β (between 0.85 and 0.93) being characteristic of the acylation of phenols, with the exception of the alcoholysis of trifluoroacetaldehyde (β was not calculated[36] but an estimate based on the authors' data leads to $\beta \simeq 0.3$), probably owing to its higher reactivity.

The influence of pyridines in the methanolysis of sulphonyl chlorides can be described by the Brønsted ($\beta = 0.55$) and Hammett ($\rho = -3.0$) equations. The high negative value of ρ shows, according to the author[107], that the first stage is rate-determining because of the high concentration of the nucleophile and the fairly high polarity of the medium. At the same time the lower solvating capacity of methanol compared with water leads to a more negative entropy of solvation (by approximately 15 e.u.) and decreases the overall rate of the process by two orders of magnitude.

As in other cases, sterically hindered 2- and 2,6-substituted pyridines (including 2-dimethylaminopyridine) exhibit a weak catalytic activity. The steric factor is particularly important when aliphatic tertiary amines are used. Thus a correlation between the rate of reaction and ΣE_S for a number of tertiary amines of approximately equal basicity, $\delta = 0.84$ and 0.72 respectively, has been found in the benzoylation of phenol and *p*-nitrophenol in dioxan[102]. However, the approach based on the summation of the steric constants of substituents attached to nitrogen is inaccurate, since, in contrast to the polar characteristics, the steric characteristics are non-additive[114]. The application of equations of the type of Eqn.(6), using the steric characteristics of amines as a whole, is apparently more promising. Indeed, we were able to show[111] that the catalytic activity of tertiary amines in the benzoylation of alcohols in tetrachloroethylene is described by Eqn.(8) and that its parameters ρ^* and δ are independent of the structure of the acylated alcohol:

$$\lg (k/k_0) = (-2.1 \pm 0.2) \sum \sigma^* + (0.91 \pm 0.09)\,E_N. \qquad (8)$$

Thus the influence of the structure of the alcohol and the amine on the rate of reaction is additive and the overall Eqn.(9) does not contain cross terms. This indicates a constant composition of the transition state for all the systems investigated in the coordinate space of the reaction, which is probably evidence for the occurrence of the reaction under these conditions by a nearly synchronous mechanism, owing to the weak solvating capacity of the solvent[40,110]. An increase of the latter increases the possibility of a shift of the transition state in the coordinate space, which leads to a relation between the rate of reaction and its sensitivity to changes in structure. This is manifested by the appearance of cross terms—in acylation in dioxan, for example, the correlation equation has the following form:

$$\lg k = 1.35 + 1.97\sigma^*_{(R)} + 1.34E_{S\,(RCH_2)} - 2.1 \sum \sigma^*_{(N)} + 0.92E_N\ , \qquad (9)$$

$$\lg k = 1.32 + 1.49E_{S\,(RCH_2)} - 1.71 \sum \sigma^*_{(N)} + 0.89E_N - 0.37\sigma^*_{(R)} \cdot E_N + \\ + 0.81 \sum \sigma^*_{(N)} \cdot E_{S\,(RCH_2)}. \qquad (10)$$

3. The Acylation of Amines by Carboxylic and Sulphonic Acid Halides and Anhydrides

The aminolysis of acid halides and anhydrides in the presence of tertiary amines is one of the most thoroughly investigated reactions owing to systematic studies by the Donets School of Chemistry¶. It has been shown for the reaction of benzoyl chloride with substituted anilines in benzene[24,117–119] that tertiary amines can be divided into

§ The steric effect of the group RO in Eqn.(7) is described by the constants E_S for the RCH_2 groups, which are approximately isosteric with the RO groups.

¶ These investigations were continued by studies on the catalytic activities of amides, *N*-oxides, and other *O*-nucleophilic catalysts[115,116], the consideration of which is outside the scope of the present review.

several groups in terms of their catalytic activity, within which the Brønsted and Hammett–Taft equations hold†. On the other hand, it has been found that the catalytic activity of tertiary amines (with comparable basicities) falls on passing from unhindered heterocyclic amines to 2-substituted pyridines, quinoline, and dialkylanilines. Aliphatic cyclic tertiary amines are much weaker catalysts than would be expected from their basicity, because they are subject to an appreciable steric hindrance. For this reason, the linear Brønsted plot (Fig. 2) corresponding to these substances lies below the corresponding plot for the pyridines, although the slopes of the straight lines are virtually the same (0.81 ± 0.05 and 0.86 ± 0.01) [119]; the points corresponding to amines such as triethylamine lie lower still. Similar relations have been observed for the aminolysis of toluene-*p*-sulphonyl bromide in a 1 : 1 nitrobenzene–cyclohexane mixture [120,121].

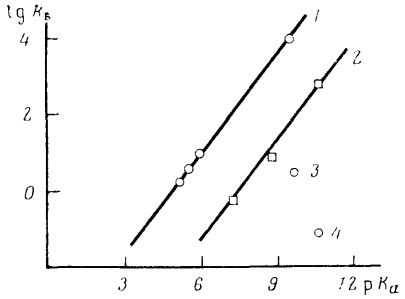


Figure 2. The Brønsted correlation for the reaction of benzoyl chloride with *m*-chloroaniline catalysed by tertiary amines [199]: 1) pyridine bases; 2) cyclic amines; 3) trimethylamine; 4) triethylamine.

The combination of a high capacity for resonance stabilisation, basicity, and steric accessibility is probably responsible for the extremely high catalytic efficiency of *N*-aryl- and *N*-alkyl-imidazoles [47,122–124]; the acylammonium salt is then unusually stable and can be fairly readily isolated and characterised [14,47]. Imidazole itself is relatively inactive as a catalyst, but its hydrochloride, which in some respects resembles acylammonium salts, is capable of transferring the acyl group to *m*-chloroaniline [125].

Further studies demonstrated the dependence of the efficiency of the catalyst on the properties of the acylating agent and the acylated substrate. Thus the catalytic activity diminishes in the aminolysis of ArCOHal with increase of the strength of the C–Hal bond, i.e. on passing from the bromide to the chloride, while the aminolysis of benzoyl fluoride is actually inhibited by pyridine [23,32]. Triethylamine catalyses the acylation of butylamine by benzoyl cyanide [126], while the aminolysis of the majority of carboxylic acid anhydrides is inhibited by pyridine [24,25,127].

† The catalytic activity of tertiary amine hydrochlorides has been noted in the aminolysis reaction [11,24,47,117–119], which is probably associated with the effect of the ion pair $C_5H_5N^+ \cdots Cl^-$ as a bifunctional catalyst.

However, catalysts may be observed on passing to the anhydrides of stronger acids: trichloroacetic [25], *p*-phenylthiobenzoic [128], and sulphonic acids [26]. On the other hand, the catalytic effect is observed following the enhancement of the nucleophilic properties of the tertiary amine, for example, in the case of 4-*NN*-dimethylaminopyridine [25], or when bifunctional catalysts of the type of 2-hydroxypyridine are used [32]. In the latter case, the change in the mechanism of catalysis is revealed by the change in its relative efficiency for different acylating agents: the k_{cat}/k_0 ratio for C_6H_5COX diminishes in the following sequence of X: F ≫ Cl > Br.

The efficiency of the catalysis increases also on enhancement of the electron-accepting properties of the substituents in the acid halide, although the effect is not very great (see Table 4, Nos. 3–6). The polarisability of the reaction centre has a much greater influence on the catalytic activity of tertiary amines; Table 4 (Nos. 8 and 9) shows that, in the aminolysis of *p*-nitrobenzenesulphonyl bromide [129], pyridine is 30–40 times more effective than in the aminolysis of benzoyl chloride. An even greater catalytic effect has been observed in the reactions of sulphonic acid anhydrides [26], despite the opposite influence of the solvent, an increase of the polarity of which has been shown [46,130] to decrease k_{cat}/k_0.

Table 4. Efficiency of the catalytic effect of tertiary amines in the acylation of anilines $RC_6H_4NH_2$ (benzene, 25 °C).

No.	Acylating agent	R	Catalyst	k_0, litre mole^{-1} s^{-1}	k_{cat}, litre^2 mole^{-2} s^{-1}	k_{cat}/k_0, litre mole^{-1}	Reference
1	C_6H_5COCl	H	Pyridine	$6.99 \cdot 10^{-2}$	8.8	136	118, 119
2	C_6H_5COCl	*p*-NO_2	Pyridine	$4.2 \cdot 10^{-5}$	0.152	3600	118, 119
3	C_6H_5COCl	*m*-Cl	Pyridine	$3 \cdot 10^{-3}$	2.0	660	127
				$3.4 \cdot 10^{-3}$	1.9	450	118, 119
4	*p*-$(CH_3)_2NC_6H_4COCl$	*m*-Cl	Pyridine	$1.74 \cdot 10^{-4}$	$7.16 \cdot 10^{-2}$	410	127
5	*p*-$NO_2C_6H_4COCl$	*m*-Cl	Pyridine	$1.71 \cdot 10^{-2}$	15.2	890	127
6	*p*-$C_6H_5C_6H_4COCl$	*m*-Cl	Pyridine	$2.72 \cdot 10^{-3}$	2.0	730	23
7	*p*-$C_6H_5C_6H_4COBr$	*m*-Cl	Pyridine	0.249	239	936	23
8	*p*-$NO_2C_6H_4SO_2Br$	H	Pyridine	$3.46 \cdot 10^{-6}$	$2 \cdot 10^{-2}$	6420	129
9	*p*-$NO_2C_6H_4SO_2Br$	*m*-Cl	Pyridine	$9.12 \cdot 10^{-8}$	$2.3 \cdot 10^{-3}$	25 100	129
10	$(CCl_3CO)_2O$	*p*-NO_2	*p*-Dimethylaminopyridine	2.86	94.7	36	25
11	$(CH_3CO)_2O$	H	*p*-Dimethylaminopyridine	$2.15 \cdot 10^{-3}$	1.02	475	25
12	$(p\text{-}NO_2C_6H_4CO)_2O$	H	*p*-Dimethylaminopyridine	$1.4 \cdot 10^{-2}$	22.8	1580	127
13	$(p\text{-}ClC_6H_4SO_2)O$ *	*m*-NO_2	*p*-$CH_3C_6H_4N(CH_3)_2$	$1.27 \cdot 10^{-2}$	156	12 000	26

*In nitrobenzene.

Analysis of the results based on Kirkwood's equation led the authors [46,130] to the conclusion that the polarity of the activated complexes in catalytic and non-catalytic reactions is approximately the same ($\mu_{\neq}$ = 19.8 and 19.6 D respectively), but in the catalytic process the activated complex is larger owing to the involvement of three molecules in its formation.

The efficiency of the tertiary amine depends significantly also on the properties of the acylated amine; thus it has been shown [118,120,129] that k_{cat}/k_0 increases with decrease of the basicity of the arylamine and the catalytic effect is shown most clearly for weakly basic amines. As a result of this, the values of ρ, characterising the sensitivity of the reaction to the influence of substituents in $ArNH_2$, decrease on passing from the non-catalytic to the

catalytic process, from −2.67 to −1.35 for the reaction with C_6H_5COCl [118] and from −3.98 to −2.8 for the reaction with p-$NO_2C_6H_4SO_4Br$.[120,129] Finally, the influence of temperature on the above processes is expressed, in conformity with the relations discussed in Section II, by a decrease of the efficiency of the catalysis with increase of temperature.

4. Reactions of Esters

The influence of tertiary amines on the reactions of esters has been investigated for a long time and in great detail partly in connection with their similarity to many enzymatic processes. Greatest attention has been devoted in this connection to imidazole, which enters into the active centres of many hydrolases and is also probably an acyl transferring agent in the biosynthesis of acetylcholine[131,132]. Imidazole is involved in nucleophilic reactions via its tertiary nitrogen atom; on the other hand, the presence of the secondary nitrogen atom makes possible the elimination of the proton from the acylammonium salt, which leads to fairly stable acylimidazoles[133].

In conformity with what has been said in Section II, imidazole and other tertiary amines may catalyse via the nucleophilic mechanism only the hydrolysis of activated esters (phenol, thiol, etc. esters)[29,134-144] if $\Delta pK_a \leq 3$ for ArOH and the imidazolium ion. When $\Delta pK_a > 3$, the cooperation of general base catalysis with nucleophilic catalysis is necessary[137] and, for $\Delta pK_a \gg 3$, only general base catalysis is observed[137,140,145] or there is no catalysis at all[136,137]. The lactonisation of the amide and ester of o-hydroxymethylbenzoic acid is catalysed by imidazole and other bases[146,147], probably via the general base mechanism, as shown by the ratio $k_{H_2O}/k_{D_2O} = 3.46$ and the Brønsted coefficient (0.87).[147] The ability of imidazole to catalyse the hydrolysis of *NO*-diacetylserine amide has also been noted[148].

The solvent has a significant influence on the ratio of the basicities of the leaving group and the amine and hence on the type of catalysis. Thus the aminolysis of 2,4-dinitrophenyl acetate in benzene and chlorobenzene[149,150] is catalysed by pyridine, in contrast to aqueous solutions, probably via the general base mechanism. The fundamental argument used by the authors has been the observation of a correlation between $\lg k_{cat}$ for catalysts of different chemical types and their proton-accepting capacity, characterised by the constants for association with phenol[149] or p-fluorophenol[150], and also the fairly high values of E_{cat}^{app} (7–10 kcal mole^{-1}).[151] On the other hand, the absence of correlation between the basicity of tertiary amines and their catalytic activity in the aminolysis of 2,4-dinitrophenyl acetate and other similar esters has been interpreted[152] as evidence for nucleophilic catalysis. Thus the problem cannot be regarded as solved.

Without going into the details of the mechanism of the reactions of esters, which have been considered in a number of monographs[18,29,89,153-155], we shall merely emphasise that the transition state in the rate-determining stage in such reactions is apparently extremely polar and close to a tetrahedral complex with separated charges[18,29,89]. This explains the decrease of the rate of reaction following the addition of alcohol to water[156]‡.

As in other instances, in the reactions of esters the catalytic activity of amines of the same type is described satisfactorily by the Hammett or Brønsted equation, but different correlation lines correspond to different classes. The Brønsted coefficient is usually approximately 0.7 to 0.8 [134,135] (the value of 1.62 obtained in one investigation[136] is probably erroneous due to the small number of compounds investigated). Substituted imidazoles are again the most active (for comparable basicities) and are followed in this respect by pyridines and the relatively less active aliphatic tertiary amines[135,136] as well as 2- and 2,6-substituted pyridines[159-162]. On the other hand, it has been found for the reaction of the esters $2,4\text{-}(NO_2)_2C_6H_3OOCR$ with aniline[152] and the hydrazides p-$R'C_6H_4CONHNH_2$[163] that the catalytic activity of pyridine increases in the following sequence of R: $CH_3 < C_6H_5 < p\text{-}NO_2C_6H_4$ and in the following sequence of R′: $H < CH_3O < Br$. Thus the observed relations are typical for nucleophilic reactions, so that the authors' hypothesis of general base catalysis appears doubtful.

It has been shown for triazoles[164] as well as pyridine and phthalazine[165] that the catalytic activity of tertiary amines increases following the appearance of several neighbouring atoms in the heterocycle, which is associated, according to the authors, with the repulsion of the neighbouring lone electron pairs, resulting in an enhancement of the nucleophilic properties of the compound[165].

The efficiency of catalysis increases significantly when bifunctional derivatives are used in which the nucleophilic attack on the nitrogen is accompanied by proton transfer, the importance of which has already been mentioned. Thus, in the hydrolysis of p-nitrophenyl acetate (NPA), 2-hydroxy-, 2-hydroxyethyl-, and 4-(γ-hydroxypropyl)-pyridines are much more active than the corresponding picolines[166]; serine and histidine are more active still. The mercaptoalkyl derivatives of imidazole and benzimidazole[167,168] and also 2-(o-hydroxyphenyl)imidazole[169] are extremely efficient as catalysts. On the other hand, 4-(β-diethylaminoethyl)- and 4-(diethylaminomethyl-imidazoles are less effective than imidazole itself[170]. It has been found[171] that the aminoalcohols $RR'NCH_2CH_2OH$ catalyse the decomposition of many phenyl esters, behaving at the same time as acyl transferring agents. According to the authors, *N*-nucleophilic catalysis does not occur in this case, the aminoalcohols undergoing *O*-acylation with subsequent rapid hydrolysis of the resulting esters.

Another interesting group of facts includes the effects observed in many instances in studies of the hydrolysis of esters, analogous to those noted in enzymatic catalysis. Thus the attainment of the maximum reaction velocity at a certain substrate concentration (Michaelis–Menten kinetics) and inhibition of the reaction by its products[172], which is characteristic of many enzymatic systems, have been observed in the hydrolysis of $p\text{-}NO_2C_6H_4OC(O)OCH_2CH_2\dot{N}^{+}\cdot(CH_3)_2C_{12}H_{25}$ in the presence of *N*-stearoylhistidine; the rate of this reaction is 2000 times higher than in catalysis by *N*-acetylhistidine[173]. Similar phenomena have been observed in the hydrolysis of 4-carboxyphenyl acetate in

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‡The decrease of the rate of acylation of neutral nucleophiles by nitrophenyl esters on passing to a micellar medium, characterised by a lower value of ϵ than water, has also been explained by the unfavourable influence of the non-polar environment[156-158].

the presence of 1-aminomethyl-4-(4'-imidazolyl)naphthalene[174]. Some of these effects (for example, kinetics simulating saturation) may be associated with the aggregation of the esters of higher aliphatic acids in water[175], but the fundamental cause is apparently the hydrophobic interaction of the catalyst with the substrate, which decreases the activation entropy. This probably accounts for the sharp increase of the rate of hydrolysis of the esters p-$NO_2C_6H_4OOCC_nH_{2n+1}$ in the presence of alkylimidazoles with increase of the number of carbon atoms in the substrate and the catalyst§ (see Table 5)[176-178].

Table 5. The influence of hydrophobic properties on the hydrolysis of the esters $C_nH_{2n+1}COOC_6H_4NO_2$ in the presence of the alkylimidazoles $C_mH_{2m+1}N$ (=N) in water at 25°C.[177]

n (in ester)	k_{OH}, litre mole^{-1} s^{-1}	k_{cat}, litre mole^{-1} s^{-1}				
		$m=2$	$m=4$	$m=6$	$m=8$	$m=10$
1	12.1	0.40	0.40	0.43	0.45	0.61
3	6.75	0.35	0.36	0.36	0.39	0.45
5	6.34	0.32	0.39	0.40	0.49	2.39
7	3.24	0.045	0.20	0.48	0.76	5.54
9	0.48	0.014	0.019	0.15	0.93	11.7

Polymeric catalysts of the hydrolysis of esters are of interest. In this respect, detailed studies have been made on partially alkylated polyvinylpyridines[65,180-184], polyaziridines[185], polyvinylimidazoles and the copolymers of vinylimidazole with other monomers[186-191,193], and the polyoxyethylene ester of N-benzoylhistidine[192]. In many instances these catalysts exhibited an efficiency several orders of magnitude higher than the corresponding monomers, the effect being particularly pronounced in the hydrolysis of esters with long hydrocarbon chains[185,190]. It is suggested that the active centres in these polymers are tertiary amino-groups, which behave as nucleophilic[65,181-183,186] or general base[185] catalysts (possibly in cooperation with other groups[186]); on the other hand, the efficiency of the catalysis is associated mainly with the concentration of the reactants in the active cavities formed by the hydrophobic parts of the polymer chain and the ammonium groups. However, one should bear in mind the fact that the effect of the concentration of the reactant may be extinguished owing to the decrease of the true reaction rate caused by the weak solvating capacity of the medium[156-158], which may be the reason for the insignificance of the effects in many instances[186,190].

(4-Imidazolyl)methoxy- or β-(4-imidazolyl)ethylaminocyclodextrins, in which the imidazole moiety and the OH group of the cyclodextrin act synchronously, combining with the acyl which is subsequently hydrolysed, constitute an unusual type of polymeric catalysts[194]. This mechanism, resembling the action of serine hydrolases, ensures the acceleration of the hydrolysis of NPA by a factor of 50 to 200.

§A similar phenomenon has been observed in the reaction of the same esters with the amines $C_nH_{2n+1}NH_2$ under the conditions of catalysis by a second amine molecule[179].

5. The Reactions of Isocyanates

It has been known for a long time that tertiary amines accelerate the reactions of nucleophiles with isocyanates[195-197]. The similarity of this process to the reactions of acid halides is clear from a review[93] and from the literature[98,198-206], namely the dependence of the catalytic activity of tertiary amines on their basicity and steric accessibility and the absence of correlation between $\lg k_{cat}$ and pK_a. On the other hand, there is satisfactory correlation based on Eqn.(6) and, as can be seen from Table 6, the reactions of isocyanates with alcohols are less sensitive to the structure of the tertiary amine than the analogous reactions of acid chlorides. When nucleophiles of the same type are varied (ROH, Table 6, Nos. 1 to 3), the values of ρ and δ remain virtually constant, while, on passing to butanethiol (Table 6, No.4), the sensitivity of the reaction to both effects increases[98], probably by virtue of the greater bulk and greater polarisability of the sulphur atom compared with the oxygen atom. Bridged cyclic amines of the type of diazabicyclo-octane (DABCO) and quinuclidine are very effective catalysts in all cases, mainly because the degree of the steric hindrance is low (DABCO is close to trimethylamine as regards the value of E_N), while the basicity is high.

Table 6. The correlation parameters of the catalytic activity of tertiary amines in the reactions of phenyl isocyanate with nucleophiles in accordance with Eqn.(6).

No.	Nucleophile	Conditions	$\lg k_0$	ρ	δ	Refs.
1	C_4H_9OH	Toluene; 19–69°	0.9	−0.94 ± 0.03	0.94 ± 0.04	97,205
2	C_4H_9OH	Cyclohexane–dioxan (2:1); 31°	0.7	−0.78 ± 0.22	0.57 ± 0.08	98,199
3	$(C_4H_9)_2CHCH_2OH$	Benzene; 24°	0.6	−0.79 ± 0.45	0.37 ± 0.15	98,200
4	C_4H_9SH	Toluene; 25°	1.6	−1.00 ± 0.23	0.67 ± 0.09	98,198

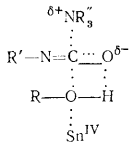
The importance of the steric factor suggests a nucleophilic mechanism of the catalytic reaction with formation as an intermediate of the dipolar ion

$$R-N=C-O-\overset{\beta}{C}H_2-\overset{\alpha}{N}R'_3 \leftrightarrow R-\overset{-}{N}-C(=O)-CH_2-\overset{+}{N}R'_3,$$

the stability of which increases owing to the resonance delocalisation of the negative charge. This leads to the possibility of observing this product by infrared spectroscopy[207] and also to the possibility of the separate determination of k_1 and k_2/k_{-1}; such data have been obtained for the reaction of phenyl isocyanate with alcohols in the presence of triethylamine and pyridine[93,196].

The efficiency of catalysis decreases in the following series of substances: butanol > water > diphenylurea[208] and increases with increase of solvent polarity[196,209] (nonspecific solvation probably plays the main role[209]) and also after the addition of organotin compounds[209]. The latter themselves catalyse the reactions of isocyanates and their

role probably consists in activating the alcohol. Here the transition state is probably



6. Various Reactions

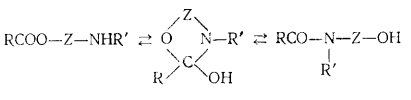
Among other reactions involving acyl transfer, the catalytic effect of tertiary amines has been observed in the aminolysis of carbamates[210] and the hydrolysis of a number of amides[211-215]. In most cases, the authors postulated the general base or general acid mechanism of catalysis[213,214] although Stauffer[212] adduced evidence supporting nucleophilic catalysis of the hydrolysis of trifluoroacetanilide by imidazole buffers.

In certain new studies, examples of unusually effective catalysis have been described. Thus the rate of hydrolysis of tetraethyl pyrophosphate catalysed by substituted benzimidazoles in the excited state has been found to be similar to the diffusional rate ($k \approx 10^{10}$–10^{11} litre mole^{-1} s^{-1}), which has been explained by the increase of the basicity of the catalyst on excitation to the singlet state and by the decrease of the energy barrier to the formation of the acylammonium salt[216].

A study of the hydrloysis of 2-hydroxy-4-nitrophenyl sulphate[217] showed that polyaziridine, partly alkylated by dodecyl- and methylene-imidazole residues, accelerates the reaction by a factor of 10^{12}, while imidazole itself exhibits only a weak catalytic activity. According to the authors, this effect is caused by the hydrophobic interaction of the substrate with the dodecyl groups and the subsequent nucleophilic catalysis by imidazole.

IV. INTRAMOLECULAR CATALYSIS

The acyl transfer reactions with the intramolecular involvement of a tertiary amino-group are in many respects analogous to the N → O acyl migration with participation of a primary or secondary amino-group, which takes place, according to modern ideas[218-223], via the following mechanism (without taking into account the possible proton transfers):

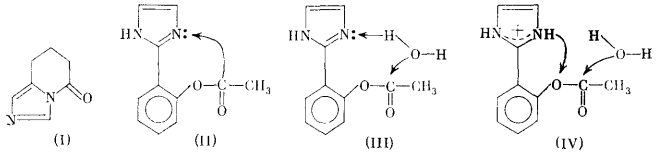


However, since the acylammonium salts are unstable, they behave merely as reactive intermediates and the tertiary amino-group may be regarded as a nucleophilic catalyst. Among reactions of this type, studies have been made mainly on the reactions of amino-esters and to a less extent on the acylation of aminoalcohols.

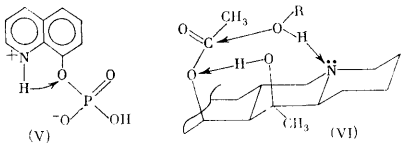
1. Hydrolysis and Other Reactions of Aminoesters

Intramolecular catalysis in the reactions of aminoesters is determined, like intermolecular catalysis, by the properties of the alkoxy-residue eliminated. If the amino-group in the anion R'_2N-Z-O^- is more basic than O^-, the acyl residue in the ester $RCOO-Z-NR'_2$ may be transferred to the nitrogen atom with formation of the acylammonium salt $RCO(R')^+_2N-Z-O^-$, which undergoes further nucleophilic attack (nucleophilic catalysis)[29]. This mechanism is characteristic of activated esters, such as aryl (4-imidazolyl)butyrates[224,225]; in this case, the intermediate is the lactam (I). The amide and the methyl ester of the same acid are hydrolysed without the participation of neutral imidazole, although in the case of the amide the influence of the protonated form of imidazole was noted. Nucleophilic catalysis has been proposed also for the hydrolysis of *o*-(4-imidazolyl)phenyl esters[226,227], but, subsequently it was concluded on the basis of the ratio $k_{H_2O}/k_{D_2O} = 3.23$ and the activation parameters that general base catalysis operates in the reactions of these esters[228].

It has been shown[144] that the mechanism of the catalysis of the hydrolysis of substituted 2-imidazolylphenyl acetates depends on pH: in the alkaline region, nucleophilic catalysis (II) operates, in a neutral medium there is general base-catalysed cooperation with attack by imidazole on water (III), while in a weakly acidic medium general acid catalysis by the protonated form of imidazole (IV) operates:



The same possibilities occur also in other instances. Thus, according to some workers[228-232], general acid catalysis obtains in the hydrolysis of the zwitter-ion of 8-quinolinyl phosphate (V)[229] and substituted 4-benzimidazolylpeptides[230], while general base catalysis, confirmed by the ratio $k_{H_2O}/k_{D_2O} = 2.35$, operates in the hydrolysis and hydrazinolysis of 8-acetoxyquinoline[228,231] and also in the solvolysis of cevadine and other Ceveratrum alkaloids [for example, compound (VI)]; in the latter case, general acid catalysis by the OH group operates simultaneously[232]:



On the other hand, in the hydrolysis of 8-hydroxyquinoline monoesters with succinic or glutaric acid, a nucleophilic mechanism of catalysis, confirmed by the ratio $k_{H_2O}/k_{D_2O} = 1.05$, has been demonstrated[233].

In a few studies, where the efficiencies of the intermolecular and intramolecular catalysis were compared, the predominance of the latter has been demonstrated. Thus, it has been found[234] that the ratio of the rate constants for the hydrolysis of the esters $(CH_3)_2N(CH_2)_3.COOC_6H_4R$ (k_I) and the bimolecular hydrolysis of aryl acetates in the presence of trimethylamine (k_{II}) varies from 1260 (for R = H) to 5370 mole litre^{-1} (for R = *p*-NO_2); here the entire gain is apparently achieved as a result of the effect associated with the mutual approach of the functional groups, resulting in a gain of translational entropy. The effect for δ-dimethylaminovalerate esters is smaller by a factor of 1.6–2.7 because the five-membered ring in the transition state is more favourable than

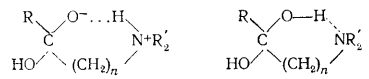
the six-membered ring. The values of k_I/k_{II} for γ-(4-imidazolyl)butyrate esters are lower by two orders of magnitude—ranging from 94 (for R = *p*-NO_2) to 24 mole litre^{-1} (for R = H).

In the hydrolysis of non-activated aminoesters, a significant catalytic effect by the tertiary amino-group has been found only in the case of 4-(β-acetoxyethyl)imidazole[224,227] and 5-acetoxymethyl-1-methylimidazole[235], which has been explained by the favourable nature of the cyclic transition state arising in this case in the O → N acyl transfer. In the remaining instances investigated, the introduction of a tertiary amino-group into the ester molecule accelerates its hydrolysis by not more than a factor of two (see Table 7) owing to the inductive effect of the amino-group[236-239]. The hydrolysis of esters of this kind is described by the general correlation equations for esters with a variable alcoholic component[238,240] and an appreciable catalytic effect (of the kind postulated, for example, by Schätzle et al.[241]) is therefore not observed.

Table 7. The influence of the amino-group on the alkaline hydrolysis of the aminoesters $RCOOCH_2CH_2X$.

R	Conditions	k, litre mole^{-1} s^{-1}				$\frac{k_{N(CH_3)_2}}{k_H}$	$\frac{k_{+NH(CH_3)_2}}{k_{+N(CH_3)_3}}$	References
		X = H	X = $N(CH_3)_2$	X = $+N(CH_3)_3$	X = $+NH(CH_3)_2$			
CH_3	Water, 25° 0.07 M $KClO_4$ I = 0.1	0.045	0.1	1.48	42.6	2.2	28.8	245
		—	—	2.0	39.1	—	19.6	246
$CH_2=C(CH_3)$	Water, 25° I = 0.5	0.035	0.042	0.60	16.5	1.2	27.5	238
C_6H_5	Water, 25° I = 1	0.03	0.058	0.56	16	1.9	28.5	249
C_6H_5	30 wt.% alcohol, 60° I = 0.1	0.058	0.011	3.7	150	1.9	40.5	237 250 252

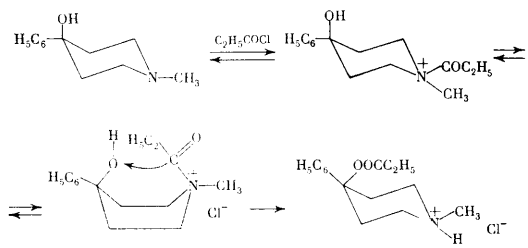
Table 7 shows that esters containing a charged ammonium group are hydrolysed much faster than their neutral analogues. For quaternary ammonium derivatives, this effect[242,243] is associated with the electrostatic interaction between the positively charged nitrogen atom and the negative charge arising in the transition state in alkaline hydrolysis and in this instance it is hardly useful to speak of catalysis, as was done by Smith and Williams[244]. On the other hand, the acceleration of the reaction by a factor of 20–40 for protonated aminoesters (see Table 7) is in all probability associated with the general acid catalysis by the N–H$^+$ group. This is confirmed by the decrease or disappearance of the above difference in compounds whose rigid structure prevents the approach of N$^+$–H to the ester group[252-256]. At the same time no evidence has been obtained for the N$^+$–H...O–C hydrogen bond in aminoesters by infrared spectroscopy[239,246-248] and PMR.[251] This suggests that the main effect in these instances is the stabilisation of a transition state close to the tetrahedral adduct (VII) as a result of proton transfer and the formation of the neutral compound (VIII) and not an increase of the charge δ$^+$ on the carbonyl carbon atom owing to the formation of a hydrogen bond, as suggested in a number of investigations[241,245,247,248]. The decrease of the degree of charge separation should lead to the "unfreezing" of the solvent and the corresponding gain of entropy of solvation. Indeed, it has been found[250] that the acceleration of the hydrolysis of the protonated forms of aminoesters is associated exclusively with the increase of the pre-exponential term (lg A). A similar conclusion was reached in a study of the hydrolysis of aminoacid esters[257]:



(VII) (VIII)

2. Acylation of Aminoalcohols

The hypothesis that nucleophilic catalysis by a tertiary amino-group is possible in the esterification reaction has been used for a long time to account for the large differences between the reactivities of the stereoisomers of heterocyclic aminoalcohols[258-263]. Thus it has been suggested[258] that 1-methyl-4-phenyl-4-piperidinols and *trans*-decahydro-4-quinolinols, having an axial OH group, react with propionyl chloride via the formation of an intermediate acylammonium salt and its intramolecular rearrangement via the mechanism



In epimers with an equatorial OH group, such rearrangement is difficult and acylation did not take place under the experimental conditions. It has been found[262,263] that only the 3-azabicyclo[3,3,1]nonan-9-ol isomer containing the OH and CH_3N groups in the *syn*-positions is acylated.

This mechanism was confirmed quantitatively for the first time in a study[264] where it was shown that, on passing from cyclohexanol to 1,3-dimethyl-4-piperidinol, the rate of benzoylation in tetrachloroethylene (at 25°C) increases by more than four orders of magnitude. This demonstrated the occurrence of intramolecular catalysis, the efficiency of which was appreciably higher for compounds with an axial OH group, which agrees well with qualitative data[258]. Comparison of the rate constants for the bimolecular process and the trimolecular benzoylation of cyclohexanol in the presence of *N*-methylpiperidine led to the conclusion that the intramolecular catalysis in these systems is approximately 100 times more effective than the intermolecular catalysis.

Data concerning the involvement of a tertiary amino-group in the acylation of acyclic aminoalcohols have been fairly contradictory until recently. Thus the acceleration of the esterification of the alcohols $(C_6H_5)_2C(OH)(CH_2)_nNR_2$ relative to non-nitrogen-containing analogues was not observed[265]. Possibly this was due to steric factors hindering the intramolecular catalysis, since a high reactivity of the aminoalcohols has been demonstrated qualitatively in a number of other investigations[266-268]. This was confirmed quantitatively for the first time in a study[269] of the reaction of benzoyl chloride with the alcohols $Ar(R)C(OH)(CH_2)_nNR'_2$ in dioxan. It was shown

that the introduction of the R'_2N group increases the reactivity of the alcohol by 6–8 orders of magnitude. The reaction was of first order with respect to the aminoalcohol in all cases, which demonstrates the occurrence of intramolecular catalysis, the efficiency of which decreases appreciably when $R' = CH_3$ is replaced by $R' = C_2H_5$ because of the steric hindrance to the formation of the aminoacyl salt. The ease of the subsequent $N \rightarrow O$ acyl migration was found to depend on the steric environment of the hydroxyl (Ar and R) and on the size of the ring formed.

The above correlation equations (9) and (10) for the benzoylation of alcohols in tetrachloroethylene and dioxan subjected to intermolecular catalysis by tertiary amines enabled us to calculate the rate of the hypothetical acylation of aminoalcohols under the conditions of catalysis by a second aminoalcohol molecule (k_{III}) and the ratio k_{II}/k_{III}, characterising the "effective" concentration of the catalyst. Table 8 shows that intramolecular catalysis is least effective in the esterification (in tetrachloroethylene) of diethylaminoethanol, which is most hindered among the alcohols investigated. The decrease of steric hindrance as a result of the increase in chain length of the replacement of the $(C_2H_5)_2N$ group by $(CH_3)_2N$ increases sharply the ratio k_{II}/k_{III}. An even more marked effect is attained when tetrachloroethylene is replaced by dioxan, which probably promotes proton transfer in the intermediate adduct.

Table 8. Acylation of aminoalcohols by benzoyl chloride at 25 °C.

Aminoalcohol	Tetrachloroethylene			Dioxan		
	$10^2 k_{III}$, litre^2 mole^{-2} s^{-1} [calc. from Eqn.(9)]	$10^2 k_{II}$, litre mole^{-1} s^{-1} (expt.)	k_{II}/k_{III}, mole litre^{-1}	$10^2 k_{III}$, litre^2 mole^{-2} s^{-1} [calc. from Eqn.(10)]	$10^2 k_{II}$, litre mole^{-1} s^{-1} (expt.)	k_{II}/k_{III}, mole litre^{-1}
$(C_2H_5)_2NCH_2CH_2OH$	0.24	0.092	0.4	0.23	4.7	20
$(C_2H_5)_2NCH_2CH_2CH_2OH$	0.23	2.2	9.6	0.20	21	108
$(CH_3)_2NCH_2CH_2CH_2OH$	5.0	35	7.0	4.5	1230	270
$(CH_3)_2NCH_2CH_2OH$	3.4	34.6	10.1	2.7	6400	2370

The steric factor probably also plays an important role in the reactivity of the stereoisomeric 2-dimethylamino-1-phenyl-1-propanols, among which the *erythro*-isomer is esterified much faster by benzoyl chloride in methylene chloride[270] than the *threo*-isomer (k = 1.0 and 0.0039 litre mole^{-1} s^{-1} respectively). According to the authors, this is also associated with the stronger hydrogen bond in the latter isomer, which decreases the accessibility of the nitrogen atom to nucleophilic attack.

V. EXAMPLES OF THE PRACTICAL APPLICATIONS OF TERTIARY AMINES AS ACCELERATORS OF ACYLATION REACTIONS

Since these problems have been described in detail[1,93], we shall consider only a few of comparatively new data. A series of studies by Korshak and coworkers on the polycondensation of aromatic acid dichlorides with bisphenols demonstrated the high catalytic efficiency of tertiary amines[7,271-272], the yield and the molecular weight of the polyarylate depending on the structure of the tertiary amine[7,99]. The polymers obtained are characterised by fairly narrow molecular weight distribution[271] and in many instances by a significant predominance of certain "frozen" rotational forms[272], which gives rise to the prospect of the synthesis of stereoregular polycondensation polymers. Thus it has been shown[273] that triethylamine gives rise to more complete interaction of diamines with tetracarboxylic acid dianhydrides accompanied by the formation of polyamides in the form of elastic films. Furthermore, tertiary amines are also effective catalysts of the synthesis of carborane-containing polyaminoamides; depending on the solvent and the structure of the tertiary amine employed, it is possible to obtain in this case soluble linear, soluble branched, or insoluble cross-linked polymers[274]. The use of tertiary amines as polycondensation catalysts leads in many instances to an improvement of the stability and mechanical and thermal properties of polyurethanes[275,276] and polyesters[277-279].

Examples of specific structural and stereospecific acylation in the presence of tertiary amines concern a different aspect of their application in acylation reactions. Thus, using triethylamine as the catalyst, Kurita achieved for the first time the direct selective *O*-tosylation of *o*-aminophenol[280]; it is of interest that, in the presence of pyridine, only *N*-acylation takes place. In the esterification of glycosides, it was also found that products involving the acylation of different hydroxyls are obtained on treatment with acetic anhydride and acetyl chloride in pyridine[281]. When sterically hindered alcohols, such as 1-methyl and 1-ethynylcyclohexanols, 2,4,6-trimethylphenol, etc., have to be acylated, 4-dialkylaminopyridine are effective catalysts[282]. The same substances have proved useful in the esterification of tertiary alcohols which are unstable in the presence of acids, namely linalool, 1,1-dimethoxy-4-methylpent-2-yn-4-ol, as well as methyl cholate and other steroid derivatives.

Generalisation and analysis of the accumulated data permit the conclusion that the possibilities of tertiary amines as acyl transfer catalysts have been by no means exhausted and further studies will undoubtedly expand the use of these compounds in industrial and laboratory practice.

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Lomonosov Moscow Institute of
Fine Chemical Engineering