RUSSIAN
CHEMICAL
REVIEWS
Uspekhi Khimii

May 1978

Translated from *Uspekhi Khimii*, 47, 777-803 (1978)

U.D.C. 541.128

# Bifunctional Catalysis

L.M.Litvinenko and N.M.Oleinik

The present state of the problem of bifunctional catalysis is considered and the influence of all possible factors (the structures of the reactants and catalysts, temperature, the properties of the medium, etc.) on the efficiency of bifunctional catalysts is discussed. The general characteristics of both the simplest bifunctional catalysts and enzymes are specified.
The bibliography includes 119 references.

CONTENTS

| | | |
|---|---|---|
| I. | Introduction | 401 |
| II. | Types of bifunctional catalysts | 402 |
| III. | Quantitative features of reaction kinetics | 404 |
| IV. | Energetic parameters in bifunctional catalysis | 410 |
| V. | The kinetic isotope effect of deuterium | 412 |
| VI. | Conclusion | 412 |

## I. INTRODUCTION

The concept of "polyfunctional catalysts" is nowadays fairly broad: substances of this kind may include both the simplest bifunctional compounds, such as acetic acid or 2-hydroxypyridine, and highly organised natural products such as enzymes. It is natural to suppose that all catalysts of this type have certain general properties, the determination of which for the simplest systems will make it possible to understand the characteristics of more complex systems. In other words, a low-molecular-weight bifunctional catalyst can be to a certain extent regarded as the simplest model of an enzyme, as has been frequently noted in the literature (see, for example, Refs. 1-4). There is no doubt that an increase in the complexity of the structure of a polyfunctional catalyst (for example, an increase of the number of groups involved in catalysis or an increase of the number of structural fragments in the skeleton to which the groups are attached) should lead to more or less significant changes in the mechanism of catalysis.

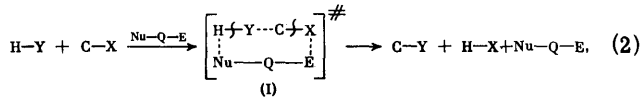
The problem of bifunctional catalysis by comparatively simple molecules is nowadays increasingly closely related to problems of polyfunctional catalysis by complex substances (polymeric catalysis, micellar catalysis, enzymatic catalysis). The ideas about bifunctional (and polyfunctional) catalysis are based on views developed by Lowry and Faulkner[5] as early as 1925 concerning the so called concerted catalysis, according to which two catalysts, acidic or basic, or in the general case electrophilic and nucleophilic, can act simultaneously on different parts of the reactants:

$$HY + C{-}X \xrightarrow{Nu+E} Nu \ldots HY \ldots C{-}X \ldots E \rightarrow C{-}Y + HX + Nu + E, \quad (1)$$

where Nu and E are respectively the nucleophilic and electrophilic catalysts accelerating the displacement by the

HY molecule (a nucleophile) of the species X (a nucleophile) being eliminated from the electrophilic molecule C–X.

In 1938 Shilov[6] put forward the following idea about bifunctional catalysis. If two catalytic groups (Nu and E) form part of the same molecule and are located in a rigorously defined manner, then such a catalyst should be more effective than in the case where the two groups form part of different molecules. As we shall see below, this idea proved to be extremely fruitful. It was tested experimentally[7] in the catalysis of the mutarotation of tetramethylglucose (TMG) in benzene by 2-hydroxypyridine. It was found that the activity of 2-hydroxypyridine is much higher than that of a mixture of phenol and pyridine at the same concentration despite the fact that 2-hydroxypyridine is inferior to the monofunctional compounds as regards both acidic and basic strength. The high efficiency of such catalysis can be accounted for solely by its bifunctional nature and the formation of cyclic transition states† of type (I) (general scheme):



(I) (2)

where Nu–Q–E is the bifunctional catalyst;

$$k_E + k_{Nu} \ll k_{Nu\text{-}Q\text{-}E}, \quad (3)$$

where $k$ are the corresponding rate constants, the subscript to which indicate the nature of a particular reaction. The involvement of cyclic transition states of this kind in the catalytic step should lower the energy barrier to the reaction (see Syrkin[8] and Section IV below) because electron transfer via the ring prevents a significant charge separation. The latter favours the reaction in a nonpolar medium, which, as will be shown below, has also been confirmed experimentally.

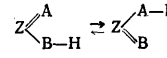
Towards the end of the 1950s and particularly in the early 1960s, studies on bifunctional catalysis were expanded. The following examples of reactions for which the action of bifunctional catalysts has been investigated more or less systematically may be quoted: the mutarotation of monosaccharides[7,9–16], enolisation reactions and processes in which enolisation is the stage activating the reactants (condensation, halogenation, etc. reactions)[17–31], reactions involving nucleophilic substitution at aromatic[32–36] and carbonyl carbon atoms (see, for example, Litvinenko[37] and other references to work by the authors of the present review) and peptide synthesis[38–41].

We believe that, on the basis of the analysis of the studies carried out to date all bifunctional catalysts can be divided into three conventional classes differing in the nature of the action of the catalyst and the type of bond formed between the catalysts and the reactants in the course of the catalytic process.

## II. TYPES OF BIFUNCTIONAL CATALYSTS

### 1. Tautomeric Bifunctional Catalysts

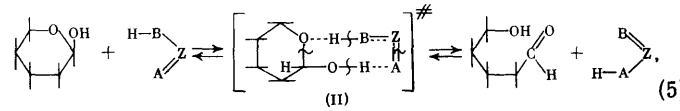
This term was introduced for the first time by Rony in 1969[11]. Catalysts of this type include all compounds which contain functional groups with opposed properties (nucleophilic and electrophilic) and which are involved in a tautomeric transformation of the catalyst:



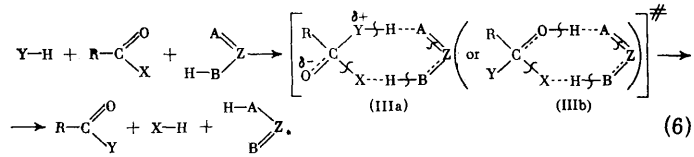
(4)

where Z is usually a carbon atom (but it can also be S, P, etc.), or a group of carbon atoms in a chain of conjugated bonds and forming part of the catalyst molecule, and A and B are usually O, S, or N. Such substances include carboxylic acids, their thio-analogues, sulphonic, sulphinic, phosphinic and other organophosphorus acids, derivatives of arsenic acid, 2-hydroxypyridine and analogous compounds, pyrazoles, etc. They are effective as catalysts when a proton has to be transferred during the reaction from one section of the reactant–substrate reaction complex to another, which promotes, overall, electron redistribution in the system and hence the reaction. The above catalysts have yet another characteristic feature—they are capable of forming hydrogen-bonded dimers (see, for example, data on the dimerisation of carboxylic acids[43], benzenesulphonic acid[43], 2-hydroxypyridine[44], and pyrazole[45]). The experimental facts show that substances incapable of such dimerisation usually do not exhibit bifunctional catalytic activity.

Catalytic activity is characteristic solely of the monomeric form of the catalyst. The formation of dimers blocks the functional centres of the catalyst and thus prevents the catalytic process, reducing the concentration of the active form of the catalyst[12,15,16,47]. The mechanism of the action of catalysts of this kind can be demonstrated in relation to the mutarotation of a monosaccharide or nucleophilic substitution at a carbonyl carbon atom:

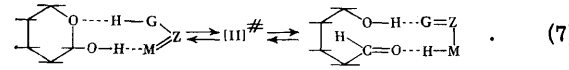


(II) (5)



(IIIa) (IIIb) (6)

Here R = aryl (Ar), alkyl (Alk), or R′CONHR″$CH_2$, X = halogen (Hal), RO, RS, RCO–O, etc., and Y–H = $H_2O$, ROH, $RNH_2$, ROCOCHR″$NH_2$, etc. In all cases bifunctional catalysts form associated species with the reactants via hydrogen bonding, which precede the cyclic transition states (II) or (III) and have structures similar to theirs. For example, the catalytic mutarotation of TMG can be represented as follows:



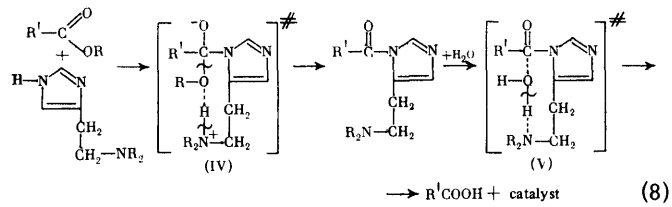
(7)

### 2. Covalent Bifunctional Catalysts

A characteristic feature of catalysts of this type is that, on interaction with the substrate, they form covalent bonds. Here we shall quote several examples of the hydrolysis of esters R′COOR and chloroalcohols as well as the elimination of 3-phosphoglyceraldehyde.

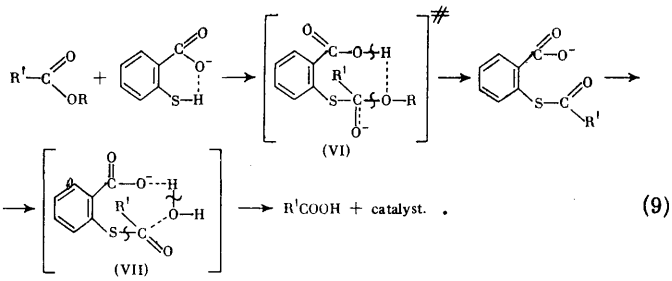
† For clarity, as in previous communications, the bond arising in transition states will be designated by dashed lines and the bond undergoing dissociation, by a crossed line.

The bifunctional mechanism of the catalysis of the hydrolysis of esters by *NN*-dialkylhistamine[48] [scheme (8)], incompletely ionised mercaptobenzoic acid[49] [scheme (9)] or catechol[50], etc. (see, for example Schatzle et al.,[51] Yakovlev and Rozengart[52], and Bender[1], pp.104–115) has been fully demonstrated:



(IV) (V)

$\longrightarrow R^1COOH + catalyst$ (8)



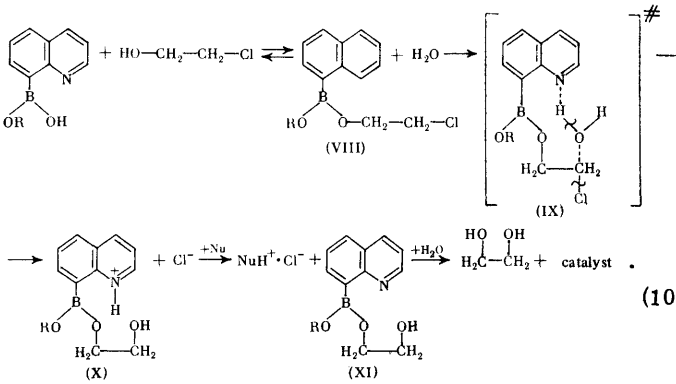
(VI) (VII)

$\longrightarrow R^1COOH + catalyst.$ (9)

According to scheme (8) polyfunctional imidazole derivatives such as *NN*-dialkylhistamines, which are more active than imidazole itself by 1–1.5 orders of magnitude, initially add to the ester via their heteroaromatic ring, in such a way that the subsequent elimination of the outgoing group with the aid of the dialkylammonium centre in the side chain [transition state (**IV**)] is promoted; this results in the formation of an intermediate acylimidazole derivative. Since this amide does not differ greatly in its reactivity from that of the initial esters, it is natural to postulate catalysis by the dialkylamino-side group also in the subsequent hydrolytic stage [transition state (**V**)]. The anions of *o*-mercaptobenzoic acid [scheme (9)] and catechol behave similarly.

As regards the nature of their activity, the bifunctional catalysts considered resemble hydrolytic enzymes, which usually form covalently linked enzyme–substrate complexes with ester molecules.

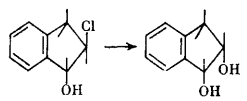
The hydrolysis of chloroalcohols $Cl-(CH_2)_n-OH$ (where $n$ = 2 or 3) in the presence of catalytic amounts of quinoline-8-boronic acid or its partial esters and collidine (Nu) in dimethylformamide is of considerable theoretical interest[53,54]:



(VIII) (IX) (X) (XI)

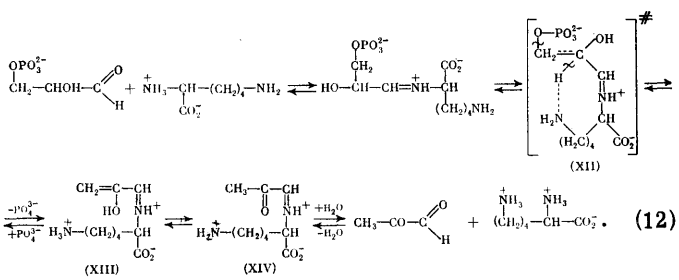
(10)

In this case quinoline-8-boronic acid accelerates the reaction approximately by an order of magnitude compared with the control experiment. It is of interest that quinoline-8-boronic acid exhibits a high stereospecificity in its activity, which may be demonstrated by the fact that, of the two possible stereoisomers of 2-chloro-1-indanol, only the *trans*-isomer undergoes catalytic hydrolysis. Under these conditions, the reaction proceeds with inversion of configuration, because only *cis*-1,2-indandiol is formed:



(11)

Certain elimination, enolisation, and isotope exchange reactions involving carbonyl compounds, catalysed by aminoacids and diamines, proceed with participation of covalently linked intermediates comprising the substrate and the catalyst. Thus lysine catalyses the conversion of 3-phosphoglyceraldehyde into pyruvic aldehyde[55] via the following mechanism:



(XII) (XIII) (XIV)

(12)

According to scheme (12), a lysine molecule forms an immonium cation with the substrate via the 2-amino-group, which then decomposes with participation of the second amino-group via the cyclic transition complex (**XII**) and gives rise to the intermediate (**XIII**) and the latter hydrolyses and is converted into pyruvic aldehyde with regeneration of the catalyst.

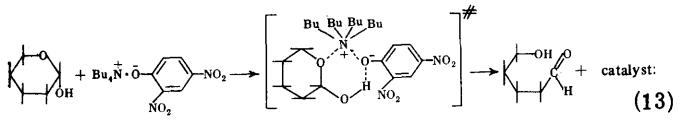
A similar mechanism of catalysis apparently obtains also in the exchange of deuterium in acetone-$d_6$ for hydrogen in an aqueous solution in the presence of diamines of the type $(CH_3)_2N-(CH_2)_n-NH_2$ (where $n$ = 2, 3, 4, or 5) and polyethylene-imines[56], which are more effective approximately by an order of magnitude than the monoamines having similar $pK_a$ values. As regards the nature of their action, the above diamine catalysts resemble the so called pyridoxal enzymes, in the presence of which pyridoxal phosphate forms with the substrate a Schiff base, which then undergoes various rearrangements (see, for example, Poltrak and Chukhrai[57] and Jencks[2], p. 112).

Whereas tautomeric catalysts must contain two functional groups with opposite properties (nucleophilic and electrophilic), which undergo interconversions, this requirement is not obligatory for covalent catalysts. They therefore include substances containing functional groups of different types (nucleophilic and electrophilic—quinoline-8-boronic acid, monoanions of mercaptobenzoic acid and catechol, etc.) as well as groups of the same type (both nucleophilic—diamines and amino-acid anions).

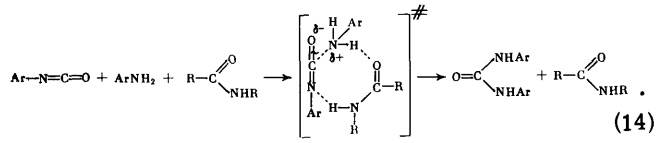
Yet another characteristic feature of covalent catalysts emerges from the foregoing considerations. Reactions with their participation must always involve intermediate stages with intramolecular catalytic action leading to the formation of cyclic transition states.

### 3. Bifunctional Solvation Catalysts

In a general form the mechanism of the action of solvation catalysts can be represented by scheme (2), but, in contrast to tautomeric catalysts, they are not directly involved in bond redistribution. Nor do these catalysts form covalent bonds with the reactants. Solvation catalysts activate via cyclic transitions states of type (I) certain sections of the reactants, either as a result of the formation of hydrogen bonds or as a result of electrostatic, dispersion, and other forces. Consequently, the nature of the forces in the interaction of a bifunctional solvation catalyst with reactants is the same as in specific and nonspecific solvation. As an example of catalytic reactions of this type, one may quote the catalysis by ion pairs formed from 2,4-dinitrophenoxide and tetra-alkylammonium of the mutarotation of TMG in benzene[16] [scheme (13)], the catalysis by amides of the reactions of phenyl isocyanate with amines[58] [scheme (14)], and the analogous reactions of ketens with alcohols[59]:




(13)



(14)

It follows from experimental data[58,59] that the above catalysts are less effective in reactions (13) and (14) by approximately 1–2 orders of magnitude than tautomeric catalysts such as carboxylic acids.

The acceleration of the solvolysis of t-butyl bromide[60] and the decarboxylation of malonic acid[61] by dihydric phenols and alcohols, which are appreciably more effective than the corresponding monofunctional analogues, may be apparently also regarded as solvation catalysis.

## III. QUANTITATIVE FEATURES OF REACTION KINETICS

Analysis of all the available results shows that, among the three classes of catalysts discussed above, bifunctional tautomeric catalysts exhibit the greatest efficiency, because they promote bond redistribution as a result of the simultaneous transfer of two protons via the cyclic system without any appreciable charge separation. Since catalysts of this class have been most thoroughly investigated, we shall consider further the main characteristics of the action of tautomeric catalysts. The data quoted below will probably prove useful also in understanding the properties of other classes of polyfunctional catalysts.

### 1. The Influence of the Structure of Bifunctional Tautomeric Catalysts on Their Activity

The influence of the structure of bifunctional catalysts on their activity has been most thoroughly studied in relation to the acylation of arylamines by carboxylic acid halides and anhydrides[62–68], the aminolysis of esters[11,69], peptide formation[39,40,70], and the mutarotation of tetramethylglucose[7,9,10–13,15] in non-polar aprotic media. In the above studies the catalytic rate constants $k_m$ were determined quantitatively on the basis of the following general relation between the observed rate constant $k_{obs}$ and the analytical catalyst concentration $m$:

$$k_{набл} = k_0 + k_m\, m\alpha, \qquad (15)$$

where $k_0$ is the non-catalytic rate constant, $\alpha$ the degree of dissociation of the catalyst dimers into monomers, and $m\alpha$ the concentration of the monomeric form of the catalyst. Eqn. (15) reflects quantitatively the fact, noted above, that only the monomeric form of the catalyst exhibits catalytic activity‡.

**Table 1.** The efficiencies of certain monofunctional and bifunctional catalysts in acylation and peptide formation* reactions (in benzene at 25°C).

| No. | Catalyst | $k_m$, (1), litre$^2$ mole$^{-2}$ s$^{-1}$ | $k_m/k_0$, (1), litre mole$^{-1}$ | $k_m$, (2), litre$^2$ mole$^{-2}$ s$^{-1}$ | $k_m/k_0$, (2), litre mole$^{-1}$ |
|---|---|---|---|---|---|
| 1 | Acetic acid | 0.450 | 132 000 | 280 | 2 900 000 |
| 2 | 2-Hydroxypyridine | 10**72 | 28 500 | 5,6 | 60 000 |
| 3 | 5-Bromo-2-hydroxypyridine | 0.112 | 83 000 | 33,0*** | 165 000 |
| 4 | *N*-Methyl-2-pyridine | 0 | 0 | 0 | 0 |
| 5 | 2-Methoxypyridine | 0 | 0 | — | — |
| 6 | Pyridine | 0 | 0 | 0 | 0 |
| 7 | 3,4-Dinitrophenol | 0**73 | 0 | — | — |
| 8 | 3-Hydroxypyridine | 0 | 0 | — | — |

* (1) acylation reaction: $C_6H_5COF + m\text{-}ClC_6H_4NH_2$, $k_0 = 3.4 \times 10^{-6}$ litre mole$^{-1}$ s$^{-1}$;[71] (2) peptide formation reaction: Z-gly-OPAP + t-BEG, $k_0 = 9.6 \times 10^{-5}$ litre mole$^{-1}$ s$^{-1}$,[70] where Z-gly = $C_6H_5CH_2OCONHCH_2CO-$, OPAP = $-O-C_6H_4-N=N-C_6H_5$, and t-BEG = t-butyl ester of glycine.

** For the interaction with *p*-anisidine.

*** Reaction in chlorobenzene.

The bifunctional nature of the catalysis in the above instances has been demonstrated in relation to a large number of examples. Swain's evidence[7] in support of the bifunctional activity of 2-hydroxypyridine in mutarotation has already been mentioned. Table 1 presents data indicating the occurrence of bifunctional catalysis by carboxylic acids, 2-hydroxypyridine, and its derivatives in the peptide formation reaction and in the acylation of amines by an acid halide in benzene§. Thus 2-hydroxypyridine and its 5-bromo-derivative (Table 1, Nos. 2 and 3) are powerful catalysts both in the peptide formation reaction and in the

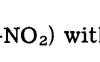
---

‡ In certain cases (mutarotation of TMG[10,12], acylation of strong amines[63], and peptide formation[39,40]) a correction must be introduced into Eqn. (15) for the formation of inactive associated species comprising the catalyst and the reactants (see also below).

§ Here and henceforth the catalytic activity of a particular catalyst is estimated as the ratio $k_m/k_0$. This quantity is extremely convenient for comparing the efficiencies of organic catalysts, exhibiting their activity in a wide variety of reactions under a wide variety of conditions.

acylation of arylamines by benzoyl fluoride, while 3-hydroxypyridine (Table 1, No. 8) and other monofunctional substances, containing only one acid or basic group, exhibit no activity (Table 1, Nos. 4–7). Acetic acid (Table 1, No. 1) exhibits a very high activity, while 3,4-dinitrophenol, which has a comparable acid strength (Table 1, No. 7, a monofunctional acid), as well as a base such as pyridine (Table 1, No. 6) show no catalytic activity whatever in the instance under consideration.

The data in Table 2 indicate the bifunctional nature of the catalysis by pyrazole in peptide formation. Indeed both phenol and *N*-methylpyrazole hardly catalyse the above reaction, while pyrazole itself is fairly effective. It is of interest that a pair of compounds such as imidazole and its *N*-methyl derivative exhibit low and approximately the same catalytic activities. Taking this factor into account as well as the fact that the disposition of the functional centres in imidazole is unfavourable for bifunctional catalysis and the considerable basicity of the latter pair of compounds (Table 2), we suggest that the usual base catalysis operates in this instance.

**Table 2.** The efficiencies of pyrazole, imidazole, and certain monofunctional compounds in the reaction of Z-gly-ONP (ONP = –O–  –$NO_2$) with t-BEG (in benzene at 25° C; $k_0 = 5.7 \times 10^{-4}$ litre mole$^{-1}$ s$^{-1}$ [74]).

| Catalyst | $k_m$, litre$^2$ mole$^{-2}$ s$^{-1}$ | $k_m/k_0$, litre mole$^{-1}$ | $pK_a$" (Ref.77) |
|---|---|---|---|
| Pyrazole (Ref.75) | 1.74 | 3000 | 2.47 |
| *N*-Methylpyrazole (Ref.75) | 0.01 | 17 | 2.04 |
| Phenol (Ref.85) | 0 | 0 | |
| Imidazole (Ref.76) | <0.49 | <850 | 6.95 |
| *N*-Methylimidazole (Ref.76) | 0.49 | 850 | 7.33 |

The bifunctional mechanism of the catalysis by carboxylic acid and 2-hydroxypyridine derivatives is described by the general scheme (6). The mechanism of the catalysis by pyrazole can be represented by an analogous scheme[75].

Table 3 as well as other data (see, for example, Rony[11,12]) show that, among all the bifunctional catalysts investigated in a wide variety of different types of reaction, the highest catalytic activity is shown by carboxylic acids, phosphinic acids, and 2-hydroxypyridine.

An attempt was made[12] to investigate the catalytic activity of strong bifunctional acids such as benzenearsenic, benzenesulphonic, benzenesulphinic, etc. acids, in the mutarotation of TMG in non-polar media. Owing to experimental difficulties, it was not possible to calculate the values of $k_m$ for the above substances. However, qualitative comparisons with other bifunctional catalysts showed that the strong acids have efficiencies comparable to those of phosphinic acids of the type $R_2POOH$, where R may be alkyl, aryl, and aryloxy-groups.

Depending on the nature of the reaction investigated, the relative activities of phosphinic acids, carboxylic acids, and 2-hydroxypyridine may vary. Thus carboxylic acids are most active in peptide formation, being followed in this respect by 2-hydroxypyridine and phosphinic acids (Table 3). In the mutarotation of TMG and in the acylation of arylamines by acetic anhydride phosphinic acids are the most effective and are followed in this respect by carboxylic acids and then 2-hydroxypyridine (Table 3, Nos. 1–8). The change in the order of the catalytic activities of bifunctional catalysts as a function of the nature of the model reaction may have a number of causes. We shall consider one of these.

**Table 3.** The efficiencies of bifunctional tautomeric catalysts ($k_m/k_0$, litre mole$^{-1}$) in various reactions in benzene and chlorobenzene at 25° C.

| No. | Catalyst | Reaction* | | | | |
|---|---|---|---|---|---|---|
| | | (1) | (2) | (3) | (4) | (5) |
| 1 | $CH_3COOH$ | 40 000** | 300[80] | 1 200[78] | 1 200 000[40] | — |
| 2 | $CCl_3COOH$ | 720 000** | 4800[63] | — | — | — |
| 3 | $C_6H_5COOH$ | 660 000 | 1200[80] | — | — | — |
| 4 | 2-Hydroxypyridine | 160 000 | 1700[71] | — | — | 30 000 |
| 5 | $(C_6H_5)HPOOH$ | 140 000 000 | — | — | — | — |
| 6 | $(C_6H_5)_2POOH$ | — | — | 105 000[67] | 14 000[79] | — |
| 7 | $(C_4H_9)_2POOH$ | — | 400[68] | 7 200[67] | 30 000[79] | — |
| 8 | $(C_6H_5O)_2POOH$ | 430 000 000 | — | — | 4 300[79] | — |
| 9 | Pyrazole | 910 | — | — | 3 000[75] | — |
| 10 | 2-Aminopyridine | 3 900 | — | — | — | 320 |
| 11 | 8-Hydroxyquinoline | — | — | — | — | 0 |
| 12 | Picric acid | 920 | — | — | — | — |

*Reactions: (1) mutarotation of TMG[12], $k_0 = 0.65 \times 10^{-5}$; (2) $C_6H_5COCl + m\text{-}ClC_6H_4NH_2$, $k_0 = 3.3 \times 10^{-3}$; (3) $(CH_3CO)_2O + m\text{-}ClC_6H_4NH_2$, $k_0 = 7.6 \times 10^{-4}$; (4) Z-gly-ONP + t-BEG, $k_0 = 5.7 \times 10^{-4}$; (5) Z-gly-OPAP + t-BEG, $k_0 = 2.0 \times 10^{-4}$ litre mole$^{-1}$ s$^{-1}$; reactions (1)–(4) were carried out in benzene and reaction (5) in chlorobenzene. **Values taken from Kergomard and Renard[15], where, in contrast to Rony and Neff[12], no account was taken of the association of the catalyst with TMG, which decreases $k_{obs}$.

When arylamines are acylated by acid anhydrides and chlorides, bifunctional catalysts more acidic than acetic and benzoic acids (for example trichloroacetic acid) exhibit, together with the catalytic effect observed at low catalyst concentrations, also an inhibitory activity[63] as the catalyst concentration rises (see Fig. 1). This can be accounted for by the interaction of the catalyst with the amine, leading to the formation of an unreactive salt:

$$R{-}COOH + R{-}NH_2 \rightleftarrows RCOO^- \cdot \overset{+}{N}H_3R \quad \text{(XVII)}. \qquad (16)$$

Salt formation interferes with catalysis even more in the aminolysis of esters by aliphatic amines[81] and in peptide formation reactions[39,40]. In these reactions even acetic acid, which in this instance exhibits the highest activity, is catalytically active only at low concentrations (up to 0.01 M). At higher concentrations inhibition takes place. It is extremely likely that this is the reason as already mentioned, why the stronger phosphinic acids exhibit a much smaller catalytic effect in the peptide formation reaction than carboxylic acids and 2-hydroxypyridine.

The high catalytic activity of tautomeric catalysts has also been confirmed by the quantum-chemical calculations carried out by Gold[13] using the Hückel method: in the calculations account was taken of the fact that during the catalytic step, a $\pi$-electron distribution, analogous to that demonstrated in scheme (5), takes place in the catalyst. The interaction indices $\xi$ calculated for these conditions

constitute a linear combination of general perturbations in the functional groups of the catalyst during the formation of the cyclic transition state (II) and characterise the energy gain as a result of such electron distribution. The values of $\xi$ for a number of catalysts are presented in Table 4. The indices reflect the capacity of the bifunctional catalyst for a tautomeric transformation in the course of the catalytic reaction. It follows from the data in Table 4 that there is a linear correlation between the values of $\lg k_{obs}$ (calculated for constant TMG and catalyst concentrations) and the interaction index $\xi$.[13] This suggests that the following linear relation should exist in its turn, other conditions being equal, between the catalytic activity of a bifunctional catalyst and the rate of conversion of its tautomeric form involved in the catalytic step into another form (the relation follows from the principle of the linear relation between the free energy changes):

$$\lg k_m = a + b \lg k_{taut}, \qquad (17)$$

where $k_{taut}$ is the rate constant for the tautomeric transformation. In this theoretical treatment the simplest case is one where both tautomeric forms are identical (carboxylic, phosphinic, sulphonic, etc. acids, pyrazole). Under these conditions, the catalyst is immediately regenerated in the course of the catalytic step. The constant $k_{taut}$ is in this instant in essence the rate constant for proton exchange involving the catalyst dimers. The rate of the process can then increase only up to a limiting value determined by the rate of diffusion of the species in solution. Under these conditions, the catalytic activity of the bifunctional catalyst evidently also reaches the maximum possible value for a simple functional structure. Catalysis by diphenyl phosphate (Table 3, No. 8), which accelerates the mutarotation of TMG in benzene by approximately nine orders of magnitude, apparently approaches this limiting case. Such activity is comparable to that of enzymes (the lower limit of the acceleration of the reaction by the latter is by 9–11 orders of magnitude; see Jencks[2], p. 23).

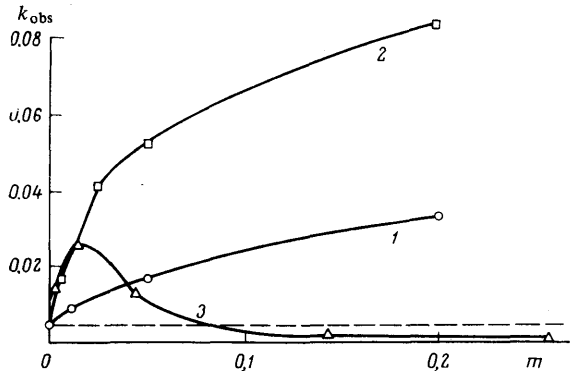
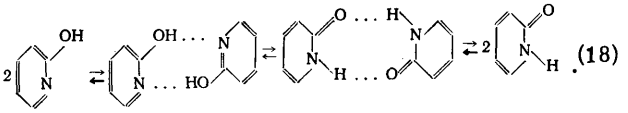



**Figure 1.** Dependence of the observed rate constant for the benzoylation of *m*-chloroaniline by benzoyl chloride on the analytical concentration (*m*) of carboxylic acids in benzene[63] at 25°C: 1) acetic acid; 2) monochloroacetic acid; 3) trichloroacetic acid.

The situation is more complex for bifunctional catalysts whose tautomeric forms are structurally non-equivalent. An example is provided by 2-hydroxypyridine, the two tautomeric forms of which are different and the equilibrium between them is determined by the solvent[82]:

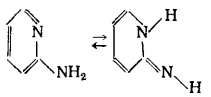

(18)

In conformity with the above considerations, the form which is more readily converted into the other tautomer, i.e. the less stable form present at a lower equilibrium concentration, should exhibit a higher catalytic activity. Or, what amounts to the same thing, the more stable form should exhibit a low catalytic activity. This conclusion is entirely logical and is indirectly confirmed by the examples quoted below.

**Table 4.** Comparison of experimental data for the catalytic activities of bifunctional catalysts in the mutarotation of TMG in benzene with the interaction indices $\xi$.[13]

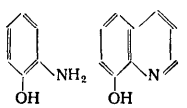
| Catalyst | $k_{obs}$, $s^{-1}$ | $\xi$ |
|---|---|---|
| Benzoic acid | 0.0636 | 0.206 |
| 2-Hydroxypyridine | 0.0163 | 0.0806 |
| 2-Hydroxy-4-methylquinoline | 0.00638 | 0.0789 |
| 2-Aminopyridine | 0.002 | 0.0230 |
| Picric acid | 0.00076 | 0 |

Substances for which tautomeric transformations are relatively unlikely show a lower catalytic activity or are altogether inactive. Thus 2-aminopyridine (Tables 3 and 4), which exists in the stable amino-form[83] (XVIII) whose conversion into the imino-form (XIX) via reaction (19) hardly occurs, behaves as a relatively ineffective catalyst in the mutarotation of TMG:


(19)

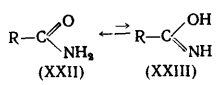
(XVIII) (XIX)

As already mentioned, 2-hydroxypyridine is an active catalyst of the peptide formation reaction and 2-aminophenol (XX)[11] and 8-hydroxyquinoline (XXI) (Table 3), which are incapable of undergoing a tautomeric transformation, are catalytically altogether ineffective:



(XX) (XXI)

Evidently carboxylic acid amides, for which form (XXIII) is thermodynamically unfavourable[84] and is not detected in a free state, do not exhibit bifunctional catalytic activity for the same reasons:


(20)

(XXII) (XXIII)

The absence of bifunctional activity in amides containing a hydrogen atom attached to the nitrogen atom has been frequently demonstrated[37,85] in relation to the acylation of arylamines by carboxylic acid halides and certain other related reactions.

Thus the bifunctional catalysis by the same amides in reactions involving phenyl isocyanates[58] and ketens[59] (see also the above discussion of solvation catalysts) must be assumed to have a solvation and not a tautomeric mechanism.

## 2. The Dependence of the Activities of Bifunctional Catalysts on Their Ability to Form Hydrogen Bonds

Yet another necessary condition for the manifestation of bifunctional catalytic activity is a distinct ability of the catalyst to form hydrogen bonds. This can be demonstrated in relation to catalysis by acetic acid and its thio-analogues of the acylation of arylamines by acetic anhydride and benzoyl chloride in benzene, and also in the mutarotation of TMG (Table 5). In the above experiments the structure of the reactant remained unchanged and only the nature of the catalyst was varied in such a way that it acquired different capacities for the formation of hydrogen bonds. Indeed, the catalytic activity of the acid fell sharply as the oxygen atoms were replaced by sulphur, although its strength increased significantly at the same time.

**Table 5.** The values of $k_m$ (litre$^2$ mole$^{-2}$ s$^{-1}$) and $k_m/k_0$ (litre mole$^{-1}$) for the reactions of benzoyl chloride and acetic anhydride with *m*-chloroaniline catalysed by acetic acid and its thio-analogues[80] and for the mutarotation of TMG[15] (in benzene at 25°C).

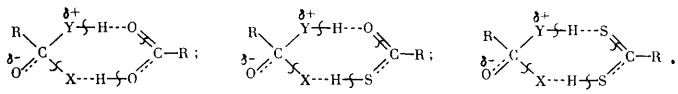
| Catalyst | $C_6H_5COCl+ArNH_2$ | | $(CH_3CO)_2O+ArNH_2$ | | Mutarotation of TMG | |
|---|---|---|---|---|---|---|
| | $k_m$ | $k_m/k_0$ | $k_m$ | $k_m/k_0$ | $k_m$ | $k_m/k_0$ |
| $CH_3$—CO—OH | 1.01 | 300 | 6.98 | 6200 | 0.26 | 40 000 |
| $CH_3$—CO—SH | 0.03 | 9 | — | — | 0.007 | 1 100 |
| $C_6H_5$—CO—SH | 0.03 | 9 | 0.47 | 400 | — | — |
| $CH_3$—CS—SH | 0 | 0 | 0 | 0 | — | — |

The main cause (although evidently not the only one) of the decrease of the efficiency of catalysis in the above series of catalysts is the reduced ability of the SH group to form hydrogen bonds[86,87], which hinders the combination of the participants in the catalytic step into cyclic transition states of type (II) or (III). Indeed, on passing from carboxylic acids to their thio-analogues, the capacity for association diminishes sharply. For example, thioacetic and thiobenzoic acids, which are relatively ineffective in catalysis, are not associated even in the liquid state[88]. However, dithioacetic acid, which exhibits no activity, is in fact capable of association (being significantly inferior in this respect to carboxylic acids), since it exists partly in the dimeric form in the liquid state; infrared spectra also indicate the presence of comparatively strong hydrogen bonds in this acid[88]. Thus the above catalysts can be arranged in the following sequences in terms of their catalytic activities and abilities to form hydrogen bonds:

$$R\text{—}COOH \gg R\text{—}COSH > R\text{—}CSSH \text{ (catalytic activity);}$$

$$R\text{—}COOH \gg R\text{—}CSSH > R\text{—}COSH \text{ (ability to form hydrogen bonds).}$$

The lack of a parallel variation of these two properties can apparently be explained by the fact that the formation of a hydrogen bond is a necessary but not sufficient condition for the manifestation of catalytic activity, because, as stated in the previous section, the ability of the catalyst to undergo a tautomeric transformation or, what amounts to the same thing, to transfer a proton via hydrogen bonds in the cyclic transition state, is more important. The rate of proton transfer is known to decrease in the following sequence: OH ... 0 > OH ...N > SH ... 0 > SH ...N > SH ...S.[89-91]. In catalysis by acetic acid rapid proton transfer may be ensured by both hydrogen bonds [see, for example, compound (XXIV)]; in the analogous reaction involving thioacetic acid [transition state (XXV)], only one of the two bonds effects proton transfer (the overall transfer is retarded), while in the presence of dithioacetic acid [transition state (XXVI)] there is no hydrogen bond of this kind, although, as already mentioned, each separately can in principle be somewhat stronger than the bond involving the SH group of thioacetic acid.



(XXIV) (XXV) (XXVI)

The important role of the hydrogen bond in bifunctional tautomeric catalysis has also been confirmed by theoretical calculations[14] (within the framework of the LCAO-MO SCF method in terms of the CNDO/2 valence approximation), carried out for the mutarotation of glucose catalysed by 2-hydroxypyridine. The calculations showed that the two hydrogen bonds in the cyclic glucose–2-hydroxypyridine complex are stronger than the two isolated bonds and initiate the rearrangement of the electron cloud of the substrate and catalyst during the catalytic step.

Thus the hydrogen bond is the factor which ensures the optimum mutual approach and relative arrangement of the bifunctional catalyst and the reactant, i.e. one may assume that in tautomeric bifunctional catalysis the catalytic reaction must be always preceded by the preliminary formation of cyclic associated species via hydrogen bonding between the reactants and the catalyst. The existence of such species is very difficult to demonstrate experimentally because, by their very nature, they must be naturally extremely unstable. However, their existence is indicated by the formation during the reactions of stable associated species stimulated by the bifunctional catalyst: the cyclic dimers of bifunctional catalysts[10,15,46,47] and associated species formed from the catalyst and one of the reactants. The presence of the latter has been noted, for example, in the catalytic acylation of amines[63], peptide formation[39,40], or the mutarotation of TMG[10]. Such associated species decrease the concentration of the active form of the catalyst and of the reactants, which is manifested by kinetic factors (see, for example, Refs. 10, 15, 39, 40, 46, 47, and 63).

## 3. The Influence of Substituents in Bifunctional Tautomeric Catalysts on Their Activity

In many instances the influence of substituents in bifunctional catalysts (carboxylic and phosphinic acids and substituted derivatives of 2-hydroxypyridine, see Table 6) has

been estimated by correlation analysis. The Taft or Hammett equation was used:

$$\lg k_m = \lg k_{m(cr)} + \rho^*\sigma^* \text{ (or } \rho\sigma). \quad (21)$$

It follows from the data in Table 6 that the introduction of electron-accepting substituents, which tend to increase the acid strength of the electrophilic part of the catalyst molecule and at the same time diminish the basic properties of the nucleophilic component, leads to increased activity of the catalyst in the vast majority of reactions investigated (with the exception of catalysis by carboxylic acids in dioxan and by phosphinic acids in benzene for reaction No. 9 in Table 6). The positive sign of $\rho^*(\rho)$ shows that the acid function of the catalyst plays the main role in the catalytic action.

Table 6. The values of $\rho^*(\rho)$ characterising the influence of substituents in a bifunctional catalyst on its catalytic activity* (values calculated from literature data are indicated in brackets; the solvents are indicated by capital letters, also in brackets, next to the numerals: B = benzene; N = nitrobenzene; C = chlorobenzene; D = dioxan).

| No. of reaction | Catalyst | RCOOH |  |  |
|---|---|---|---|---|
| | | t-$C_4H_9$, $CH_3$, $C_6H_5$, $CH_2Cl$, $CCl_3$ etc. | $C_4H_9$, $C_6H_5$, $C_6H_5O$ | H, 5-$CH_3$, 4-$CH_3$, 5-Cl, 5-Br |
| 1 | $C_6H_5COF + p\text{-}CH_3O-C_6H_4NH_2$ | — | — | (+1.8)(B)[71] |
| 2 | $C_6H_5COCl + m\text{-}Cl-C_6H_4NH_2$ | +0.41 (B) (Ref.66) | — | (~0) (B)[71] |
| 3 | $C_6H_5COCl + m\text{-}NO_2-C_6H_4NH_2$ | +0.13 (N) (Ref.66) | — | — |
| 4 | $(CH_3CO)_2O + m\text{-}Cl-C_6H_4NH_2$ | +0.68 (B) (Ref.66) | +0.79 (B)[67] | — |
| 5 | $(CH_3CO)_2O + m\text{-}NO_2-C_6H_4NH_2$ | +0.56 (N) (Ref.66) | — | — |
| 6 | $(CH_3CO)_2O + p\text{-}NO_2-C_6H_4NH_2$ | +0.72 (B) (Ref.66) | — | — |
| 7 | $CH_3CO-OC_6H_3(NO_2)_2 + C_6H_5NH_2$ | +0.18 (B) (Ref.69) +0.14 (D) (Ref.69) | — | — |
| 8 | Z-gly-OPAP + t-BEG | — | — | (+2.4) (X)[70] |
| 9 | + t-BEG | +0.24 (B)[40]** (−0.18) (D)[39]*** | −0.25 (B)[79]** | — |
| 10 | Mutarotation of TMG | (+0.50(B)[15] | — | — |

*The values of $\rho$ are approximate, because it is not known which value should be adopted for substituents in the 5-position: $\sigma_m$ or $\sigma_p$.

**R = H.

***R = $C_6H_5CH_2$–.

The low absolute values of $\rho^*$ ($\rho$), sometimes approaching zero, usually constitute an additional confirmation of the bifunctional nature of the catalysis, because the increase of the strength of the acid function in the catalyst molecule should stabilise the cyclic structure of the transition state and the weakening of the nucleophilic function should play a destabilising role to approximately the same extent.

The compensation effect is manifested particularly clearly in catalysis by carboxylic and phosphinic acid in the aminolysis of esters and in peptide formation (see reactions Nos. 7 and 9, Table 6). The low value of $\rho^*$ in the above instances can be accounted for by the fact that acylating agents with outgoing groups which are difficult to eliminate take part in these reactions (ArO is split off with greater difficulty than Cl, RCO–O, etc.[92]); in the elimination of these groups the abstraction of a proton from the attacking amine assumes great importance[93] and the role of the basic function of the bifunctional catalyst increases. The latter leads to more complete compensation of the effect of the acid and basic functions. The suggested enhancement of the role of proton abstraction from the attacking amine in the rate-determining stage with decrease in the tendency of the outgoing group to be eliminated is supported by the increased efficiency of base catalysis on passing from reactions involving acid anhydrides and halides, where there is no base catalysis[94], to the aminolysis of esters where the catalytic process involving a base-catalytic mechanism predominates over the non-catalytic process[93]. The role of the basic catalyst in the latter reactions reduces to the elimination of a proton from the attacking amine.

The negative values of $\rho^*$ in the catalysis of the peptide formation reaction by carboxylic acids in dioxan and by phosphinic acids in benzene (Table 6, No. 9) may indicate that in this instance the basic function of the bifunctional catalyst predominates over the acid function in the catalytic step.

## 4. The Influence of the Nature of the Reactants on the Activity of Bifunctional Catalysts

It follows from the data in Table 3 that a change in the structure of the reactants has a very significant influence on the catalytic activity of bifunctional catalysts. We shall consider a few more examples. Suppose that the outgoing group X in the acylating agent consists of various halogen atoms (ranging from F to I), the nature of which determines to a significant extent the strength of the hydrogen bonds involving them. It follows from the data in Table 7 that in the case of the fluoro-derivative, which exhibits a particularly striking ability to form a hydrogen bond, acetic acid has an exceptionally high catalytic activity (see the values of $k_m/k_0$), which falls sharply on passing to reactions involving the remaining acid halides. It has been shown[96] that under these conditions there is a linear correlation between the activity of the catalyst and the capacity of the outgoing group (the halogen) for the formation of a hydrogen bond. The increase of the ability of the halogen to form a hydrogen bond facilitates, as already mentioned, the formation of cyclic transition states of type III and hence promotes the catalytic processes.

The high activity of acetic acid in the reaction involving anhydrides (Table 7) can also be explained by the fact that the anhydride oxygen atom is able to form strong hydrogen bonds.

Table 8 shows that the catalytic activity of acetic acid increases on passing from the reaction of $p$-nitrophenyl thioacetate with benzylamine to the corresponding reaction of $p$-nitrophenyl acetate, which is also consistent with all the foregoing considerations. In this connection one should also mention that in the series of thioesters the catalytic activity of acetic acid increases with enhancement of the electrondonating properties of the outgoing thiophenoxide group ArS. In the latter case the cyclic transition complex is formed via ring closure involving a hydrogen bond of the type $\rangle$S...H–O–. This type of hydrogen bond can be fairly stable[97], while the opposite type $\rangle$O...H–S is always very weak. This is why carboxylic acids catalyse the aminolysis of thioesters, while thiocarboxylic acids are almost ineffective in the reactions of acid anhydrides and halides.

Thus the experimental study of the influence of the structure of the reactants on the catalytic activity of the

same bifunctional catalyst has confirmed the great importance of the formation of strong hydrogen bonds in cyclic transition states.

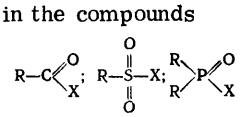
**Table 7.** Catalytic activity of acetic acid in the aminolysis of carboxylic acid halides[95] and anhydrides[78] (in benzene at 25° C).

| Reaction | $k_0$, litre mole$^{-1}$ s$^{-1}$ | $k_m$, litre$^2$ mole$^{-2}$ s$^{-1}$ | $k_m/k_0$, litre mole$^{-1}$ |
|---|---|---|---|
| $C_6H_5COHal$ + *p*-anisidine | | | |
| for Hal=F | 0.000225 | 66.1 | 294 000 |
| Hal=Cl | 1.21 | 171 | 141 |
| Hal=Br | 81.6 | 3250 | 40 |
| Hal=I | 192 | 7150 | 37 |
| $(CH_3CO)_2O$ + aniline | 0.00470 | 110 | 23 000 |

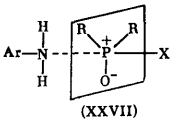
**Table 8.** The catalytic activity of acetic acid in the reaction of phenyl thioacetate and phenyl acetate derivatives with benzylamine[81] (in benzene at 25° C).

| R | $10^5k_0$, litre mole$^{-1}$ s$^{-1}$ | $k_m$, litre$^2$ mole$^{-2}$ s$^{-1}$ | $k_m/k_0$, litre mole$^{-1}$ |
|---|---|---|---|
| | $CH_3$—CO—S—$C_6H_4$R | | |
| 2.4-$(NO_2)_2$ | 113 000 | 0 | 0 |
| *o*-$NO_2$ | 1 630 | 145 | 9 000 |
| *p*-$NO_2$ | 101 | 99 | 100 000 |
| *m*-Cl | 1.3 | 12 | 900 000 |
| H | 0.15 | 6.5 | 4 000 000 |
| | $CH_3$—CO—O—$C_6H_4$R | | |
| 2.4-$(NO_2)_2$ | 59 000 | 0 | 0 |
| *p*-$NO_2$ | 29 | 25 | 800 000 |

From the standpoint of the influence of the structure of the reactant on the catalytic activity, the problem of the efficiency of the same bifunctional catalyst (for example, a carboxylic acid) in the aminolysis of acylating agents differing in the nature of the electrophilic centre is of interest. Comparison of data for catalytic nucleophilic substitution reactions at unsaturated carbon, sulphur, and phosphorus atoms in the compounds



showed that bifunctional catalysis by the acids RCOOH is clearly manifested only in the first instance[98]. This finding can be accounted for by the fact that the reaction involving substitution at a carbonyl carbon atom proceeds via the formation of transition states or intermediates [see scheme (6)] in which the constituent fragment of the bifunctional catalyst is complementary to the fragment formed from the reactants. Thus in the stereochemical sense a catalytic reaction involving substitution at the carbonyl carbon atom is entirely feasible. On the other hand reactions in which substitution is carried out at sulphur and phosphorus atoms proceed via transition states (intermediates) with the bipyramidal structure (**XXVII**):



(XXVII)

where the nucleophilic and electrophilic centres, which might be attacked by the bifunctional catalyst, are in the axial positions, i.e. are separated to the maximum possible extent. Cyclic transition complexes in the above two instances cannot therefore be achieved for stereochemical reasons.

The above examples show yet again how important is not only the nature of the functional centres in bifunctional catalysts and reactants but also their favourable disposition, necessary for the formation of a cyclic transition complex.

**Table 9.** The influence of substituents in the acylating agent and the primary arylamine on the catalytic activity of acetic acid characterised by $k_m/k_0$ (litre mole$^{-1}$) (in benzene at 25° C).

| R | Reaction | | | |
|---|---|---|---|---|
| | $C_6H_5COCl$ + R—$C_6H_4NH_2$[99] | $(CH_3CO)_2O$ + R—$C_6H_4NH_2$[76] | $(CH_3CO)_2S$ + R—$C_6H_4NH_2$[100] | *m*-Cl—$C_6H_4$—$NH_2$ + R—$C_6H_4COCl$[101] |
| *m*-$CH_3O$ | — | — | — | 215 |
| H | 193 | 23 000 | 16 000 | 306 |
| *p*-Cl | 273 | — | — | — |
| *m*-Cl | 300 | 12 000 | 13 000 | — |
| *m*-$NO_2$ | — | 6 700 | 15 000 | 487 |
| *p*-$NO_2$ | 285 | — | — | 476 |

The influence of substituents in both reactants (Table 9) on the catalytic activity of acetic acid in aminolysis has been investigated in a number of studies. It has been found that substituents in the *m*- and *p*-positions, both in the acylated amine and in the acylating agent, have only a slight influence on the catalytic activity of the bifunctional catalyst. However, if the substituent is directly at the reaction centre, as, for example, in *N*-alkyl-*m*-nitroaniline, then its effect is manifested to a much greater extent. Data concerning the influence of *N*-alkyl substituents in *m*-$NO_2$–$C_6H_4$–NHR on the catalytic activity of acetic acid in the reaction involving acetic anhydride in benzene at 25° C[102] are presented below:

| R | $10^3k_m$, litre$^2$ mole$^{-2}$ s$^{-1}$ | $k_m/k_0$, litre mole$^{-1}$ |
|---|---|---|
| H | 850 | 6500 |
| $CH_3$ | 28 | 340 |
| $C_2H_5$ | 11 | 240 |
| iso-$C_3H_7$ | 0.058 | 87 |

The data presented show that a gradual increase in the bulk of the substituent leads to a significant decrease of catalytic activity owing to the steric effect, while the role of the inductive effect is hardly significant under these conditions (cf. also in the data in Table 9). Consequently, N-alkyl groups in an aliphaticaromatic amine create steric hindrance to the formation of cyclic transition states, which reduces the activity of the bifunctional tautomeric catalyst.

### 5. The Influence of the Medium on the Activity of Bifunctional Catalysts

The problem of the influence of the medium on the activity of bifunctional catalysts has been investigated in many instances in relation to the reactions considered in this review. Analysis of the available results shows that, with increase of the polarity of a non-specific solvent, the reaction rate constants decrease in bifunctional catalysis. The quantitative dependence of the rates of catalytic reactions on the polar properties of the solvent is illustrated in Fig. 2, where the values of $\lg k_m$ are compared with the Kirkwood function. Line I refers to reactions involving the formation of a simple amide linkage in catalysis by acetic acid[78] and line II characterises the formation of a peptide bond catalysed by 2-hydroxypyridine[70]. The observed negative influence of the polarity of the medium agrees with the bifunctional mechanism of the catalysis. Indeed, as already mentioned, the small separation of the charges in the cyclic transition state of type III makes the polarity of the latter lower than that of the initial reactants. For this reason, polar solvents stabilise the initial state and hinder the formation of cyclic transition complexes, which reduces the rate.

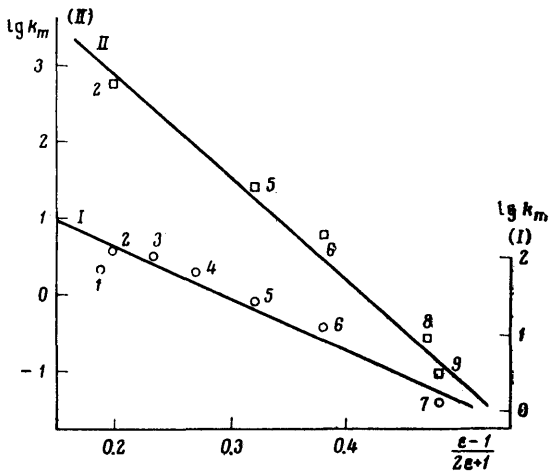



**Figure 2.** Dependence of $\lg k_m$ on $(\epsilon - 1)/(2\epsilon + 1)$ for the reaction of acetic anhydride with *m*-chloroaniline catalysed by acetic acid[78] (I) and for the reaction of the *p*-phenylazophenyl ester of *N*-benzyloxycarbonylglycine with *t*-butyl glycinate catalysed by 2-hydroxypyridine[70] (II) at 25° C; solvent: 1) hexane; 2) cyclohexane; 3)–5) cyclohexane–chlorobenzene mixtures with mole fractions of the latter of 0.106, 0.260, and 0.515 respectively; 6) chlorobenzene; 7) nitrobenzene; 8) benzonitrile; 9) acetonitrile. The values of $\lg k_m$ are plotted on the left-hand and right-hand ordinate axes for II and I respectively.

The results of a study of the catalytic activity of carboxylic acids in the reaction of 2,4-dinitrophenyl acetate with aniline in benzene and dioxan[69] at 25° C are presented below:

| Catalyst | $k_m/k_0$, litre mole$^{-1}$ | |
|---|---|---|
| | benzene | dioxan |
| $(CH_3)_3C—COOH$ | 11 000 | 5 |
| $CH_3—COOH$ | 11 000 | 6 |
| $ClCH_2—COOH$ | 19 000 | 10 |

The data presented (see also Rony[12]) show that the replacement of a non-specific solvent by a specific one (such as dioxan or alcohol¶), capable of forming strong hydrogen bonds with the reactants and the catalyst, also leads to a sharp decrease of catalytic activity because solvation by a specific solvent of the participants in the catalytic process and primarily of the catalyst itself, hinders the formation of cyclic transition states. Consequently the enhancement of the solvating capacity of the solvent (both specific and non-specific) leads to a decreased efficiency of bifunctional catalysis. Hence follows a conclusion which is important in practice: bifunctional catalysts are most effective in non-polar and weakly solvating media.

On the basis of the foregoing considerations, it is natural to expect that in water, which is a highly polar and specific solvent, bifunctional catalysis would be very difficult. For this reason, 2-hydroxypyridine behaves in aqueous solutions as an ordinary general basic catalyst, whose catalytic constant for the mutarotation of TMG falls on the usual Brønsted plot for basic substances with a slope $\beta = 0.37$.[12] Consequently the advantage of 2-hydroxypyridine as a bifunctional catalyst fully disappears in an aqueous medium. However, many reactions occurring in water are known in which bifunctional catalysis is nevertheless postulated. The carbonyl group is involved in one way or another in the above reactions; carboxylic acids, hydrogen phosphate anions, and dihydrogen phosphate anions may be used as bifunctional catalysts (in the hydrolysis of iminolactones[103], the addition of hydrogen peroxide to aldehydes[104], the hydration of aldehydes[105] and carbon dioxide[106], the hydrolysis of 1,3-diphenyl-2-imidazolium chloride[107], amides[108], acetimidate esters[109], etc.). One should note that the efficiency of bifunctional catalysts in water may be considerable[109].

Table 6 shows that, on passing from a non-polar solvent to a polar or specific solvent, the quantity $\rho^*$, characterising the sensitivity of the catalytic activity of the catalyst to the inductive influence of substituents in the latter (cf. reactions Nos. 2 and 3 and also 4, 5, and 6 in Table 6) decreases. The constant $\rho^*$ sometimes changes sign under these conditions (reaction No. 9). In the latter case a specific solvent (dioxan) forms hydrogen bonds with the catalyst, reducing its acid function in the catalytic step[69], so that the basic function becomes dominant in catalysis (see also subsection 4 in this Section). Evidently, a similar function is fulfilled, albeit to a lesser extent, by non-specific solvents when their polarity is altered, which accounts for the decrease of $\rho^*$ on passing from benzene to nitrobenzene.

## IV. ENERGETIC PARAMETERS IN BIFUNCTIONAL CATALYSIS

The formation of cyclic transition states of type I is accompanied by a decrease of the energy barrier relative to processes proceeding via linear transition states

¶ Phosphinic acids in alcohol do not catalyse the peptide formation reaction in contrast to their solutions in benzene[79].

(Tables 10 and 11; see also Section I). One of the main causes of such decrease of the activation energy on formation of cyclic transition states is electron transfer via the ring, i.e. via a closed bond redistribution chain (BRC) (see Poltorak and Chukhrai[57], p. 264), which prevents any significant charge separation and hence decreases the associated energy barrier. In addition, Shilov[110] examined yet another cause of the decrease of the activation energy, consisting in the steric characteristics of the formation of the cyclic transition state, as a result of which preference must be given to cyclic rather than linear transition states (even in the absence of a closed BRC system in the former). In other words, the cyclic system fixes the reacting species in the positions most favourable for the chemical process (the Franck–Condon principle). Both these factors are apparently manifested in catalysis by bifunctional tautomeric catalysts, while in the case of bifunctional covalent and solvation catalysts, where there is no electron transfer via a ring (there is no BRC), only the second factor operates, as a result of which the last two classes of catalysts are appreciably inferior, as already mentioned, to the first as regards their efficiency.

In discussing the energetic parameters of bifunctional catalysis, account must be taken of the complexity of catalytic reactions, i.e. of the fact that they consist of many stages. Since the catalyst forms preliminary associated species with the reactants (see Section I), the catalytic rate constant may be represented as the product of at least two constants:

$$k_m = K^* k'_m, \qquad (22)$$

where $K^*$ is the equilibrium constant for the formation of the preliminary associated species and $k'_m$ the rate constant for the reaction with participation of this associated species. According to Eqn. (22), the observed activation energy $E_a$ is defined by the equilibrium[111]

$$E_a = E'_{a(m)} - \bar{Q}_V, \qquad (23)$$

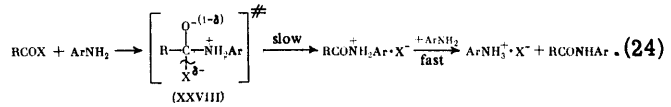
where $E'_{a(m)}$ is the activation energy for the stage characterised by the constant $k'_m$ and $\bar{Q}_V$ the heat of formation of the preliminary associated species. Since $\bar{Q}_V > 0$, it follows that $E_a$ is always less than the true value $E'_{a(m)}$. For this reason, the observed activation energies for catalytic reactions are negative in certain cases (see below), when $\bar{Q}_V > E'_{a(m)}$.

The energetic parameters were determined for the mutarotation of TMG (Table 10) and the acylation of arylamines by carboxylic acid chlorides, anhydrides, and esters (Table 11) stimulated by bifunctional catalysts. It follows from Table 10 that bifunctional catalysts of different types—2-hydroxypyridine and benzoic acid for the mutarotation of TMG—have virtually identical values of $E_a$ and $\Delta S^{\#}$. On passing to basic monofunctional catalysts (pyridine and diethylamine), the values of $E_a$ increase and those of $\Delta S^{\#}$ decrease. If the activation energies for catalysis by diethylamine and pyridine are extrapolated to the basicity of 2-hydroxypyridine, we obtain a value in excess of 20 kcal mole$^{-1}$. Consequently the activation energy for catalysis by 2-hydroxypyridine is lower by ~ 10 kcal mole$^{-1}$ than the value predicted for general base catalysis. This corresponds to an increase of the rate of reaction by a factor of ~ $10^7$. The increase of activation entropy on passing from basic to bifunctional catalysts is difficult to account for. For example, it has been suggested that this is associated with the change in the solvation shell of the transition complex (the freezing of the solvent in this shell)[12].

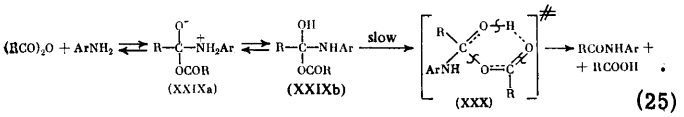
Whereas in the mutarotation of TMG the change from a monofunctional to a bifunctional catalyst leads to acceleration, mainly owing to the sharp decrease of the activation barrier, in the acylation reaction there is no such clear-cut behaviour. We may note that in acylation one may compare only the energetic parameters of the non-catalytic reaction (monofunctional catalysts are virtually ineffective) and the reaction stimulated by the bifunctional catalyst. Here it is possible to distinguish two groups of catalytic reaction.

1. Reactions to which correspond non-catalytic processes proceeding via non-cyclic transition states of type (XXVIII) [scheme (24)][100]. Reactions Nos. 1 and 3[100] and No. 5[112] belong to this class (Table 11).

2. Reactions to which correspond non-catalytic processes proceeding via cyclic transition states of type (XXX) or analogous states [scheme (25)][78,113]. These are reactions Nos. 2 and 4[100] and possibly Nos. 6[112] (Table 11):




(24)




(25)

Table 10. Energetic parameters for general base and bifunctional catalysis in the mutarotation of TMG in benzene[10,11].

| Catalyst | $E_a$, kcal mole$^{-1}$ | $-\Delta S^{\neq}$, e.u. | $pK_a^{base}$ in $H_2O$ |
|---|---|---|---|
| Benzoic acid | 11.4 | 21.5 | — |
| 2-Hydroxypyridine | 11.4 | 23.1 | 0.75 |
| Diethylamine | 14.3 | 26.3 | 10.98 |
| Pyridine | >16.6 | 26.3 | 5.17 |

Table 11. Energetic parameters for non-catalytic (I) and carboxylic acid-catalysed (II) acylation of $C_6H_5NH_2$ in benzene (the catalyst was $C_6H_5COOH$ in reaction Nos. 1 and 4 and $CH_3COOH$ in all others).

| No. of reaction | Acylating agent | $E_a$, kcal mole$^{-1}$ | $-\Delta S^{\neq}$, e.u. | $E_a$, kcal mole$^{-1}$ | $-\Delta S^{\neq}$, e.u. |
|---|---|---|---|---|---|
| | | I | | II | |
| 1 | $C_6H_5COCl$[100] | 7.7 | 40.2 | 1.4 | 49.8 |
| 2 | $(CH_3CO)_4O$[78] | 0 | 71.7 | 0,9 | 48,2 |
| 3 | $(CH_3CO)_2S$[100] | 8.7 | 38.3 | −1.8 | 54,2 |
| 4 | $(C_6H_5CO)_2O$[100] | 5.7 | 56.5 | 1.9 | 51.2 |
| 5 | $CH_3CO-SC_6H_3(NO_2)_2$[112] | 13.1 | 38.4 | 2.4 | 54.7 |
| 6 | $CH_3CO-SC_6H_5$[112] | 5.7 | 72.2 | 5.6 | 50.7 |

On passing from a non-catalytic to a catalytic process, both the activation energy and activation entropy for the first group of reactions decrease. This change of each energetic parameter has the opposite effect, as regards

sign, on the rate of the process, but the positive influence of the change in activation energy greatly predominates, so that catalysis ensues. This is understandable because cyclic transition states are involved in the catalytic process, unlike the non-catalytic process, which favours a decrease of activation energy. The decrease of activation energy mentioned above can be explained by the high degree of order [114] in the structure of the transition state in catalytic reactions, which is also consistent with its cyclic structure.

In another group of reactions, the change from a non-catalytic to a catalytic process entails virtually no change in activation energy, because both processes proceed via cyclic transition states. On the other hand, the rate increases mainly as a result of the increase of activation entropy. The latter apparently shows that in this instance the structure of the transition state in the non-catalytic reaction is more ordered than that in the catalytic reaction.

The activation energies for all reactions catalysed by carboxylic acids are very high (Table 11), while the activation entropies are almost constant. On this basis one may assume that the mechanism of the catalysis by carboxylic acids is the same for all the acylating agents investigated, i.e. is described by the general scheme (6).

## V. THE KINETIC ISOTOPE EFFECT OF DEUTERIUM

The cyclic structure of the transition state and the synchronous transfer of hydrogen atoms in the catalytic reaction with participation of bifunctional tautomeric catalysts is also confirmed by data obtained by isotopic labelling. Thus, when deuterated amines (in $NH_2$) and acetic acid (in OH) are used, a primary isotope effect is clearly observed in the case of acid halides (Table 12), becoming more intense on passing from the acid chloride to the fluoride, which forms stronger hydrogen bonds. This is consistent with the fact that, under the influence of a bifunctional tautomeric catalyst, two hydrogen atoms must be transferred in the rate-determining stage of the reaction. The increase in the ability of the reactant to form hydrogen bonds is in this case associated with the increase of the isotope effect (cf. $C_6H_5COCl$ and $C_6H_5COF$). The comparatively small isotope effect is consistent with the possibility of hydrogen transfer via a cyclic transition state [116].

**Table 12.** The kinetic isotope effect of deuterium in the reactions of benzoyl chloride and acetic anhydride catalysed by acetic acid ($CH_3COOH$ or $CH_3COOD$) (in toluene at 25° C).

| Reaction | $k_m^H/k_m^D$ |
|---|---|
| $C_6H_5COCl + p\text{-}Cl\text{—}C_6H_4NH_2$ [96] | 1.91±0.19 |
| $C_6H_5COF + p\text{-}Cl\text{—}C_6H_4NH_2$ [96] | 3.34±0.50 |
| $(CH_3CO)_2O + p\text{-}Cl\text{—}C_6H_4NH_2$ [115] | 1.00±0.10 |
| $(CH_3CO)_2O + m\text{-}NO_2\text{—}C_6H_4\text{—}NH\text{—}CH_3$ [115] | 0.86±0.26 |

On the other hand, in reactions of acetic anhydride catalysed by a carboxylic acid the isotope effect is altogether absent, in contrast to the reactions of acid halides (Table 12). The latter can be accounted for by the fact that in reactions of acetic anhydride a symmetrical transition state (IIIb) may be postulated in the catalytic process, where B, A, and X are oxygen atoms. Swain's "solvation rule" [117] is therefore applicable in this instance; according to this rule, there is no isotope effect under the following conditions: firstly, if hydrogen is transferred between atoms of the same type; secondly, if the hydrogen in the transition state is not involved in reacting bonds [117], i.e. bonds which are ruptured and formed directly at the reaction centre.

In catalytic reactions involving anhydrides it is found that both parts of Swain's rule are satisfied. Furthermore, both hydrogen atoms in (IIIb) are transferred under completely identical conditions and synchronously, which leads to the cancelling of all the influences resulting from the replacement of hydrogen atoms by deuterium atoms.

In the analogous reactions of acid halides, where a transition state (IIIa) may be formed in conformity with the mechanism of the non-catalytic process, the first part of the rule never holds. The transfer of both protons should therefore not take place entirely symmetrically and, as already mentioned, a small but appreciable isotope effect is observed.

## VI. CONCLUSION

As already mentioned at the beginning of the review bifunctional catalysts with a simple structure can be justifiably regarded as the simplest models of enzymes, because there is a definite similarity between these classes of substances. The similarity is manifested primarily by the fact that in both instances a major role is played by the preliminary association of the catalyst and the reactants, which results in the mutual approach and suitable relative orientation of the functional centres of the catalyst and the reactants, facilitating the reaction. Calculations [118] have shown that such mutual approach in enzymatic reactions reduces the length of the hydrogen bond to such an extent that a tunnel proton transfer at a rate exceeding that of diffusion-controlled processes becomes possible.

The next common feature of bifunctional catalysts and enzymes is the formation at the instant of the catalytic step of bond redistribution chains, which combine the reactant and catalyst molecules in the transition state into a single electronic system. The difference is that in enzymatic catalysis many-centre contacts are generated between the reactants and the catalysts, while in bifunctional catalysts only two-centre contacts, giving cyclic transition states, are produced. It is possible to distinguish two types of cyclic transition states.

1. States in which there is electron transfer via the ring formed when BRC undergo ring closure (bifunctional tautomeric catalysis). The occurrence of reactions via such states is particularly favourable, so that tautomeric catalysis is more effective than other types of bifunctional catalysis.

2. States in which BRC are either absent (solvation catalysis) or do not occur throughout the ring but only in the region where the catalyst is in contact with the reactants (bifunctional covalent catalysis).

Transition states of the first type are formed with participation of the catalyst, which contains two groups with opposite properties—electron-donating and electron-accepting—as a result of which these catalysts may be referred to as electrophilic-nucleophilic. Transition states of the second type may be formed, apart from the

electrophilic-nucleophilic catalysts, by catalysts containing in their molecules active functional groups with identical properties. One can then speak, for example, of nucleophilic-nucleophilic [see, for example scheme (8)] or electrophilic-electrophilic catalysts. Although the possibility of the existence of catalysts of this kind is easy to imagine, they are nevertheless still unknown.

In order to explain certain aspects of enzymatic catalysis, a hypothesis has been used recently[119], according to which the hydrophobic sections of the enzyme form around the catalytic groups in its active centre a non-polar aprotic medium which ensures the most favourable conditions for the catalytic activity of these groups. The optimum conditions for bifunctional tautomeric catalysis occur, as shown above, precisely in non-polar aprotic media, which, firstly, confirms the above hypothesis, and, secondly, indicates yet another feature common to the two types of catalysis compared.

The problem associated with the selectivity of the action of organic catalysts is more complex. The fundamental difference between organic catalysts and enzymes is in fact associated with this factor and not solely with activity. Organic catalysts are naturally very selective but they are nevertheless greatly inferior in this respect to enzymes. A further search for ways of increasing the selectivity of the action of organic catalysts will apparently involve the synthesis of more complex molecules with a definite distribution of functional groups, some of which, for example, may play the role of substrate binding and orientation centres, while others are the catalytic groups proper.

In the search for more complex bifunctional and polyfunctional catalysts distinguished by a high activity and selectivity account must be taken of the conclusions reached in this review. (1) Bifunctional tautomeric catalysts exhibit the highest activity. (2) Their catalytic activity is manifested most strikingly in a solvent with a low solvating capacity. (3) Bifunctional catalytic activity is particularly high when conditions for the formation of strong hydrogen bonds are created in cyclic transition complexes. This depends on the nature of the catalyst itself and on the properties of the reactants and the medium. (4) Both the presence of the relevant functional groups in the bifunctional catalyst molecule and their steric disposition, ensuring the formation of a cyclic transition state, are very important for the manifestation of a high activity by such a catalyst. This is determined not only by the structure of the bifunctional catalyst but to an equal extent by the properties of the initial reactants.

REFERENCES


1. M.L.Bender, "Catalysis of Nucleophilic Reactions of Carboxylic Acid Derivatives", Chem.Rev., 60, 53 (1960) (Translated into Russian), Izd.Mir, Moscow, 1964, p.157.
2. W.P.Jencks, "Catalysis in Chemistry and Enzymology" (Translated into Russian), Izd.Mir, Moscow, 1971, p.163.
3. P.G.Ashmore, "Catalysis and Inhibition of Chemical Reactions" (Translated into Russian), Izd.Mir, Moscow, 1966, p.66.
4. S.A.Bernhard, "Structure and Function of Enzymes" (Translated into Russian), Izd.Mir, Moscow, 1971, p.208.
5. T.Lowry and I.Faulkner, J.Chem.Soc., 2883 (1925).
6. E.A.Shilov, Dokl.Akad.Nauk SSSR, 18, 643 (1938).
7. C.Swain and J.Brown, J.Amer.Chem.Soc., 74, 2538 (1952).
8. Ya.K.Syrkin, Izv.Akad.Nauk SSSR, Ser.Khim., 239, 388, 600 (1959).
9. C.Swain, A.DiLeilo, and J.Cordner, J.Amer.Chem.Soc., 80, 5983 (1958).
10. P.Rony, J.Amer.Chem.Soc., 90, 2824 (1968).
11. P.Rony, J.Amer.Chem.Soc., 91, 6090 (1969).
12. P.Rony and R.Neff, J.Amer.Chem.Soc., 95, 2896 (1973).
13. H.Gold, J.Amer.Chem.Soc., 90, 3402 (1968).
14. H.Gold, J.Amer.Chem.Soc., 93, 6387 (1971).
15. A.Kergomard and M.Renard, Tetrahedron, 24, 6643 (1968).
16. A.Kergomard and M.Renard, Tetrahedron Letters, 769 (1968).
17. A.A.Yasnikov, K.I.Matkovskii, and E.M.Gaivoronskaya, Ukrain.Khim.Zhur., 28, 88 (1962).
18. T.S.Boiko, N.V.Volkova, and A.A.Yasnikov, Ukrain.Khim.Zhur., 29, 1179 (1963).
19. I.V.Melnikov and A.A.Yasnikov, Ukrain.Khim.Zhur., 30, 723 (1964).
20. I.V.Mel'nichenko, E.A.Shilov, and A.A.Yasnikov, Ukrain.Khim.Zhur., 30, 599 (1964).
21. A.A.Yasnikov, E.A.Shilov, and N.V.Volkova, Ukrain.Khim.Zhur., 30, 1313 (1964).
22. N.V.Volkova and A.A.Yasnikov, Dokl.Akad.Nauk Ukrain.SSR, 901 (1965).
23. N.V.Volkova, E.A.Shilov, and A.A.Yasnikov, Ukrain.Khim.Zhur., 31, 56 (1965).
24. N.V.Volkova, L.E.Koshechkina, and A.A.Yasnikov, Ukrain.Khim.Zhur., 34, 370 (1968).
25. L.P.Koshechkina, E.A.Shilov, and A.A.Yasnikov, Ukrain.Khim.Zhur., 35, 55 (1969).
26. L.S.Mushketik, N.V.Volkova, E.A.Shilov, and A.A.Yasnikov, Ukrain.Khim.Zhur., 38, 685 (1972).
27. L.P.Koshechkina, I.V.Mel'nichenko, and A.A.Yasnikov, Ukrain.Khim.Zhur., 38, 1248 (1972).
28. L.P.Koshechkina and I.V.Mel'nichenko, Ukrain.Khim.Zhur., 40, 172 (1974).
29. J.Hine, F.Rogers, and R.Notari, J.Amer.Chem.Soc., 90, 3279 (1968).
30. J.Hine, M.Sholod, and J.Jensen, J.Amer.Chem.Soc., 93, 2321 (1971).
31. J.Hine and W.Sachs, J.Org.Chem., 39, 1937 (1974).
32. B.Bitter and H.Zollinger, Angew.Chem., 70, 246 (1958).
33. H.Zollinger, Angew.Chem., 73, 125 (1961).
34. B.Bitter and H.Zollinger, Helv.Chim.Acta, 44, 812 (1961).
35. F.Pietra and D.Vitali, Tetrahedron Letters, 5701 (1966).
36. Nakano Naomi, E.Smissman, and R.Schowen, J.Org.Chem., 38, 4396 (1973).
37. L.M.Litvinenko, Ukrain.Khim.Zhur., 30, 317 (1964).
38. H.Beyerman, Maassen van den Brink, and F.Weygand et al., Rec.Trav.chim., 84, 213 (1965).
39. N.Nakamizo, Bull.Chem.Soc.Japan, 42, 1071, 1078 (1969).
40. L.M.Litvinenko, V.V.Kosmynin, Yu.A.Sharanin, and L.P.Drizhd, Reakts.Sposobn.Org.Soed., 34, 999 (1972).
41. L.M.Litvinenko, Yu.A.Sharanin, V.V.Kosmynin, and L.P.Drizhd, Dokl.Akad.Nauk SSSR, 200, 854 (1971).
42. J.Steigman and W.Cronkright, Spectrochim.Acta, 26A, 1085 (1970).

43. H. Kehiaian and C. Nenitzescu, Ber., 90, 685 (1957).
44. M. Krackow, C. Lee, and H. Mautner, J. Amer. Chem. Soc., 87, 892 (1965).
45. D. Anderson, J. Duncan, and F. Rossotti, J. Chem. Soc., 140 (1961).
46. L. M. Litvinenko, D. M. Aleksandrova, and N. I. Pilyuk, Ukrain. Khim. Zhur., **25**, 81 (1959).
47. L. M. Litvinenko and N. M. Oleinik, Ukrain. Khim. Zhur., **32**, 174 (1966).
48. V. Franzen, Angew. Chem., **72**, 139 (1960).
49. G. Schonbaum and M. Bender, J. Amer. Chem. Soc., **82**, 1900 (1960).
50. V. I. Rozengart, in "Aktual'nye Voprosy Sovremennoi Biokhimii" (Current Problems in Modern Biochemistry), Medgiz., Moscow, 1962, p. 47.
51. F. Schätzle, M. Rottenberg, and M. Thurkauf, Helv. Chim. Acta, **42**, 1708 (1959).
52. V. A. Yakovlev and E. V. Rozengart, Dokl. Akad. Nauk SSSR, **137**, 1467 (1961).
53. R. Letsinger, S. Daudegaouker, W. Vullo, and J. Morrison, J. Amer. Chem. Soc., 85, 2223 (1963).
54. R. Letsinger and J. Morrison, J. Amer. Chem. Soc., 85, 2227 (1963).
55. N. Ya. Kozlova, I. V. Mel'nichenko, and A. A. Yasnikov, Ukrain. Khim. Zhur., **34**, 1145 (1968).
56. J. Hine, M. Cholod, and R. King, J. Amer. Chem. Soc., 96, 835 (1974).
57. O. M. Poltorak and E. S. Chukhrai, "Fiziko-Khimicheskie Osnovy Fermentativnogo Kataliza" (Physicochemical Foundations of Enzymatic Catalysis), Izd. Vysshaya Shkola, Moscow, 1971, p. 220.
58. J. Briody and D. Narinesingh, Tetrahedron Letters, 4143 (1971).
59. H. Pracejus and R. Samtleben, Tetrahedron Letters, 2189 (1970).
60. K. Okamoto and H. Shingu, Bull. Chem. Soc. Japan, **34**, 1131 (1961).
61. M. Haleem, Coll. Czech. Chem. Comm., 35, 2854 (1970).
62. L. M. Litvinenko and D. M. Aleksandrova, Ukrain. Khim. Zhur., **26**, 66 (1960).
63. L. M. Litvinenko, D. M. Aleksandrova, and S. F. Prokopovich, Ukrain. Khim. Zhur., 27, 494 (1961).
64. L. M. Litvinenko and N. M. Oleinik, Zhur. Obshch. Khim., **33**, 2287 (1963).
65. L. M. Litvinenko, N. M. Oleinik, and G. D. Titskii, Dokl. Akad. Nauk SSSR, **157**, 1153 (1964).
66. L. M. Litvinenko, N. M. Oleinik, and M. N. Sorokin, Ukrain. Khim. Zhur., **34**, 357 (1968).
67. L. M. Litvinenko, G. D. Titskii, and O. P. Stepko, Dokl. Akad. Nauk SSSR, **202**, 1127 (1972).
68. G. D. Titskii, O. P. Stepko, and L. M. Litvinenko, Zhur. Org. Khim., 9, 2341 (1973).
69. L. M. Litvinenko, N. M. Oleinik, Yu. S. Sadovskii, and L. T. Golovan', Zhur. Org. Khim., 11, 359 (1975).
70. L. P. Drizhd, Candidate's Thesis, Donetsk State University, 1975.
71. L. M. Litvinenko, V. A. Savelova, and A. V. Skripka, Dokl. Akad. Nauk SSSR, **216**, 1327 (1964).
72. L. M. Litvinenko, N. M. Oleinik, and G. V. Semenyuk, Ukrain. Khim. Zhur., 35, 278 (1969).
73. L. M. Litvinenko, G. V. Semenyuk, and N. M. Oleinik, Dokl. Akad. Nauk SSSR, **176**, 1107 (1967).
74. V. V. Kosmynin, Yu. A. Sharanin, and L. M. Litvinenko, Zhur. Org. Khim., 8, 3 (1972).
75. L. M. Litvinenko, N. M. Oleinik, and I. P. Garkusha-Bozhko, Zhur. Org. Khim., **11**, 86 (1975).
76. N. M. Oleinik and I. P. Garkusha-Bozhko, "XI Respublikanskaya Konferentsiya po Fizicheskoi Khimii, Tezisy Dokladov" (The XIth All-Republic Conference on Physical Chemistry, Abstracts of Reports), UkrNIINTI, Kiev, 1974, Section 1, No. 2, p. 62.
77. "Fizicheskie Metody v Khimii Geterotsiklicheskikh Soedinenii" (Physical Methods in the Chemistry of Heterocyclic Compounds), Izd. Khimiya, Moscow–Leningrad, 1966, p. 110.
78. N. M. Oleinik, M. N. Sorokin, and L. M. Litvinenko, Ukrain. Khim. Zhur., 38, 343 (1972).
79. L. M. Litvinenko, B. I. Geras'kov, N. M. Oleinik, and G. D. Titskii, "XI Respublikanskaya Konferentsiya po Fizicheskoi Khimii, Tezisy Dokladov" (The XIth All-Republic Conference on Physical Chemistry, Abstracts of Reports), UkrNIINTI, Kiev, 1974, Section 1, No. 1, p. 41.
80. L. M. Litvinenko and N. M. Oleinik, Symposium, "Kataliz i Katalizatory" (Catalysis and Catalysts), Izd. Naukova Dumka, Kiev, 1965, p. 120.
81. N. M. Oleinik, L. M. Litvinenko, L. P. Kurchenko, and N. V. Vasilenko, Ukrain. Khim. Zhur., **42**, 58 (1976).
82. A. R. Katritzky, Chimia (Switz.), **24**, 134 (1970).
83. C. Anggal and R. Werner, J. Chem. Soc., 2911 (1952).
84. I. I. Grandberg, "Organicheskaya Khimiya" (Organic Chemistry), Izd. Vysshaya Shkola, Moscow, 1974, p. 375.
85. L. M. Litvinenko and G. D. Titskii, Dokl. Akad. Nauk SSSR, **166**, 366 (1966).
86. G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond" (Translated into Russian), Izd. Mir, Moscow, 1964, p. 174.
87. L. J. Bellamy, "The Infrared Spectra of Complex Molecules" (Translated into Russian), Inostr. Lit., Moscow, 1963, p. 499.
88. L. J. Bellamy, "Advances in Infrared Group Frequencies" (Translated into Russian), Izd. Mir, Moscow, 1971, p. 306.
89. M. Eigen, Discuss. Faraday Soc., 39, 7 (1965).
90. G. S. Denisov, E. M. Kazakova, and E. V. Ryl'tsev, Zhur. Prikl. Spektrosk., 8, 690 (1968).
91. M. Ahrens and G. Maas, Angew. Chem., 80, 848 (1968).
92. D. Satchell, Chem. Ind. (London), 683 (1974).
93. N. M. Oleinik, L. M. Litvinenko, Yu. S. Sadovskii, B. G. Igolkina, A. A. Popkova, and S. E. Terekhova, Dokl. Akad. Nauk SSSR, **213**, 390 (1973).
94. L. M. Litvinenko and A. I. Kirichenko, Dokl. Akad. Nauk SSSR, **126**, 97 (1967).
95. L. M. Litvinenko and G. V. Semenyuk, Reakts. Sposobn. Org. Soed., 7, 1083 (1970).
96. N. M. Oleinik, L. M. Litvinenko, and M. N. Sorokin, Zhur. Org. Khim., 9, 1693 (1973).
97. I. V. Zuika and Yu. A. Bankovskii, Uspekhi Khim., **42**, 39 (1973) [Russ. Chem. Rev., No. 1 (1973)].
98. L. M. Litvinenko, V. A. Savelova, G. V. Semenyuk, N. G. Razumova, and L. F. Fedorova, Paper deposited at the All-Union Institute of Scientific and Technical Information (VINITI) [No. 1783 (1975)].
99. L. M. Litvinenko and D. M. Aleksandrova, Ukrain. Khim. Zhur., **27**, 487 (1961).
100. L. M. Litvinenko, N. M. Oleinik, and L. P. Kurchenko, Reakts. Sposobn. Org. Soed., 6, 832 (1969).

101. G.V.Semenyuk, N.M.Oleinik, and L.M.Litvinenko, Zhur.Obshch.Khim., 38, 2009 (1968).
102. L.M.Litvinenko and N.M.Oleinik, Reakts.Sposobn. Org.Soed., 2, No.2 (4), 57 (1965).
103. B.Cunningham and G.Schmir, J.Amer.Chem.Soc., 88, 551 (1966).
104. E.Sander and W.Jencks, J.Amer.Chem.Soc., 90, 4377 (1968).
105. J.Pocher and J.Meany, J.Phys.Chem., 71, 3113 (1967).
106. B.Gibbson and J.Edsall, J.Biol.Chem., 238, 3502 (1963).
107. D.Robinson and W.Jencks, J.Amer.Chem.Soc., 89, 7088 (1967).
108. R.Schowen and G.Zuorick, J.Amer.Chem.Soc., 88, 1223 (1966).
109. R.Chaturvedi and G.Schmir, J.Amer.Chem.Soc., 90, 4413 (1968).
110. E.A.Shilov, Zhur.Vses.Khim.Obshch.im.Mendeleeva, 7, 419 (1962).
111. N.M.Oleinik, Yu.S.Sadovskii, L.M.Litvinenko, and L.Ya.Tkacheva, Zhur.Org.Khim., 10, 2553 (1974).
112. L.M.Litvinenko, N.M.Oleinik, L.P.Kurchenko, V.K.Yushko, Ukrain.Khim.Zhur., 38, 1235 (1972).
113. L.M.Litvinenko, N.M.Oleinik, and M.N.Sorokin, Symposium, "Voprosy Stereokhimii" (Problems of Stereochemistry), Izd.Kiev, Gos.Univ., Kiev, 1971, No.1, p.43.
114. V.A.Roiter, "Vvedenie v Teoriyu Kinetiki i Kataliza" (Introduction to The Theory of Kinetics and Catalysis), Izd.Naukova Dumka, Kiev, 1971, p.35.
115. L.M.Litvinenko, N.M.Oleinik, and M.N.Sorokin, "Vvedenie v Teoriyu Kinetiki i Kataliza" (Introduction to The Theory of Kinetics and Catalysis), Izd. Naukova Dumka, Kiev, 10, 770 (1974).
116. G.P.Miklukhin, "Izotopy v Organicheskoi Khimii" (Isotopes in Organic Chemistry), Izd.Akad.Nauk Ukrain.SSR, Kiev, 1961, p.634.
117. C.Swain, K.Kuhn, and R.Schowen, J Amer.Chem. Soc., 87, 1553 (1965).
118. H.Gold, Int.J.Quant.Chem., 5, 353 (1971).
119. F.Menger and A.Vitale, J.Amer.Chem.Soc., 95, 4931 (1973).

Institute of Physical Organic Chemistry
and the Chemistry of Coal of the Academy
of Sciences of Ukrainian SSR, Donetsk
State University, Donetsk