Translated from *Uspekhi Khimii*, 47, 2044 - 2064 (1978) U.D.C. 547.571; 547.595; 546.171.8; 541.127; 541.124

Schmidt Reaction with Aldehydes and Carboxylic Acids

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Modern views on the mechanism and applications are discussed. A list of 112 references is included.

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I. INTRODUCTION

In 1923 Schmidt, on investigating the reaction of hydrogen azide with various organic compounds, discovered that carbonyl compounds undergo rearrangement in the presence of acid catalysts[1]. Thus aldehydes are converted into formamides and nitriles, ketones into amides, and carboxylic acids into amines:

$$RCHO + HN_3 \xrightarrow{H^+} RCN + RNHCHO \quad (1)$$

$$RCOR' + HN_3 \xrightarrow{H^+} RCONHR' + RNHCOR' \quad (2)$$

$$RCOOH + HN_3 \xrightarrow{H^+} RNH_2 \quad (3)$$

Some years later Braun and Österlin used this reaction to obtain aliphatic[2], alicylic[3], and aromatic[4] amines from carboxylic acids. Since that time the Schmidt reaction has found widespread application as a convenient method for obtaining *N*-substituted amides, amines, nitriles, and several other compounds.

Since the conversion of carboxylic acids into amines occurs with retention of optical activity[3,5], and is not accompanied by *cis-trans* isomerisation[6-8], it has been used as a convenient model in solving several important theoretical problems associated with the stereochemistry of molecular rearrangements[5,6]. The reaction of carboxylic acids with hydrogen azide has been employed to investigate the structure of alkaloids[9-11] and as an analytical method in studying the mechanism of the solvolysis of alkyl bromides[12].

During recent years the Schmidt reaction has still been the subject of numerous investigations. Experimental results obtained up to 1962 were summarised by Wolff[13] and by Smith[14]. Surveys have recently appeared[15,16] on the Schmidt reaction with ketones. The present Review examines fresh results on the reactions of aldehydes and carboxylic acids with hydrogen azide, paying attention mainly to their mechanism and applications.

II. MECHANISM OF REACTIONS OF ALDEHYDES AND CARBOXYLIC ACIDS WITH HYDROGEN AZIDE

The action of hydrogen azide on aldehydes and carboxylic acids is an acid-catalysed reaction. Protic acids—sulphuric and polyphosphoric (in most cases the former)—are used as catalysts. In discussing the mechanism of these reactions we must obviously consider first of all the behaviour of the reactants in aqueous sulphuric acid.

1. Behaviour of Aldehydes, Carboxylic Acids, and Hydrogen Azide in Aqueous Sulphuric Acid

Aldehydes are weak organic bases and are protonated in aqueous sulphuric acid, with the proton adding to the carbonyl oxygen[17]:

$$R-\overset{\overset{O}{\|}}{C}-H + H^+ \rightarrow R-\overset{\overset{OH}{|}}{\underset{+}{C}}-H \ , \quad (4)$$

A considerable number of studies have been made on the protonation of aldehydes, but in most cases aromatic aldehydes were investigated, since aliphatic aldehydes are unstable in aqueous mineral acids. The sole method for assessing the basicity of aliphatic aldehydes is therefore to measure the spectral shifts due to the hydrogen bond. On the basis of data at present available it may be postulated that pK_a values for the simplest aliphatic aldehydes lie between -7 and -8 H_0 units.

Protonation has been studied in greatest detail on substituted benzaldehydes. Basicity data were first obtained during the mid-1950s, when Schubert et al.[18], and later Yates and Stewart[19], made pK_a determinations on a large number of substituted benzaldehydes. It was postulated that these compounds were Hammett bases. Their basicity constants correlated well with the σ^+ constants of the substituents. The basicity of benzaldehyde of aqueous sulphuric acid has more recently been reinvestigated by several workers[20], who have concluded that protonation of this aldehyde is described better by the acidity function H_A than by H_0.

As previous determinations of the basicity constants of aldehydes had used out-of-date values for the acidity function of aqueous sulphuric acid, and in some cases employed insufficiently rigorous methods for processing the experimental results, a fresh study has recently been made[21,22] of the basicity of a series of substituted benzaldehydes. These compounds are protonated similarly to Hammett bases, except in the case of *p*-methoxybenzaldehyde, whose divergence is obviously due to specific solvation of the methoxy-group. Benzaldehyde and 1'-deuterobenzaldehyde in sulphuric and deuterosulphuric acids have almost identical basicities[23], and a similar situation is observed with the corresponding 2,4,6-trimethylbenzaldehydes[18]. The slight differences in the basicity constants are not due to variation in the acid–base properties of these compounds, since they lie within the limits of accuracy with which the ionisation ratios have been determined.

Like aldehydes, carboxylic acids are weak organic bases, and are protonated in aqueous sulphuric acid, with the proton adding to the carbonyl oxygen atom:

$$R-\overset{\overset{O}{\|}}{C}-OH + H^+ \overset{K_1}{\rightleftarrows} R-\overset{\overset{OH}{|}}{\underset{+}{C}}-OH \ . \quad (5)$$

The basicity of carboxylic acids has been investigated in some detail[17], for study of the mechanisms of acid-catalysed reactions involving carboxylic acids, including the Schmidt reaction, is impossible in the absence of knowledge of their equilibrium constants in mineral acids. Depending on the acidity of the medium, furthermore, protonated carboxylic acids may undergo secondary ionisation to form acylium ions[24,25]

$$R-\overset{\overset{OH}{|}}{\underset{+}{C}}-OH + H^+ \overset{K_a}{\rightleftarrows} R-\overset{+}{C}O + H_3O^+ \qquad (6)$$

which provide a convenient model in studies of the properties and the structure of carbonium ions[26,27].

The basicity of aliphatic carboxylic acids has been investigated by ultraviolet, infrared, and nuclear magnetic resonance spectroscopy. Some workers assumed that these acids are Hammett bases[28,29]. During recent years, however, this view has been criticised, and it is suggested that such acids as acetic are protonated by a so called hydration mechanism[30,31].

The protonation of aromatic carboxylic acids has been widely investigated. The early work showed that substituted benzoic acids are Hammett bases[32,33]. Later results indicated[34–37] that the protonation of benzoic acids is not described by the acidity function H_0. Such deviations have been observed in the protonation of salicylic[37], 2,2′-diphenic[34], and *o*-benzoylbenzoic[35] acids. For the latter acids this might be due to secondary ionisation of the protonated compound and formation of an acylium ion. Vinnik et al.[38] pointed out the difficulties arising in the interpretation of experimental results on the protonation of such acids. Ultraviolet and n.m.r. spectroscopy have recently been used to study the basicity of a series of mono-, di-, and tri-substituted benzoic acids in aqueous sulphuric acid[39]. It was concluded that, despite some inconsistency in available data, there are grounds for supposing that substituted benzoic acids are protonated similarly to Hammett bases. With benzoic acid a temperature dependence of protonation and the basicity have been studied in deuterosulphuric acid[39].

With increase in the concentration of sulphuric acid, as already noted, protonated carboxylic acids may undergo dehydration with formation of acylium ions. Investigation by n.m.r. spectroscopy of the behaviour of a series of aliphatic carboxylic acids in concentrated sulphuric acid or oleum showed[26] that e.g. with acetic acid reaction (6) is observed in 15% oleum, but a still more acid medium is required for propionic and isobutyric acids. Data on the formation of aromatic acylium ions, obtained in a study of the cryoscopic properties of solutions of benzoic acids in concentrated sulphuric acid[24,40], showed that formation of acylium ions is favoured by the presence of two electron-donor *ortho*-substituents in the benzene ring. This is obviously because such substituents stabilise the acylium ion and destabilise the protonated form of benzoic acid. For 2,4,6-trimethylbenzoic acid attempts were made[25,41] to estimate the equilibrium (6) constant, by means of the acidity functions H_0 and I_0 respectively. It was shown subsequently, however, that such processes should be described by the acidity function H_R.[42,43] Indeed, in the case of 2,4,6-trimethylbenzoic acid formation of the acylium ion is well described[39] by this last acidity function, with $pK_a = -19.87$.

It must be emphasised that published data obtained by different workers on the basicity of particular carbonyl compounds are often difficult to compare, for inadequate methods of calculating ionisation ratios are used in processing the experimental results. Yet it has been noted repeatedly[33,44] that this stage is extremely important in studying the basicity of organic bases. Certain difficulties arise also in discussing the basicity constants of aldehydes and carboxylic acids obtained by different physicochemical methods, especially nuclear magnetic resonance. The reasons have been examined by several workers[17,39,45]. Finally, it is obviously a simplification to describe the protonation of aldehydes and carboxylic acids by means of the Brønsted equations (4) and (5).

It has recently been suggested that carbonyl compounds are protonated by a "dehydration" mechanism[46]:

$$\begin{gathered} B \cdot b\ H_2O + H^+ \cdot x\,H_2O \rightleftarrows B \cdots H^+ \cdot n\,H_2O + (b + x - n)\,H_2O \\ B \cdots H^+ \cdot n H_2O \rightleftarrows B \cdots H^+ \cdot (n-1)\,H_2O + H_2O \\ \cdots\cdots\cdots\cdots\cdots\cdots\cdots \\ B \cdots H^+ \cdot H_2O \rightleftarrows \overset{+}{B}H + H_2O \end{gathered} \qquad (7)$$

where B is the base (aldehyde or carboxylic acid). The occurrence of such processes in the protonation of weak organic bases has been established quite convincingly by laser Raman spectroscopy[47,48]. This view is supported also by kinetic data on certain acid-catalysed reactions[46], including the Schmidt reaction[49]. However, the lack of constants of the equilibria (7) presents certain difficulties in interpreting the kinetic results.

Table 1. Basicity of hydrogen azide determined by various methods.

Method	$-pK_a(H_2N_3^+)$	Ref.
Partition in $CHCl_3$–H_2SO_4	6.9	51
Vapour pressure (Henry's law)	7.02	52
Ultraviolet spectroscopy	7.19	55
Kinetic data	5.4	53
	6.6	54

Hydrogen azide is protonated in aqueous sulphuric acid

$$HN_3 + H^+ \rightleftarrows H_2\overset{+}{N}_3 \qquad (8)$$

$$H_2\overset{+}{N}_3 + H^+ \rightleftarrows H_3N_3^{2+} \qquad (9)$$

a possibility first pointed out by Hantzsch[50]. More recently Bak and Praestgaard[51] found by a partition method that the basicity of hydrogen azide is $pK_a(H_2N_3^+) = -6.9$. Almost the same value has been obtained (−7.02) by measuring the vapour pressure over solutions of perchloric acid[52], and kinetic methods yield similar results[53,54]. It has been postulated in all cases that hydrogen azide is a Hammett base. Study of its basicity by ultraviolet spectroscopy has shown[55] that its protonation is actually described by the acidity function H_0. Table 1 gives values obtained by different methods for the basicity of hydrogen azide. The approximate value obtained by Hantzsch[50] for singly protonated hydrogen azide was $pK_a(H_3N_3^{2+}) \approx -10.2$. Recent kinetic determinations[54,55] give limits of −9.60 and −9.99 H_0 units. The basicity of deuterium azide in a D_2O–D_2SO_4 mixture obtained by ultraviolet spectroscopy[56] differs from the value for hydrogen azide: $pK_a(D_2N_3^+) = -7.56$.

In studying the mechanism of the Schmidt reaction it must be borne in mind that hydrogen azide decomposes in aqueous mineral acids[57]. In 73.8–98.7% sulphuric acid at

60° C the decomposition is an acid-catalysed process[55], the activated species being $H_2N_3^+$. The mechanism of this reaction can be represented as

$$HN_3 + H^+ \overset{K_1}{\rightleftarrows} H_2N_3^+ + H^+ \overset{K_2}{\rightleftarrows} H_3N_3^{2+} \quad (10)$$
$$\downarrow k$$
$$\text{Products}$$

where K_1 and K_2 are the basicity constants of HN_3 and $H_2N_3^+$ respectively, and k is the true rate constant. The effective rate constant is then related to the true rate constant by the formula

$$k_{\text{eff}} = \frac{k}{K_1/h_0 + h_+/K_2 + 1},$$

or

$$k_{\text{eff}} = k \cdot A, \quad (11)$$

in which

$$A = (K_1/h_0 + h_+/K_2 + 1)^{-1}.$$

The equation to the regression line for the dependence (11) is

$$\lg k_{\text{eff}} = (0.85 \pm 0.05) \lg A - (2.18 \pm 0.02)$$
$$r = 0.98;\ n = 14;\ s = 0.05\ . \quad (12)$$

Kinetic results obtained in 73.8–89.6% sulphuric acid, in which the activity of water is quite high, were treated by Bunnett's method[58] in conformity with the equation

$$\lg k_{\text{eff}} - \lg \frac{h_0}{h_0 + K_1} = \omega \lg a_{H_2O} + c. \quad (13)$$

The equation to the regression line is

$$\lg k_{\text{eff}} - \lg \frac{h_0}{h_0 + K_1} = (0.13 \pm 0.03) \lg a_{H_2O} + (1.80 \pm 0.06)$$
$$r = 0.91;\ n = 7;\ s = 0.02.$$

The value of $\omega < 1$ indicates that water is not involved in forming the activated complex.

Table 2. Activation energy of decomposition of hydrogen azide.

H_2SO_4, %	75.9	86.3	96.3
E_a, kcal mole^{-1}	31.2	23.2	19.8

Additional information on the mechanism of the decomposition of hydrogen azide has been obtained from a study of the kinetics at different temperatures. Table 2 shows that the activation energy does not remain constant with variation in the concentration of sulphuric acid. This is obviously due to partial change in the reaction mechanism on passing from the dilute to the concentrated acid. It may be postulated that non-protonated hydrogen azide also decomposes, although the rate is considerably smaller than that of the main reaction. Some departure from unity in the slope of the relation (12) is obviously due to the same causes. Kinetic study shows[56] that the decomposition of deuterium azide in $D_2O + D_2SO_4$ has the same mechanism as that of hydrogen azide ($k_D/k_H \simeq 4$).

The acid–base equilibria preceding the reaction of aldehydes and carboxylic acids with hydrogen azide must be borne in mind when studying its mechanism. The basicity constants of carbonyl compounds and hydrogen azide required for calculation of the reaction rate constants should be determined under comparable conditions.

2. Mechanism of Reaction of Aldehydes with Hydrogen Azide

It was assumed earlier that the Schmidt reaction had the same mechanism for aldehydes and for ketones. Thus McEwen et al.[59] and later Smith and Antoniades[60] supposed that, by analogy with ketones, aldehydes react in the protonated form with hydrogen azide; the resulting protonated azidoalkanol (I) loses water to give the iminodiazonium ion (II), which is subsequently converted into the reaction products:

$$\text{RCHO} + HN_3 \overset{+H^+}{\rightleftarrows} \underset{\substack{| \\ HN_3^+}}{\overset{\overset{OH}{|}}{RC}}\!-\!H \overset{-H_2O}{\rightleftarrows} \underset{\substack{\| \\ NN_2^+}}{RC}\!-\!H \rightleftarrows \underset{\substack{\| \\ N_2N^+}}{RC}\!-\!H \xrightarrow{-N_2,\ -H^+} \text{RCN} \quad (14)$$

(I) (IIa); *anti*- (IIb); *syn*-

$$\text{(IIa)} \xrightarrow{-N_2} RN{=}\overset{+}{C}H \xrightarrow{+H_2O} RNHCH \overset{-H^+}{\rightleftarrows} RNHCH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad OH \qquad\quad O$$

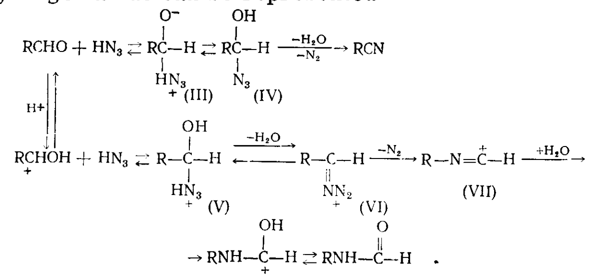
It is generally accepted for unsymmetrical ketones[15] that the iminodiazonium ion can exist as *syn* and *anti* isomers. The more bulky substituent, located in the *anti* position with respect to the diazo-group, migrates to the nitrogen atom to form an iminocarbonium ion. This important postulate will explain the preferential formation of one of the isomeric amides in the Schmidt reaction with ketones. Hence the corresponding formamide should be the sole reaction product in the case of aldehydes. In fact, however, nitriles are formed together with formamides when aldehydes react with hydrogen azide[61]. In order to explain this inconsistency it was suggested[59] that formation of the nitrile form the *syn*-iminodiazonium ion (IIb) involves detachment of a proton by the action of such a base as water or the hydrogen sulphate ion.

Subsequent detailed kinetic study of the reaction of aldehydes with hydrogen azide established that this postulate was incorrect. Furthermore, fresh results were obtained showing that the Schmidt reaction had different mechanisms with ketones and with aldehydes: ketones react in the protonated form, whereas aldehydes react in both protonated and non-protonated forms[62]. This explains the formation of two products — a nitrile and a formamide — in proportions depending on the acidity of the medium[63]: the proportion of formamide in the product increases with acidity, and the nitrile is favoured by diminished acidity. For example, the only product of the reaction of benzaldehyde with hydrogen azide in 71.2% sulphuric acid, in which the protonated form of the aldehyde is almost completely absent, is benzonitrile, but in the 87.4% acid only formanilide is produced. The ratio of the reaction products changes precisely in the range of sulphuric acid concentrations in which the acid–base equilibrium of benzaldehyde is observed. This enables the ratio to be calculated by means of the equation

$$\lg F = \text{p}K_a - H_0, \quad (15)$$

where $F = [\text{Fo}]/[\text{H}]$ is the ratio of the final concentrations of formamide and nitrile, $\text{p}K_a$ relates to the conjugate acid of the aldehyde, and H_0 is the Hammett acidity function. Hence the formation of nitriles and formamides form aldehydes and hydrogen azide can be regarded as two parallel reactions involving respectively non-protonated and protonated forms of the aldehyde.

Thus the mechanism of the reaction of aldehydes with hydrogen azide can be represented



(16)

Interaction of the non-protonated aldehyde with the azide forms the ambipolar ion (III), which isomerises into the azidoalkanol (IV). The latter is converted into the nitrile by dehydration and the elimination of nitrogen.

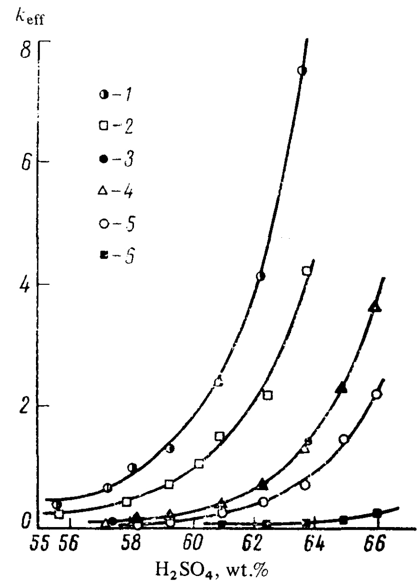


Figure 1. Influence of concentration of sulphuric acid on effective rate constants of the reaction of hydrogen azide with benzaldehydes containing various substituents: *1*) *p*-methyl; *2*) none; *3*) *p*-chloro; *4*) *p*-bromo; *5*) *m*-chloro; *6*) *m*-nitro.

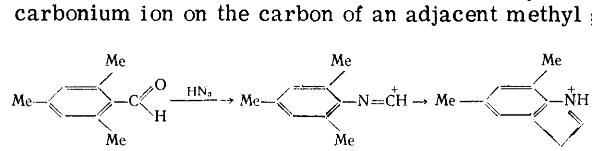
Such a reaction mechanism is quite consistent with the kinetic results. Kinetic study of the action of a series of substituted benzaldehydes[49] on hydrogen azide is moderately concentrated aqueous sulphuric acid, in which the non-protonated form of the aldehyde is reactive, has established a monotonic increase in reaction velocity with acid concentration (Fig. 1). This is because the aldehyde reacts as a complex with a hydrated proton. When weak organic bases (aldehydes) dissolve in aqueous mineral acids, such complexes $B \ldots H^+.nH_2O$ are supposed[46] to be formed (scheme 7). As the mineral acid becomes more concentrated, these complexes undergo dehydration to the protonated base. This involves a gradual advance by the proton from the "initial position of attack" [46] to the aldehydic oxygen atom, which tends to increase the reactivity of the complex. It thus becomes clear why the rate of reaction of the non-protonated aldehyde with hydrogen azide increases with the sulphuric acid concentration.

True rate constants for each type of complex cannot be calculated because of the absence of values for the equilibrium (7) constants. This leads to some difficulties in determining the limiting stage, since the ρ–σ method cannot be used for these purposes. However, existing data suggest that addition of hydrogen azide to the non-protonated aldehyde is the rate-determining stage. This is supported by a study[23] of the kinetic isotope effect in the reaction of benzaldehyde with hydrogen azide and by activation parameters (Table 3) †, which are typical of nucleophilic addition at a carbonyl group. The opposite kinetic isotope effect is observed for the reaction of benzaldehyde with hydrogen azide in D_2SO_4 in comparison with H_2SO_4: $k_D/k_H \simeq 4$. Yet no kinetic isotope effect is observed when benzaldehyde is replaced by 1′-deuterobenzaldehyde in sulphuric acid[23].

Table 3. Activation parameters for reaction of benzaldehyde with hydrogen azide.

$[H_2SO_4]$, %	E_a, kcal mole^{-1}	$H^{\neq}$, kcal mole^{-1}	$\Delta S^{\neq}$, e.u.
53.1	14.6	14.0	−12.8
55.6	15.6	14.9	−9.1
57.9	15.3	14.7	−8.1

According to Eqn. (16) the first stage in concentrated aqueous sulphuric acid is addition of hydrogen azide to the protonated aldehyde to form the protonated 1-azidoalkanol (V). Dehydration of (V) gives the iminodiazonium ion (VI), which eliminates nitrogen and undergoes rearrangement to the iminocarbonium ion (VII). The action of water on this ion (VII) yields the formamide. Existence of an iminocarbonium ion as an intermediate species is confirmed by the formation of "anomalous products" with certain aldehydes. Thus the reaction between 2,4,6-trimethylbenzaldehyde and hydrogen azide yields not only 2,4,6-trimethylformanilide but also the cation of 5,7-dimethylindole[22] as a result of intramolecular attack by the iminocarbonium ion on the carbon of an adjacent methyl group:



(17)

The kinetics of the reaction of aldehydes with hydrogen azide in concentrated aqueous sulphuric acid has been studied in detail. For a series of substituted benzaldehydes[62,64] the steady-state principle is applicable to the reaction, since intermediate products accumulate neither before nor

† The slight increase in entropy of activation is fully consistent with the postulate that aldehydes react as complexes having different degrees of hydration.

after the rate-determining stage. The relation between the true rate constant k' and the effective constant k_{eff} is then

$$k_{eff} = \frac{k' \cdot h_0}{(K_1 + h_0)(1 + h_0/K_2 + h_0 \cdot h_+/K_2 \cdot K_3)} \quad (18)$$

or

$$\lg k_{eff} = \lg A + \lg k', \quad (19)$$

where

$$A = h_0/[(K_1 + h_0) \cdot (1 + h_0/K_2 + h_0 \cdot h_+/K_2 \cdot K_3)],$$

h_0 and h_+ are the Hammett acidity of the medium and the acidity for singly charged cations, K_1 is the basicity constant of the aldehyde, and K_2 and K_3 are those of hydrogen azide and of its monoprotonated form. Thus for benzaldehyde in 90.5–97.8% sulphuric acid good correlation is observed between $\lg k_{eff}$ and $\lg A$ (formula 19). The equation to the regression line is

$$\lg k_{eff} = (0.99 \pm 0.05) \lg A + (5.05 \pm 0.09)$$
$$r = 0.99;\ n = 8;\ s = 0.05.$$

The action of hydrogen azide on aldehydes is a multistage process, so that the true rate constant k' calculated by means of Eqn. (18) can be assigned to any of these stages—addition of hydrogen azide to the aldehyde, dehydration, or rearrangement.

Table 4. Rate constants of reactions of substituted benzaldehydes RC_6H_4CHO with hydrogen azide in H_2SO_4 (at 20° C).

R	$[H_2SO_4]$, %	$10^{-3}k_{eff}$, M^{-1} min^{-1}	lg k'	R	$[H_2SO_4]$, %	$10^{-3}k_{eff}$, M^{-1} min^{-1}	lg k'
p-CH_3	89.0	0.101	—	*p*-Br	94.5	0.176	5.63
p-CH_3	90.2	0.044	4.10	*p*-Br	97.6	0.032	
p-CH_3	92.8	0.019	—				
H	96.3	0.021		*m*-Cl	96.7	0.407	
			5.05				6.60
H	97.8	0.008		*m*-Cl	98.3	0.121	
p-Cl	90.0	0.601		*m*-NO_2	95.8	3.640	
p-Cl	92.7	0.458	5.52	*m*-NO_2	97.6	2.890	7.63
p-Cl	95.8	0.086					

The method of ρ–σ analysis has been successfully applied to ascertain the rate-determining stage[64]. Thus the true rate constants of substituted benzaldehydes (Table 4) correlate with the substituent constants σ^+. The equation to the regression line is

$$\lg k' = (3.515 \pm 0.091)\sigma^+ + (5.126 \pm 0.032),$$
$$r = 0.99;\ n = 6;\ s = 0.02.$$

From the absolute magnitude and the sign of the reaction constant ρ the limiting stage in the reaction of benzaldehydes, as with ketones[65], is addition of non-protonated hydrogen azide to the protonated aldehyde.

3. Mechanism of Reaction of Carboxylic Acids with Hydrogen Azide

The mechanism of the reaction of carboxylic acids with hydrogen azide was not discussed at all in the early work. The first attempt is evidently that by Briggs and Lyttleton[66], who tried to formulate a mechanism on the basis of a study of a series of substituted benzoic acids. A little later Newman and Gildenhorn[67] suggested a mechanism for the acid-catalysed reaction. They considered that the carboxylic acid reacts either in a protonated form or as an acylium ion; in either case the final products are the corresponding amine and carbon dioxide.

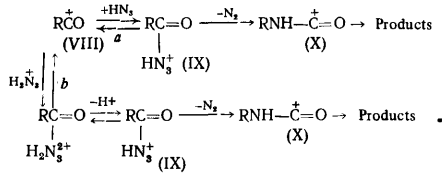
In a subsequent study of the Schmidt reaction with various carboxylic acids and also a detailed kinetic study fresh data were obtained largely supplementing and refining these views. Taking into account the protolytic equilibria preceding the main process, we can represent the mechanism of the reaction with carboxylic acids as

$$RCOOH + H^+ \rightleftarrows [RCO_2H_2]^+ \quad (20)$$

$$[RCO_2H_2]^+ + H^+ \rightleftarrows R\overset{+}{C}O + H_3O^+ \quad (21)$$

$$HN_3 + H^+ \rightleftarrows H_2N_3^+ \quad (22)$$

$$H_2N_3^+ + H^+ \rightleftarrows H_3N_3^{2+} \quad (23)$$



(24)

Such a mechanism is fully consistent with kinetic studies[57,68–70].

Table 5. Kinetics of reaction of 2,4,6-trimethylbenzoic acid with hydrogen azide in H_2SO_4 (at 15° C).

Expt.	$[H_2SO_4]$, %	$-H_0$	lg k_{eff}	Expt.	$[H_2SO_4]$, %	$-H_0$	lg k_{eff}
1	77.2	6.84	0.41	11	92.2	9.28	2.12
2	79.0	7.12	0.85	12	93.5	9.50	2.23
3	80.9	7.44	1.25	13	95.1	9.80	2.26
4	83.8	7.87	1.74	14	96.5	10.08	2.28
5	86.1	8.25	1.94	15	97.3	10.24	2.22
6	87.5	8.48	2.06	16	98.7	10.46	2.13
7	88.9	8.72	2.09	17	99.3	10.76	1.90
8	89.6	8.84	2.12	18	99.8	11.18	1.44
9	90.5	9.00	2.09	19	100.0	11.84	0.28
10	91.0	9.10	2.08				

Important results have been obtained for the reaction of 2,4,6-trimethylbenzoic acid with hydrogen azide in 77.2 to 100% sulphuric acid (Table 5 and Fig. 2).[70] The dependence of the logarithm of the effective reaction rate constant on the acidity function of the medium H_0 exhibits a characteristic break in the range 88.9–95.1% sulphuric acid (Fig. 2). The reaction velocity successively increases, decreases, and again increases in this acidity range, in which the content of the acylium ion increases sharply[39], while the proportion of free hydrogen azide decreases[55]. The explanation for such a complicated dependence of lg k_{eff} on H_0 is that both free and protonated forms of hydrogen azide react with the acylium ion of 2,4,6-trimethylbenzoic acid.

The kinetic equation describing this process is

$$k_{\text{eff}}\frac{K_2}{h_R}\left(1+\frac{K_1}{h_0}+\frac{h_R}{K_2}\right)\left(1+\frac{K_3}{h_0}+\frac{h_+}{K_4}\right)=K'k'\frac{K_3}{h_0}+K''k'' \qquad (25)$$

or

$$k_{\text{eff}}D=K'k'\frac{K_3}{h_0}+K''k'', \qquad (26)$$

where K_1, K_3, and K_4 are the basicity constants of the carboxylic acid, hydrogen azide, and monoprotonated hydrogen azide, K_2 is the equilibrium constant for protonated acid and acylium ion, k' and k'' are the true rate constants of reactions (a) and (b) respectively (scheme 24), K' and K'' are the equilibrium constants of the stages preceding the rate-determining stage, h_0, h_R, and h_+ are the Hammet acidity of the medium and the acidities for triarylmethanols and singly charged cations, and

$$D=\frac{K_2}{h_R}\left(1+\frac{K_1}{h_0}+\frac{h_R}{K_2}\right)\left(1+\frac{K_3}{h_0}+\frac{h_+}{K_4}\right).$$

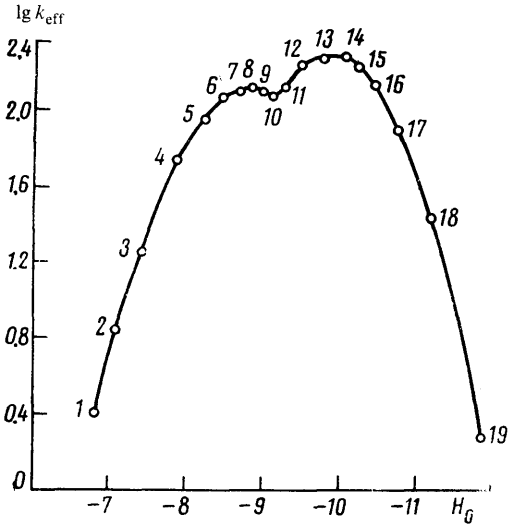


Figure 2. Dependence of effective rate constant for reaction of 2,4,6-trimethylbenzoic acid with hydrogen azide on the acidity function (for numbering of points see Table 5).

Under the boundary conditions with $h_0 \ll K_4$ or $h_0 \gg K_3$ (path a or b) Eqn. (25) becomes

$$\lg k_{\text{eff}}=\lg K'k'+\lg B \qquad (27)$$

$$\lg k_{\text{eff}}=\lg K''k''+\lg C, \qquad (28)$$

where

$$B=\frac{K_3h_R}{K_2h_0(1+K_1/h_0+h_R/K_2)(1+K_3/h_0+h_+/K_4)}$$

$$C=\frac{h_R}{K_2(1+K_1/h_0+h_R/K_2)(1+K_3/h_0+h_+/K_4)}.$$

Statistical treatment of the experimental results gave equations to the regression line for relations (27), (26), and (28) — experiments 1–6, 7–13, and 14–19 respectively (Table 5):

$$\lg k_{\text{eff}}=(4.26\pm0.08)+(0.51\pm0.17)\lg B, \qquad (29)$$
$$r=0.99;\ n=6;\ \alpha=0.975;\ f=12;$$

$$\lg k_{\text{eff}}D=(1.23\pm0.35)\cdot10^6\frac{K_3}{h_0}+(5.66\pm35)\cdot10^2; \qquad (30)$$
$$r=0.99;\ n=7;\ s=3.4\cdot10^3;$$

$$\lg k_{\text{eff}}=(3.98\pm0.06)+(1.39\pm0.04)\lg C; \qquad (31)$$
$$r=0.97;\ n=6;\ \alpha=0.95;\ f=12.$$

Good correlation of lg k_{eff} with lg B and with lg C is observed (Eqns. 29 and 31), which confirms the mechanism of the reaction of carboxylic acids with hydrogen azide (scheme 24). However, the slopes of these relations differ from unity. For this reason Eqns. (29)–(31) cannot be used to calculate the true rate constants k' and k''. Thus the reactive species is the acylium ion (VIII). In moderately concentrated sulphuric acid the first stage involves addition of free hydrogen azide to this ion (path a). At high acidities the protonated form reacts with the acylium ion (path b). In media of intermediate acidity the reaction occurs by a mixed mechanism. Independently of the reaction path (a) or (b) the first stage involves formation of the protonated acyl azide (IX). Elimination of nitrogen and rearrangement convert (IX) into the protonated isocyanate (X), which then reacts with water to give the reaction products.

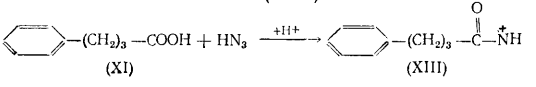
Unfortunately, existing data do not permit an assessment of the mode of rearrangement of the acyl azide (IX) — whether in one stage

$$R-\overset{O}{\overset{\|}{C}}-NH-\overset{+}{N}_2 \xrightarrow{-N_2} R-NH-\overset{+}{C}=O \qquad (32)$$

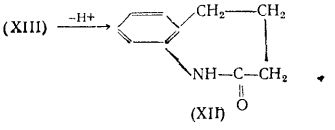
or in two stages

$$R-\overset{O}{\overset{\|}{C}}-NH-\overset{+}{N}_2 \xrightarrow{-N_2} R-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H \rightarrow R-NH-\overset{+}{C}=O \qquad (33)$$

For example, the action of hydrogen azide on γ-phenylbutyric acid (XI) in the presence of sulphuric acid forms not only the corresponding amine but also the lactam (XII) [71], presumably by intramolecular attack by the positively charged nitrogen on an *ortho* carbon atom of the benzene ring in the intermediate ion (XIII):



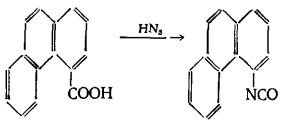
(34)



(35)

This suggests that rearrangement of the azide (IX) takes place in two stages. On the other hand, the lactam (XII) could be formed by a concerted mechanism with simultaneous detachment of nitrogen and electrophilic attack on the *ortho* carbon atom. Since there is no direct evidence in support of either mechanism, it is difficult to decide by which route (32 or 33) rearrangement of the protonated acyl azide takes place. Nevertheless, preference must be given to the synchronous mechanism by analogy with the Curtius reaction of the same type [72]. This suggestion is supported by the retention of configuration in the reaction of carboxylic acids with hydrogen azide [5–8, 73, 74].

Intermediate formation of an isocyanate from a carboxylic acid and hydrogen azide was demonstrated by Rutherford and Newman[75], who isolated the corresponding isocyanate in the reaction of phenanthrene-4-carboxylic acid:



(36)

The reaction of a carboxylic acid with hydrogen azide involves several stages, and the problem of which is rate-determining is important for an understanding of the overall mechanism. Kinetic results obtained[76] for a series of substituted benzoic acids in 99.9% sulphuric acid (Table 6) have been used to define the limiting stage. At this acid concentration ($H_0 = -11$) almost all the azide is present in the protonated form[55], and the reaction follows path (*b*) of scheme (24). The kinetics can then be represented by the equations

$$A^+ + B^+ \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C^{2+} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} C^+ \xrightarrow{k_3} D^+, \qquad (37)$$

[*c*] [*d*] [*e*]

where A^+ is the acylium ion, B^+ is the protonated hydrogen azide, C^{2+} and C^+ are the doubly and singly protonated acyl azide respectively, and D^+ is the protonated isocyanate. The effective rate constant k_{eff} is then related to the true rate constant k'' by Eqn. (28). Since no data are available on the acidity function H_R for sulphuric acid at concentration exceeding 99.9%,[39,43] equilibrium constants K_2 cannot be evaluated for substituted benzoic acids (except in the case of 2,4,6-trimethylbenzoic acid[39]). Hence formula (28) cannot be used to calculate the true rate constants for these compounds. This leads to difficulties when the Hammett equation is used to investigate the reaction mechanism. Nevertheless, under certain conditions effective rate constants can be used to correlate kinetic data for the action of hydrogen azide on substituted benzoic acids.

Table 6. Second-order rate constants for reaction of substituted benzoic acids RC_6H_4COOH with hydrogen azide in 99.9% H_2SO_4 (at 60°C).

Cpd.	R	k_{eff}, $M^{-1}\,min^{-1}$	Cpd.	R	k_{eff}, $M^{-1}\,min^{-1}$
1	H	12.59	5	*m*-F	2.34
2	*p*-Cl	8.32	6	*m*-NO_2	0.32
3	*p*-Br	8.32	7	*p*-NO_2	0.24
4	*m*-Br	3.31			

For scheme (37) either (*c*) or (*e*) can theoretically be the rate-determining stage, and they are indistinguishable kinetically. Only the protolytic equilibrium (*d*) is definitely not the limiting stage. If the rate constants k_1, k_{-1}, and k_3 are mutually comparable, the Hammett equation is quite inapplicable[77]. Provided that $k_1 \gg k_3$ or $k_3 \gg k_{-1}$, a correlation should be observed between $\lg k_{eff}$ and the substituent constants[78]. Combining the Hammett equation with the relation (28), we then obtain

$$\rho\sigma = \lg\frac{k_{eff}}{k_{0eff}} + \lg\frac{K_{a}}{K_{0a}} + \lg\frac{(1 + K_1/h_0 + h_R/K_a)}{(1 - K_{01}/h_0 + h_R/K_{0a})}. \qquad (38)$$

The last term on the right-hand side of (38) can be neglected, since in 99.9% sulphuric acid $K_1 \ll h_0$ and $K_2 \gg h_R$. If the rate constants of the reactions of substituted benzoic acids with hydrogen azide and the equilibrium constants K_2 correlate with the same substituent constants σ^+, we then have

$$\lg\frac{k_{eff}}{k_{0eff}} = (\rho_1 - \rho_2)\tau^+. \qquad (39)$$

A correlation is indeed observed between $\lg k_{eff}$ and σ^+ (Fig. 3), and the equation to the regression line is

$$\lg k_{eff} = -(2.33 \pm 0.15)\sigma^+ + (1.21 \pm 0.07), \qquad (40)$$

$$r = 0.99;\ n = 7;\ s = 0.11.$$

However, the constant obtained in this way is an effective value, and it is difficult to assess the reaction mechanism from its sign and absolute magnitude.

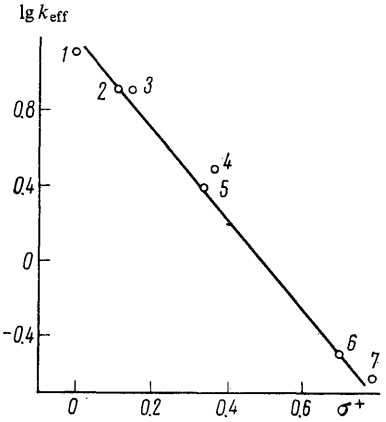


Figure 3. Dependence of effective reaction rate constants for benzoic acids on substituent constants σ^+ (for numbering of points see Table 6).

The correlation (40) indicates that the rate constants k_1, k_{-1}, and k_3 are not comparable, and that the rate of the reaction of substituted benzoic acids with hydrogen azide is increased by the presence of electron-donor substituents. Yet the opposite pattern is found for the analogous reactions of ketones and aldehydes, when addition of hydrogen azide to the protonated carbonyl compound is the rate-determining stage[64,65]. Furthermore, the tendency of substituted phenyl groups to migrate in reactions involving rearrangement of the carbon skeleton increases in the presence of electron-donor substituents[79,80]. These results obviously indicate that the rearrangement (*e*) is the rate-determining stage in the reaction of benzoic acids with hydrogen azide. The same conclusion was reached by Rabinowitz et al.[81], who found an approximately 15% decrease in reaction velocity when the carbonyl carbon-12 atom in carboxylic acids was replaced by carbon-14. This is supported by the absence of a kinetic isotope effect for the reaction of benzoic acids[70] in D_2O–D_2SO_4 relative to the H_2O–H_2SO_4 system of the same composition (79.3%): k^D_{eff} and k^H_{eff} are respectively 0.027 and 0.035 $M^{-1}\,min^{-1}$. Some difference between these constants is obviously due to differences in the value of D_0 and H_0[82,83] and in the basicity constants of

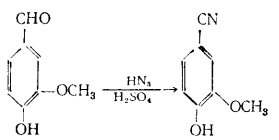
hydrogen azide in deuterosulphuric[56] and sulphuric[55] acids. The opposite kinetic isotope effect is found for the reaction of ketones and aldehydes with hydrogen azide: k^D/k^H = 4–6.[23,84]

III. APPLICATIONS OF REACTION

The reaction of aldehydes with hydrogen azide-provides a simple method for obtaining formamides and nitriles. However, several manuals of organic synthesis[85] state that it is difficult to control the proportions of the products. Actually, the factors governing the ratio of formamide to nitrile have become known only after the reaction mechanism has been finally established. This reaction can now be expected to be an effective method for obtaining various formamides and nitriles. It is noteworthy that the Schmidt reaction enables nitriles to be obtained from readily available compounds in a single stage, with sulphuric acid as catalyst. This method has advantages over others, since in most cases metal cyanides are used to obtain nitriles, or else the reaction occurs in several stages.

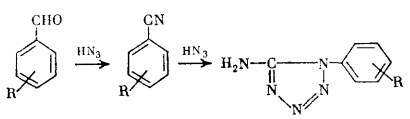
With acetaldehyde hydrogen azide forms acetonitrile[86]. This is apparently the only example of the application of the Schmidt reaction to aliphatic aldehydes. Such a situation is obviously due to their instability in aqueous sulphuric acid.

Aromatic aldehydes have been studied in greater detail. Thus McEwen et al.[59] investigated the action of hydrogen azide on a series of substituted benzaldehydes in the presence of sulphuric acid. They showed that the yields of formamides and nitriles can vary within wide limits depending on the acid concentration. From 4-hydroxy-3-methoxybenzaldehyde[87] the corresponding nitrile was obtained in 70% yield:



(41)

With excess of hydrogen azide and substituted benzaldehydes in the presence of concentrated sulphuric acid 5-amino-1-aryltetrazoles are formed[88,89]:

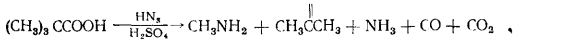


(42)

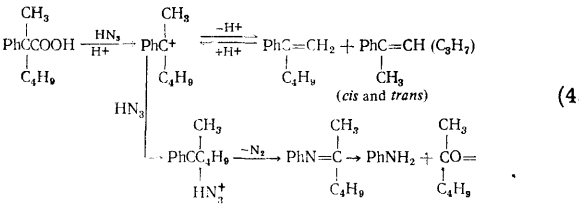
In this case tin chloride can be used together with sulphuric acid as catalyst[89], but the yield of tetrazoles is lower.

Since the early work of Schmidt the reaction of carboxylic acids with hydrogen azide has been widely used as a convenient method for obtaining various amines. This is due to the advantage of the Schmidt reaction over other processes for obtaining amines, e.g. the related Curtius and Hofmann rearrangements, as it occurs in a single stage. Other advantages are its simplicity, the availability of the initial reactants, and the quite mild conditions, The catalysts may be sulphuric acid[4,70,73], polyphosphoric acid[90,91], and mixtures of sulphuric and trichloroacetic acids[92,93] and of trifluoroacetic acid and anhydride[75]. In most cases sulphuric acid is used. Hydrogen azide is used as a solution in an inert solvent[74,94] (chloroform, benzene) or is generated *in situ* by adding sodium azide to the reaction mixture[95–97]. The latter procedure eliminates contact with the explosive and toxic hydrogen azide without lowering the yield of products. Aliphatic[98–100], alicyclic[3,74,94,101], bicyclic[102], and aromatic[4,103–106] acids react with hydrogen azide. The presence of a heteroatom (boron, nitrogen, oxygen) in the acid molecule[9,10,101,107] does not hinder the normal course of the reaction.

Aliphatic carboxylic acids of normal structure are converted into good yields of the corresponding amines[98]. However, acids containing alkyl or aryl substituents in the α position undergo secondary reactions. For example, $\alpha\alpha$-dimethylpropionic ("trimethylacetic") acid[108] forms a mixture of several products:

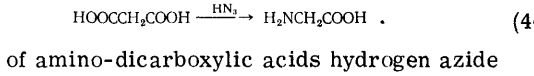


A similar pattern is observed with 2-methyl-2-phenylhexanoic acid[91,109]. These departures from the "normal" reaction are due to decarboxylation of the initial acid to the corresponding carbocation and its subsequent reactions:



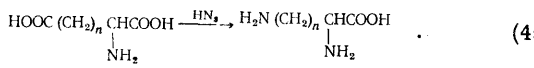
(43)

In aliphatic dicarboxylic acids only one carboxyl reacts if it is separated from the other by less than two carbon atoms[99]:



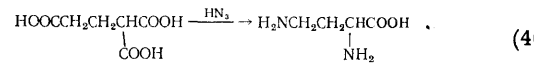
(44)

In the case of amino-dicarboxylic acids hydrogen azide reacts with the carboxyl that is more remote from the amino-group[99]:



(45)

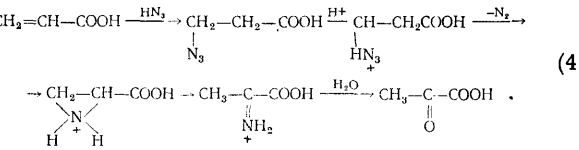
Similarly, tricarboxylic acids yield diamino-carboxylic acids[100]:



(46)

Tetracarboxylic acids are converted into the corresponding tetramines[110].

Unsaturated aliphatic acids such as acrylic undergo a complicated reaction yielding pyruvic acid[111]:

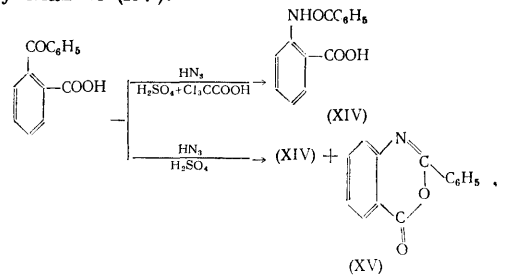


(47)

As already noted, alicyclic and bicyclic mono- and dicarboxylic acids react with hydrogen azide to form the corresponding amines, unaccompanied by *cis–trans* isomerisation. Thus the Schmidt reaction has been used to obtain *cis*- and *trans*-cyclobutane-1,2-diamines[74] and *cis*-cyclohexane-1,2-diamine[6,7].

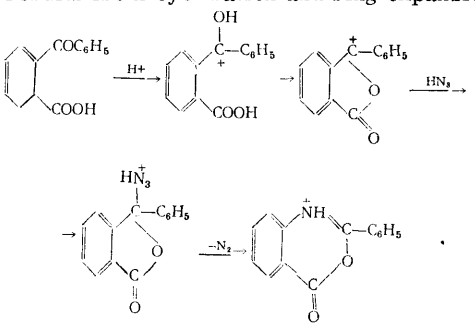
The Schmidt reaction with aromatic carboxylic acids has been especially widely studied. Thus substituted benzoic acids[4,103–106] are converted by hydrogen azide in the corresponding anilines in good yields. If electron-accepting substituents are present in the benzoic acids, 100% sulphuric acid[105] or even oleum[103,106] must be used as catalyst.

Interesting results were obtained with *o*-benzoylbenzoic acid[92,93]. If a mixture of sulphuric and trichloroacetic acids is used as catalyst, benzanilide (XIV) is formed, but with concentrated sulphuric acid as catalyst this is accompanied by oxazine (XV):



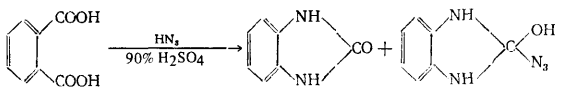
(48)

Oxazine results from cyclisation and ring expansion:



(49)

Aromatic dicarboxylic acids have been less studied than benzoic acids. In the presence of concentrated sulphuric acid phthalic acid gives an 80% yield of anthranilic acid with traces of *o*-phenylenediamine[4]. If 90% sulphuric acid is used, a mixture of two products—benzimidazolinone and 2-azido-2-hydroxybenzimidazoline—is formed[112]:



(50)

The information given in the present Review on the reactions of aldehydes and carboxylic acids with hydrogen azide indicates the considerable progress made in this field. Future research will undoubtedly bring interesting knowledge on the mechanism of acid-catalysed rearrangements and reveal fresh opportunities for the application of these reactions to organic synthesis.

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