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THE KINETICS AND MECHANISM OF MANNICH BASE DISSOCIATION IN AQUEOUS BUFFERS

V. M. BELIKOV, YU. N. BELOKON', M. M. DOLGAYA and N. S. MARTINKOVA

Institute of Organo-Element Compounds, Academy of Sciences, Moscow, U.S.S.R.

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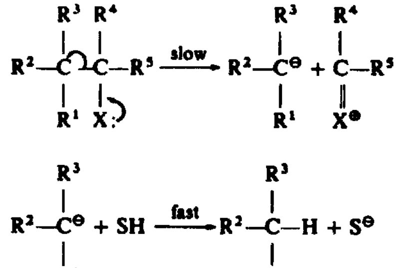
Abstract—We have measured the rates of decomposition in water of 1-N-methylamino-2-methyl-2-nitropropane, 1-N-dimethylamino-2-methyl-2-nitropropane, 1-N-diethylamino-2-methyl-2-nitropropane, 1-N-di-n-propylamino-2-methyl-2-nitropropane, 1-N-diisopropylamino-2-methyl-2-nitropropane, 1-N-diethylamino-2,2-dinitropropane, 1-N-dimethylamino-2-ethyl-2-nitrobutane, 1-N-diethylamino-2-ethyl-2-nitrobutane, 1-piperidyl-2-methyl-2-nitropropane at different pH and temperatures. The proposed reaction mechanism involves unimolecular dissociation of an unprotonated base as the rate-determining step with formation of immonium ions and carbanions. The dissociation rates are greatly influenced by the size both of the alkyl substituents at the amine nitrogen and of the leaving group. An excellent correlation is observed between these rates and the hydrolysis rates of 3,3-substituted mono-*p*-bromophenyl glutarate esters. This fact indicates that alkyl groups exert a predominantly steric effect on the reaction velocity. Possible mechanisms are discussed.

HETEROLYSIS of a C—C bond is one of the most important elementary steps in organic syntheses. The decarboxylation of acids containing electron withdrawing substituents or (reverse) reactions such as Claisen, Perkin, Michael and Mannich condensations may be cited as reactions incorporating such a stage. All these reactions are essentially S_E1 processes.

SCHEME 1.



In step 1, rate-determining cleavage of the C—C bond is facilitated by electron-release from a substituent, X, which results in a carbanion and a corresponding electrophilic particle. In step 2, a solvent molecule transfers a proton to the generated carbanion in a fast step.

Investigations of structural factors influencing the rate and thermodynamics of the C—C bond cleavage are rather scanty. One of the few examples is the effect of bases on decarboxylation of acids with electron-withdrawing substituents.[1–6] The reaction rate has been shown to increase as the stability of the generated carbanion increases, however attendant steric factors also influence the reaction rate to a great extent and in the same direction. For example, in the halogen-substituted acids (trifluoro-, trichloro-, tribromo- and triiodoacetic acids) the influence of both of these factors increases progressively.[7]

The relative contributions of these factors cannot be quantitatively separated at present.

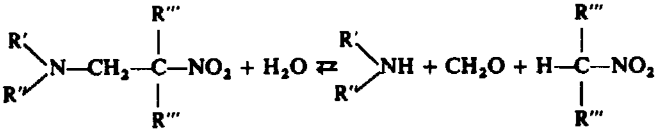
These results together with other published data[8] permit some preliminary conclusions as to the structural factors influencing the reactivity of a decomposing substance analogous to the situation with S_N1 reactions.[9]

Increased stability of the carbanion and the electrophilic component, as well as an increasing anion centre nucleophilicity and increased ground state steric strain relieved in the transition state all greatly enhance the reactivity.

By contrast, the stabilization of electron-release by H-bond formation with the solvent inhibits a decomposition reaction.

In the present paper we have attempted to estimate quantitatively the effects of structural variation on cleavage of the C—C bond. We have chosen the reversible decomposition of Mannich bases, formed by condensation of amines, formaldehyde and nitro compounds as a model reaction, because in such compounds one can vary the nature both of a leaving group (nitro compound carbanion) and the amine component. Keeping the steric factors constant, it is also possible to vary the stability of the leaving group and *vice versa*. The reaction involves no rearrangements and the stability of the leaving group can be estimated by measuring the dissociation constants of the conjugate acid. Finally the decomposition of Mannich bases is of interest because the forward and reverse reactions proceed through the same transition state according to the principle of microscopic reversibility. Thus a study of the reverse reaction may also shed light on the forward reaction, i.e. Mannich condensation.

Scheme 2



$$R'R''N{-}CH_2{-}C(R''')_2{-}NO_2 + H_2O \rightleftharpoons R'R''NH + CH_2O + H{-}C(R''')_2{-}NO_2$$

The mechanism of this reaction has been the subject of some controversy,[10, 11] and the exact nature of the intermediate particle generated from formaldehyde and the amine which participates in the rate limiting stage of the entire process is an open question. It should be noted that in all quantitative studies on the mechanism of this reaction, only the forward reaction has been considered.[10, 11] Owing to its intricacy, unequivocal interpretation of the reaction mechanism involving all the factors is rather troublesome and sometimes impossible.

On this basis the investigation of the reverse reaction, therefore, i.e. (decomposition to starting components) seemed to be more promising.

RESULTS

The following compounds were investigated: 1-N-methylamino-2-methyl-2-nitropropane (I), 1-N-dimethylamino-2-methyl-2-nitropropane (II), 1-N-diethylamino-2-methyl-2-nitropropane (III), 1-N-di-n-propylamino-2-methyl-2-nitropropane (IV), 1-N-diisopropylamino-2-methyl-2-nitropropane (V), 1-N-diethylamino-2,2-dinitropropane(VI), 1-N-dimethylamino-2-ethyl-2-nitrobutane(VII), 1-N-diethylamino-2-ethyl-2-nitrobutane (VIII) and 1-piperidyl-2-methyl-2-nitropropane (IX).

In aqueous solutions within the substrate concentration range (10^{-3}–10^{-4}M) all compounds quantitatively decompose to the respective amines, nitro compounds and formaldehyde.

A kinetic study of the decomposition reaction was performed in phosphate and acetate buffer solutions employing both spectrophotometric and polarographic techniques.

Compounds I–V decompose to give the 2-nitropropyl carbanion absorbing at 223 mμ (ε_{max} 11,700).[12] Solutions of this anion obey the Lambert–Ber law, and the absorption of the anion is much greater than that of other reaction components (the extinction coefficients of which do not exceed 100 at this wave length). Compounds VII and VIII decompose to 3-nitropentyl carbanion absorbing at 231·5 mμ (ε_{max} 10,400). Interaction of 2-nitropropyl and 3-nitropentyl carbanions with the proton donors is much slower in the pH range studied (4·80–12·80) than is the decomposition itself. Thus the reaction kinetics could be conveniently studied by measuring optical density changes of solutions at 223 mμ and 231·5 mμ.

The Mannich bases (II, III, V and VII) are reduced on the dropping mercury electrode producing a diffuse wave whose limiting current is proportional to the concentration of the base.

All reaction products except 2-nitropropane are polarographically inactive, but the rate of 2-nitropropane generation is sufficiently slow as to have no effect on the entire process, as has already been mentioned.

Thus the reaction kinetics can also be studied by following the change of a limiting current at a certain potential (Experimental).

These two different techniques, when used parallel, yield results, coincident within the experimental error.

The decomposition of VI is very rapid in the pH range employed for the study of other compounds and its rate of dissociation may be followed by the polarographic techniques at H_0 from 0·3 to 0·8, by following the decrease in concentration of the starting compound.

The quantity of decomposed β-nitroamine equals exactly the quantity of nitro compound generated. The kinetics of the decomposition of all the compounds studied were generally straight-forward, and rates exhibited a first-order dependence on the nitroamine concentration at a constant pH and constant ionic strength over a wide range of concentrations.

Experimental data for the decomposition of I–VIII are presented in Tables 1 and 2. Plots of log K_{obs} *vs* pH for I–V, VII and VIII are given in Fig. 1.

Attention is drawn to the fact that for compounds I, II, III and VII at certain pH's, a curve assymptotically approaches a constant value. Initially these plots are straight lines having a unit slope. The same slope is observed for the compounds IV, V and VIII. A plot of K_{obs} *vs* H_0 for VI at 10° is shown in Fig. 2. This plot is also a straight line of unit slope.

Increases in ionic strength have an adverse effect on the reaction rate (Table 1), whereas variations in buffer composition and in buffer capacity of the media have no effect on the reaction velocity.

TABLE 1. DECOMPOSITION OF MANNICH BASES IN WATER AT IONIC STRENGTH 0·1 AND 25°* (IN ALL THE CASES WHERE TEMPERATURE IS NOT INDICATED)

1-Methylamino-2-methyl-2-nitropropane (I)

pH	$k_{obs} \times 10^4$ (mole/l sec)	Method
7·54	2·05	S
8·21	3·25	S
8·78	3·63	S
11·58	3·81	S
12·78	3·63	S

1-Dimethylamino-2-methyl-2-nitropropane (II)

t°C	pH	k_{obs} (mole/l sec)	Method
25	5·66	$8{\cdot}4.10^{-4}$	P*
25	5·87	$1{\cdot}1.10^{-3}$	P
25	5·96	$1{\cdot}4.10^{-3}$	P
25	6·25	$2{\cdot}4.10^{-3}$	P
25	6·53	$3{\cdot}9.10^{-3}$	P
25	7·11	$5{\cdot}3.10^{-3}$	P
25	9·59	$5{\cdot}7.10^{-3}$	P
25	8·80	$6{\cdot}2.10^{-3}$	S
25	9·70	$5{\cdot}77.10^{-3}$	S
25	10·25	$5{\cdot}80.10^{-3}$	S
25	10·60	$6{\cdot}05.10^{-3}$	S
30	5·66	$1{\cdot}6.10^{-3}$	P
35	5·66	$2{\cdot}88.10^{-3}$	P
40	5·66	$5{\cdot}65.10^{-3}$	P
45	5·66	$1{\cdot}0.10^{-2}$	P
10	10·25	$9{\cdot}68.10^{-4}$	P
30	10·25	$1{\cdot}27.10^{-2}$	P
35	10·25	$1{\cdot}69.10^{-2}$	P
42	10·25	$3{\cdot}70.10^{-2}$	P

1-Diethylamino-2-methyl-2-nitropropane (III)

pH	k_{obs} (mole/l sec)10^2	Method
4·90	0·037	P
5·98	0·402	S
6·13	0·50	P and S
6·20	0·73	P and S
6·40	1·01	S
6·68	1·48	S
6·80	1·95	S
7·00	2·90	S
7·22	4·33	S
7·58	5·60	S
7·80	6·30	S
8·88	8·50	S
10·25	8·30	S
10·94	8·40	S
11·38	8·80	S
6·68	1·05†	S
6·68	0·83‡	S

1-di-n-propylamino-2-methyl-2-nitropropane (IV)

pH	k_{obs} (mole/l sec)10^3	Method
5·03	2·02	S
5·38	4·14	S
5·57	5·97	S
5·83	10·60	S
6·25	27·70	S*
6·46	35·50	S

1-Diisopropylamino-2-methyl-2-nitropropane (V)

t°C	pH	k_{obs} (mole/l sec) $\times 10^2$	Method
10	4·80	0·21	P
10	4·90	0·25	S
10	5·02	0·383	S
10	5·60	1·23	S
10	5·80	2·02	S
10	6·01	3·11	S
10	6·10	4·18	S
10	6·30	6·38	S
10	6·47	9·50	S
10	6·62	13·40	S
10	6·80	18·75	S
6	5·05	0·188	S
18	4·99	0·982	S
25	4·96	2·24	S
30	4·96	5·05	S

1-Dimethylamino-2-ethyl-2-nitrobutane (VII)

pH	k_{obs} (mole/l sec)10^3	Method
5·87	2·40	P
6·25	4·40	P
6·46	5·99	P
6·65	7·65	P
6·98	10·06	P
7·71	13·10	P
8·43	13·90	S

1-Diethylamino-2-ethyl-2-nitrobutane (VIII)

pH	k_{obs} (mole/l sec)10^3	Method
5·60	5·31	S
6·25	21·60	S
6·46	34·00	S
6·98	81·60	S

1-Piperidyl-2-methyl-2-nitropropane (IX) (decomposition in 0·1N KOH)		
t°C	$k_{obs}.10^2$	Method
25	2·47	S
20	1·48	S
15	0·84	S
10	0·41	S

* S—spectrophotometric method.
P—polarographic method.
† The constant was measured at $\mu = 1$.
‡ The constant was measured at $\mu = 2$.

* Each k_{obs} is an average of 2–3 measurements deviating by no more than 3–5%.

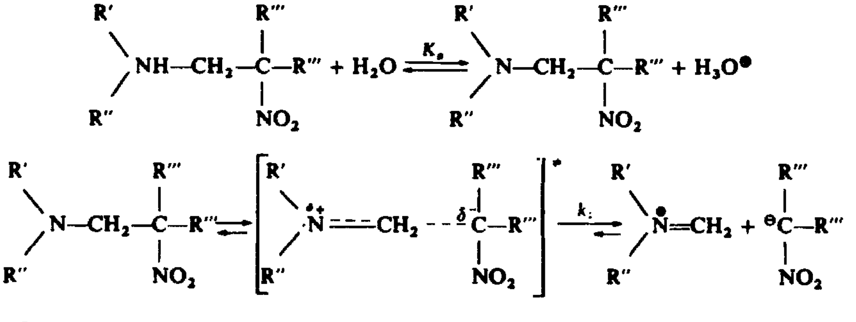
TABLE 2. DECOMPOSITION OF 1-DIETHYLAMINO-2,2-DINITROPROPANE (VI) IN AQUEOUS SULPHURIC ACID ($\mu = 0{\cdot}1$)

t°C	H_0	k_{obs} (mole/l sec)
10	1·05	1·6.10^{-2}
10	0·96	1·2.10^{-2}
10	0·76	6·16.10^{-3}
10	0·61	3·86.10^{-3}
10	0·58	3·66.10^{-3}
10	0·47	2·99.10^{-3}
10	0·37	2·26.10^{-3}
10	0·34	2·16.10^{-3}
10	0·26	1·56.10^{-3}
10	0·18	1·29.10^{-3}
15	0·61	8·35.10^{-3}
20	0·61	1·39.10^{-2}
25	0·61	2·39.10^{-2}

DISCUSSION

Our data on the decomposition of Mannich bases are in complete accord with the following mechanism:

SCHEME 3



The first stage of the reaction is effectively at acid-base equilibrium between the Mannich base and its conjugate acid. The second stage is rate determining, involving C—C bond cleavage and formation of a carbanion and an immonium cation.[10] This contention is well supported by the experimental facts.

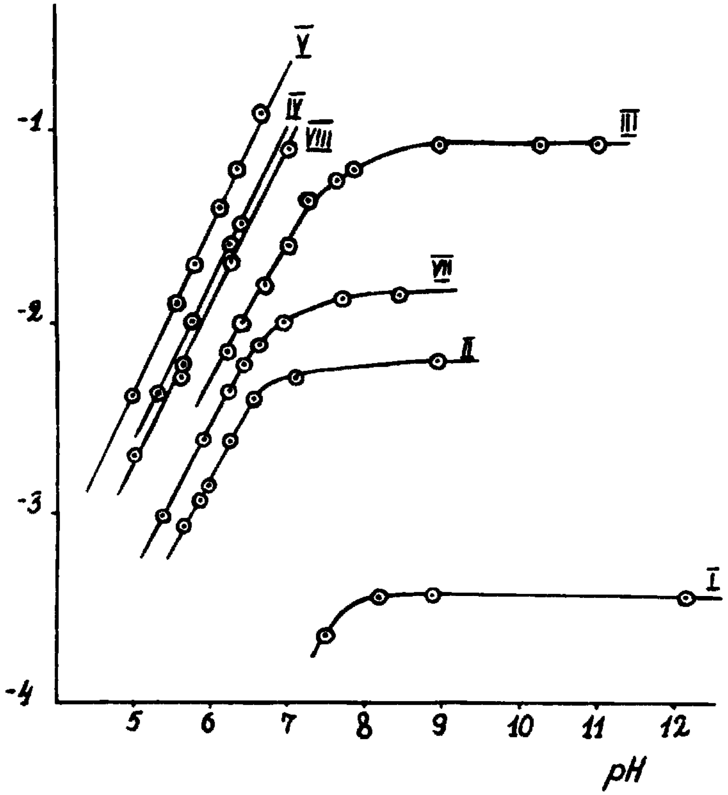


FIG. 1 The plots of log k_{obs} of Mannich bases decomposition versus pH at 25° and $\mu = 0{\cdot}1$.

(a) There is no general acid or base catalysis but there is evidence of specific catalysis of the reaction by OH ions[13] (see above).

These results indicate that the rate-determining step is preceded by an acid-base equilibrium, the position of which is effected by the pH of the solution. There is no base or acid catalysis in the rate-determining step of the reaction.

(b) The reaction velocity for bases I, II, III and VII reaches a limiting value at alkali concentration (Fig. 1) corresponding to complete conversion of AH^+ to A. At this point the observed rate constant equals the rate for C—C bond cleavage (k_r).

(c) The increase of ionic strength influences the observed rate by shifting the acid base equilibria to the left.

An alternative mechanism can be envisaged with participation of a water molecule in the second rate-determining step of the reaction. This scheme can also explain all the observed facts, however such a mechanism would necessarily demand general base catalysis for the rate-determining step. The latter could not be detected even with a strongly nucleophilic phosphate ion.[14]

Finally, activation energies and entropies (Table 3) are of the magnitude expected for unimolecular decomposition of the Mannich base as the rate-determining step of the reaction (Table 3).

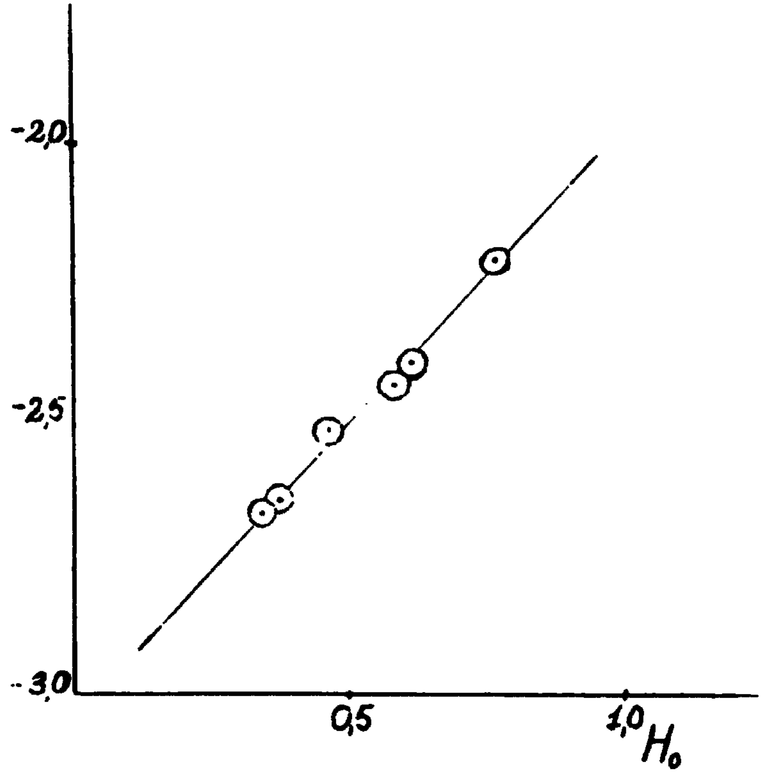


FIG. 2 The plot of log k_{obs} of VI *vs* H_0 at 10°.

According to the principle of the microscopic reversability, the reverse reaction, i.e. Mannich base formation, should have condensation of a nitro compound with an immonium cation formed from an amine and formaldehyde as the rate-determining step.

Scheme III is described by the following equation,

$$1/k_{obs} = 1/k_r + \frac{a_{H_3O^\oplus}}{K_a \cdot k_r}$$

where k_{obs} is the observed rate constant, k_r is the rate constant for the C—C bond cleavege and K_a is the dissociation constant of the conjugated acid of the Mannich base. This expression is a modification of the well-known equation for OH catalyzed reactions.[15]

A typical plot of $1/k_{obs}$ *vs* $a_{H_3O^\oplus}$ for the III is shown in Fig. 3. The slopes and the intercepts give K_a and k_r values respectively for the compounds II, III and VII at 25° (Table 3). For compounds IV, V and VII this method cannot be used, since the pH range where $K_a \geqslant a_{H_3O^\oplus}$ for these compounds does not lie within the limits of our experimental techniques.

Intercepts of the plot $1/k_{obs}$ *vs* $a_{H_3O^\oplus}$ are too small for precise measurement, and in order to separate k_r and K_a in this case we used correlation equations (Experimental).

The values of k_r and K_a for the series I–V and V–VIII are given in Table 3.

TABLE 3. IONIZATION CONSTANTS OF CONJUGATE ACIDS, REAL RATES OF DECOMPOSITION, ENTHALPY AND ENTROPY OF DECOMPOSITION OF MANNICH BASES

Structure of compound		K_a mole/l	k, sec^{-1}	Constants determination method	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$
$MeNHCH_2C(Me)_2NO_2$	I	—	$(3{\cdot}55 \pm 0{\cdot}21)\cdot 10^{-4}$	Kinetic data	$24{\cdot}0 \pm 1{\cdot}0$	1·34
$Me_2NCH_2C(Me)_2NO_2$	II	$(3{\cdot}3 \pm 0{\cdot}2)\cdot 10^{-7}$	$(6{\cdot}1 \pm 0{\cdot}2)\cdot 10^{-3}$	"	$19{\cdot}5 \pm 0{\cdot}8$	−4·0
$Et_2NCH_2C(Me)_2NO_2$	III	$(5{\cdot}0 \pm 0{\cdot}6)\cdot 10^{-8}$	$(8{\cdot}5 \pm 0{\cdot}15)\cdot 10^{-2}$	"	$14{\cdot}4 \pm 1{\cdot}9$	−15·8
$n\text{-}Pr_2NCH_2C(Me)_2NO_2$	IV	$4{\cdot}47\cdot 10^{-8}$	0·39	K_a obtained from correlation equations	— —	—
$i\text{-}Pr_2NCH_2C(Me)_2NO_2$	V	$1{\cdot}5\cdot 10^{-8}$	16·4	"	—	—
$Et_2NCH_2C(Me)_2NO_2$	VI	$1{\cdot}0\cdot 10^{-5}$	$6{\cdot}0\cdot 10^{2}$	K_a obtained from correlation dependence	—	—
$Me_2NCH_2C(Et)_2NO_2$	VII	$(2{\cdot}91 \pm 0{\cdot}07)\cdot 10^{-7}$	$(1{\cdot}34 \pm 0{\cdot}13)\cdot 10^{-2}$	Kinetic data	$19{\cdot}4 \pm 1{\cdot}0$	−2·7
$Et_2NCH_2C(Et)_2NO_2$	VIII	$5{\cdot}0\cdot 10^{-8}$	0·27	—	—	—
 $N\text{-}CH_2\text{-}C(Me)_2NO_2$	IX	—	$(2{\cdot}47 \pm 0{\cdot}12)\cdot 10^{-2}$	Kinetic data	$20 \pm 0{\cdot}5$	0

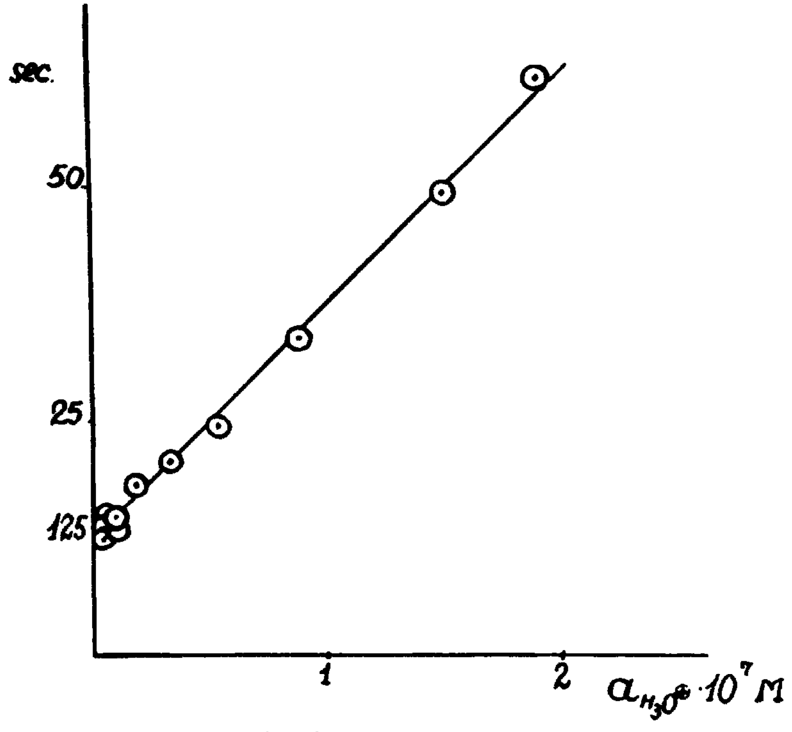


FIG. 3 $1/k_{obs}$ of III *vs* hydroxonium ion activity.

As already mentioned the rate of decomposition of compound VI is measurable only in sulfuric acid solution at acidity function of 0·3 to 0·8. The plot of log k_{obs} *vs* H_0 for this compound is given in Fig. 2, and is linear with unit slope. This observation is consistent with reaction according to scheme III.

The rate equation is

$$\text{rate} = k_r \frac{C_{VI}\, f_{VI}}{f^{\ddagger}} = \frac{k_r \cdot K_a C_{VIH}\, f_{VIH}}{A_{H\oplus}\, f^{\ddagger}}$$

where C_{VIH} is the concentration of protonated Mannich base, C_{VI} is the concentration of free base.

Since the protonated form of the Mannich base and the activated complex differ in composition only by a single proton, they have the same relationship as B and $BH^{\oplus}$. Hence $\frac{A_{H\oplus}\, f^{\ddagger}}{f_{VIH}}$ may be expected to be equal to h_0 and the log of the rate constant will be a linear function of H_0 with a slope of unity:

$$k_{obs} = \frac{k_r K_a}{h_0}\ ;\ \lg k_{obs} = \lg(k_r \cdot K_a) + H_0$$

Unfortunately we were unable to determine k_r and K_a directly from the kinetic data, since compound VI under the experimental conditions is completely protonated. In order to find the values for compound VI we employed an approximate correlation which exists between amine dissociation constants in acetonitrile[16] and in water. The stability of VI as well as of other β-nitroamines allowed determination of its K_a value in this solvent and consequently an approximate estimation of its K_a and k_r values in water (Experimental).

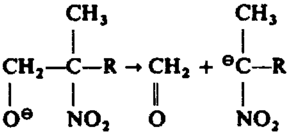
The values of K_a and k_r for all the β-nitroamines studied are presented in Table 3, together with the enthalphies and entropies of activation for the C—C bond cleavage. This point needs some classification. The observed rate constant at $A_{H_3O^\oplus} \geqslant K_a$ equals $k_r \cdot K_a$. The energy of activation so determined is a sum of $\Delta H^\ddagger + \Delta H_a$ under these experimental conditions (where ΔH_a is the dissociation enthalpy of the conjugated acid of the β-nitroamine). Only at $A_{H_3O^\oplus} < K_a$ does the experimental activation energy correspond to the true activation energy of the Mannich base decomposition.

We are thus in a position to discuss how structural factors influence the rate and the thermodynamics of the C—C bond cleavage.

Firstly, III and VI closely resemble each other sterically but differ in the stability of their leaving groups. Hence the approximate 6000 fold difference between k_r for VI and III is a quantitative measure of the increase caused by this factor. This can be compared with the rate of water-catalysed dissociation of 1,1-dinitroethane which is 10^5 times as great as the dissociation rate for 2-nitropropane.[12, 17]

The difference in the decomposition rates of β-nitroalcohols of comparable structure is 100.[18]

SCHEME 4



$$\underset{\substack{|\\ O^\ominus}}{CH_2}—\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ NO_2}}{C}}—R \rightarrow \underset{\substack{\|\\ O}}{CH_2} + {}^\ominus\overset{\substack{CH_3\\ |}}{\underset{\substack{|\\ NO_2}}{C}}—R$$

when R = CH_3, NO_2.

These facts can be rationalized on the basis of the Hammond postulate.[19] The transition state may be expected to be nearer to the products for the water catalysed dissociation than for the nitroalcoholate decomposition, and the Mannich base dissociation can be considered as an intermediate case. Surprisingly, the acidity constant of 1,1-dinitroethane is only $10^{2.6}$ as large as that of 2-nitropropane[20, 21] and the difference of their conjugate-base carbon basicities is also of the same magnitude.[17] At present we cannot explain why such a small difference in the stability of the leaving group results in such a large difference in transition state energies.

Data obtained provide certain evidence on the "pushing" effect of the lone electron pair on the amine nitrogen. By analogy with protolytic reactions one may suggest *apriori* that the Brönsted catalysis law is also valid for the series investigated: i.e. the stronger the base, the greater is its decomposition rate. Indeed, comparison of the decomposition constants for sodium 2-nitroisobutylate and 1-amino-2-methyl-2-nitropropane* seems to support the applicability of this law (Table 4).

There is, however, no correlation in the β-nitroamine series between amine basicity

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* The value K_a for this compound was estimated from the correlation equation for the p*Ka* of amines,[22] and its k_r value was determined from the graph of log k_r *vs* E_s for the β-nitroamines investigated.

TABLE 4. EFFECT OF A NUCLEOPHILIC CENTER ON THE C—C BOND CLEAVAGE

Compound	p*Ka*	k_r (sec^{-1})
$HO\,CH_2\,C(Me)_2\,NO_2$	14·1	2·34
$NH_2\cdot CH_2\,C(Me)_2\,NO_2$	7·26	$3{\cdot}16.10^{-7}$
$HO\,CO\,C(Me)_2\,NO_2$	1·98	$1{\cdot}95.10^{-3}$

and decomposition rate (Table 3) and the rate for the nitroisobutyrate ion decomposition is even larger than that of 1-amino-2-nitro-2-methylpropane.

On the basis of their basicity one would have anticipated quite the opposite results. Thus the Brönsted catalysis law cannot be reliably applied to reactions of the S_E1 type.

The effect of alkyl substituents on the amine nitrogen on the rate of the Mannich base decomposition proved to be interesting and unexpected.

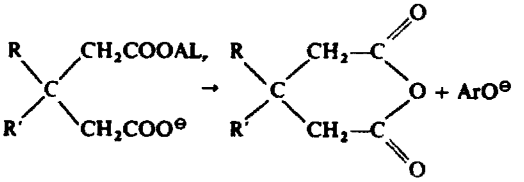
The effect is large. For example, V decomposes 10^5 times faster than I, even though the only factor changed is the substituents at the amine nitrogen, and, as already mentioned, the transition state of the process lies near to the products. Thus the transition state is probably characterized by a considerable charge separation with a partly developed double bond character at the nitrogen. Hence inductive and the hyperconjugative effects of the alkyl groups stabilizing the formed immonium cation seem to offer at first a reasonable explanation for the order of reactivity.

However, there is no correlation of the reaction rates with the inductive substituent constants of the alkyl groups. Attempts to take account of the steric effects by applying the two-parameter correlation ($\log k = \log k^\circ + \rho^*\sigma^* + \delta_s \Sigma E_s$) also failed.

A correlation does exist between the observed rate constants and Taft's steric substituents constants but the deviations are large.

The values of k_r do however correlate well with the rates of solvolysis of 3,3-disubstituted mono-*p*-bromophenyl glutarate (Scheme V). The latter reaction has been shown to be influenced only by the effective bulk of the substituent groups.[23]

SCHEME 5



where $R = H$, $R' = CH_3$ and $R = R' = CH_3$, C_2H_5, n-C_3H_7, i-C_3H_7.

In Fig. 5, the log k_r values are plotted for this study *vs* the solvolysis rate constants for the corresponding substituents at the 3,3-position. The best straight line is constructed by the least square method (correlation coefficient −0·991).

Comparison of k_r for II–VII and III–VIII (Table 3) provides further proof of the importance of steric effects in this reaction.

The rate of decomposition of VII is twice the rate of decomposition of II. Compound VIII is more reactive than III by a factor of 3. This increase can be ascribed only to steric effects because the 3-nitropentyl anion formed in the case of VII and VIII cannot be considered less basic than the 2-nitroproprpyl anion. 3-Nitropentane

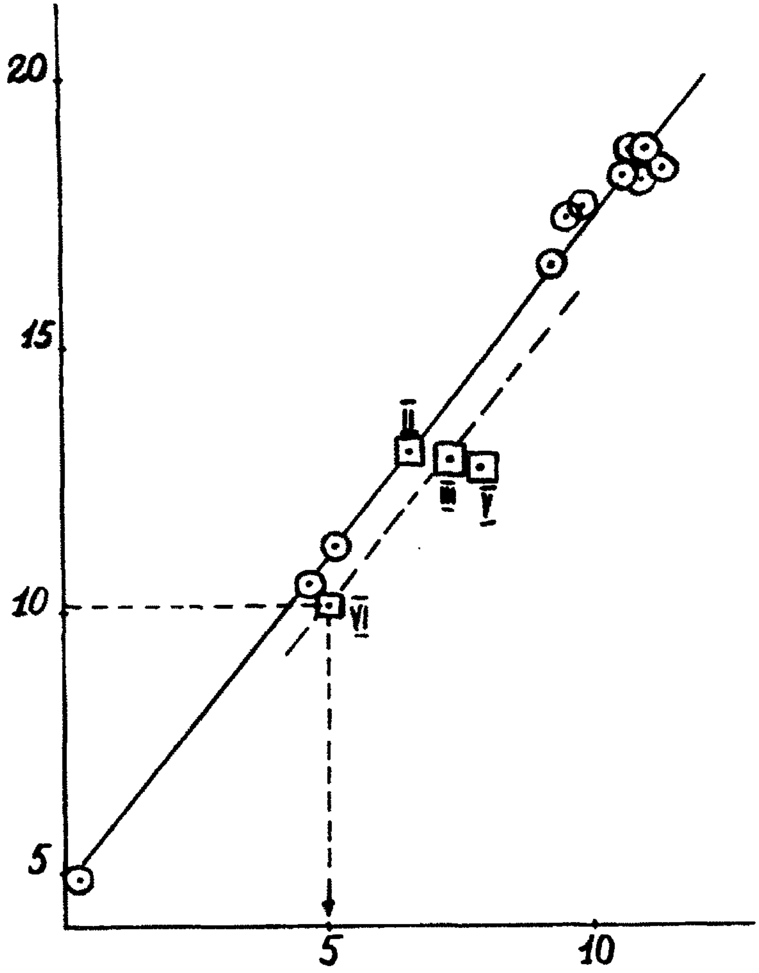


FIG. 4 Correlation of ionization constants of amine conjugated acids in water and acetonitrile: O—literature data. The squares correspond to β-nitroamines. Numbers correspond to those in the text.

dissociates at least five times slower than 2-nitropropane (Experimental). In addition, the inductive effect of substituents on the amine nitrogen in compound IX must be as large as in III.[22] The observed k_r value is intermediate between that for II and III. The analogous deviations of piperidine from the expected behaviour can also be traced to its steric peculiarity.[24]

It is interesting to note that no inductive contribution from alkyl substituents was observed in this reaction. The electrical effects are probably too small to be separated from the predominant steric effects of alkyl groups in the Mannich base decomposition.

Three possible mechanisms may be postulated to account for the predominantly steric rate-accelerating effect of the alkyl groups in the reactions studied.

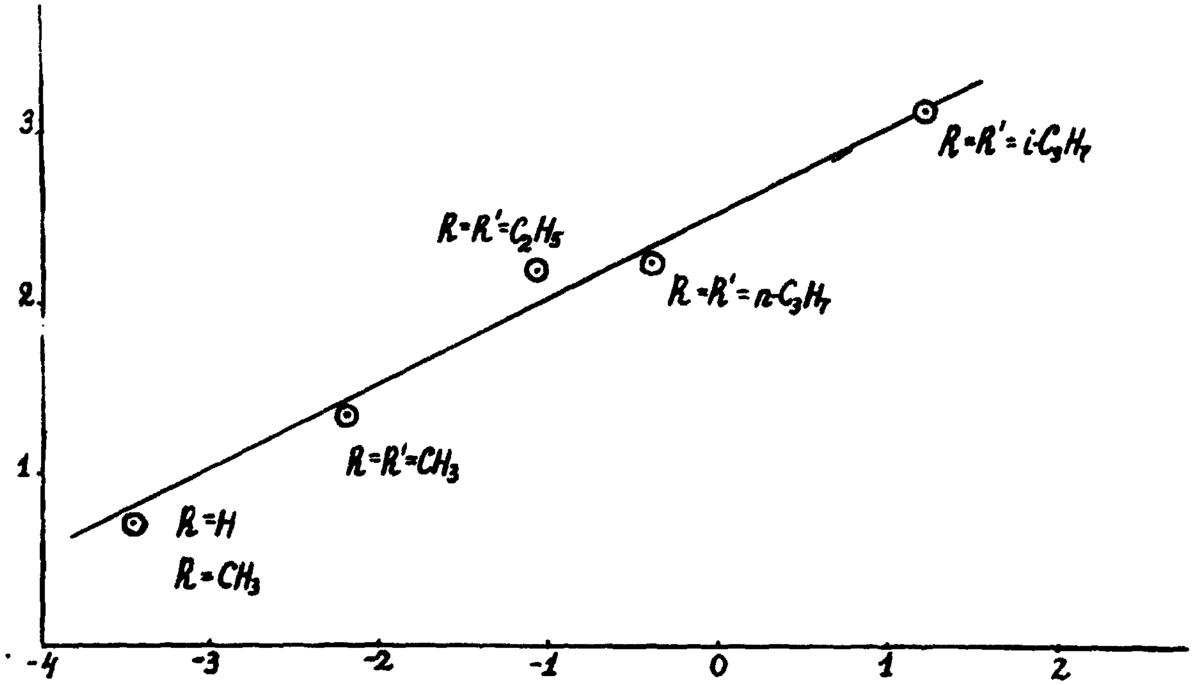


Fig. 5 Logarithms of decomposition rate constants of β-nitroamines *vs* the logarithms of hydrolysis rate constants of glutarate monoesters having the same substituents.

1. Large ground-state destabilizations and relief of steric strains in the transition state of the reaction provides the simplest explanation of the effect. A Stuart model of V is a good illustration of a sizeable destabilization of the ground state. The Me groups of V are so closely packed that rotation is impossible. There seems to be no alternative explanation for the greater dissociation rate of VII and VIII compared to II and III.

This mechanism should lead to a decrease in $\Delta H^{\ddagger}$ and an increase in $\Delta S^{\ddagger}$, however the opposite is in fact true (cf. Table 3), so that alternative mechanisms must be considered.

2. An increase in population of the most reactive conformation arising from the effective bulk of substituents is the basis for a second possible mechanism. The excellent correlation between the dissociation constants and rates of hydrolysis of 3,3-substituted mono-*p*-bromophenylglutarate esters (cf. above) in which rate acceleration is of steric origin supports this view.

But then the k_r changes should result mainly from the $\Delta S^{\ddagger}$ variation.[26] This has no experimental support. As can be readily seen, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ both make contributions to the $\Delta F^{\ddagger}$ changes.

3. A third possible mechanism takes account of the steric effects of the alkyl groups which hinder solvation of the amine long pair. Evidence of such hindrance has been clearly demonstrated.[27]

Decreasing amine solvation would result in its increasing nucleophilicity (steric hindrance to an external attack is of no importance here). Thus this mechanism may explain the increase in the rate with an increase of alkyl groups size. The modes of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ changes can also be explained on this basis. The decrease in $\Delta H^{\ddagger}$ may be a consequence of increased nucleophilicity of the amine lone pair, and the accompanying decrease in $\Delta S^{\ddagger}$ is probably associated with greater structure of solvents in the transition state as compared to the ground-state for the bulky substituents.

A combination of the first and third mechanisms affords the most logic explanation of the steric effects observed for alkyl groups. It should be noted that the results of the present investigation can be interpreted as further proof of the absence of any positive inductive properties of the alkyl groups. This point of view is now gaining more experimental support.[28, 29]

EXPERIMENTAL

Preparation and purification of reagents. The phosphate and acetate buffers were prepared from the "kh.ch" grade reagents. KOH solution (ch.d.a grade) contained no $CO_3^{=}$ ions. The pH of buffers were measured on a "Radiometer" PHM-4c instrument. Water was twice distilled before use (the second time under N_2). Sulfuric and chloric acids were of "kh.ch." grade. Picric acid was recrystallized thrice from acetone and dried in vacuum at 50°. Tetraethylammonium picrate, prepared by the prescribed method,[30] was recrystallized thrice from alcohol and dried in vacuum over $CaCl_2$ and P_2O_5 at 50°. Acidity functions of the aqueous sulfuric acid solutions were estimated at 25° from the literature data.[31] In the chosen H_0 range, change of H_0 with temperature[32] was negligible.

Synthesis of Mannich bases

1-*Methylamino-2-methyl-2-nitropropane* (I). 3·6 g of paraform was slowly added to a cooled and stirred 25% soln of methylamine (0·36M) in water. The mixture was then stirred at room temp for 2 hr and added with stirring to a previously prepared 2-nitropropane (0·12M) soln in 18·5 ml of 0·13M KOH. A stream of CO_2 gas was passed through the reaction mixture, the latter was extracted with ether, the ether extracts were dried over calcinated $MgSO_4$ and distilled successively from glass and then from quartz flasks, b.p. 64–65°/9 mm, n_D^{20} 1·4363; lit.[33] b.p. 60–62°/6 mm, n_D^{20} 1·4368.

1-*Dimethylamino-2-methyl-2-nitropropane* (II) was prepared by the described method[34] from dimethylamine hydrochloride, formaldehyde and 2-nitropropane. The product purified by vacuum distillation had b.p. 58–60°(6 mm; n_D^{20} 1·4327; lit.[34] b.p. 65–66°/10 mm, n_D^{20} 1·4330.

1-*Diethylamino-2-methyl-2-nitropropane* (III) was prepared[34] from diethylamine, formaldehyde and 2-nitropropane. The product thus obtained was purified by vacuum distillation: b.p. 85–87°/11–12 mm, n_D^{25} 1·4400; lit.[35] b.p. 63–64°/2 mm, n_D^{25} 1·4393.

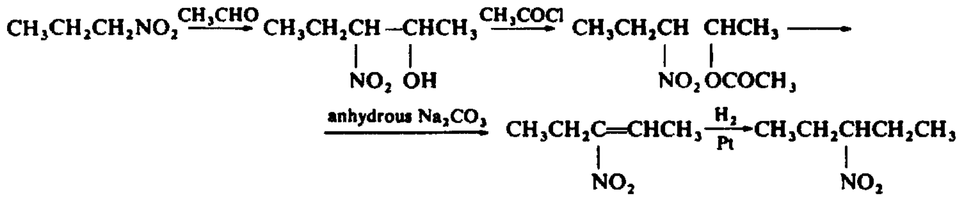
1-*Di-n-propylamino-2-methyl-2-nitropropane* (IV) was prepared analogously to I, b.p. 112–115°/12 mm; n_D^{20} 1·4437. (Found: C, 59·27, 59·51; H, 10·95, 10·99; N, 13·99, 14·15. Calc for $C_{10}H_{22}N_2O_2$: C, 59·41; H, 10·89; N, 13·86).

1-*Diisopropylamino-2-methyl-2-nitropropane* (V) was prepared[36] from diisopropylamine, paraformaldehyde and 2-nitropropane in benzene. The product was distilled *in vacuo*, b.p. 100–101°/6 mm; n_D^{20} 1·4500; lit.[36] b.p. 96·5–97°/2 mm; n_D^{20} 1·4505.

1-*Diethylamino-2,2-dinitropropane* (VI) was prepared by the lit. method,[37] b.p. 68–69°/0·5 mm, n_D^{25} 1·4515; lit.[37] b.p. 55/0·02 mm, n_D^{25} 1·4515. The product was distilled from a quartz flask before use.

3-*Nitropentane* was prepared according to the scheme:

SCHEME 6



$$CH_3CH_2CH_2NO_2 \xrightarrow{CH_3CHO} CH_3CH_2\underset{NO_2}{CH}-\underset{OH}{CH}CH_3 \xrightarrow{CH_3COCl} CH_3CH_2\underset{NO_2}{CH}\ \underset{OCOCH_3}{CH}CH_3 \longrightarrow$$

$$\xrightarrow{\text{anhydrous } Na_2CO_3} CH_3CH_2\underset{NO_2}{C}{=}CHCH_3 \xrightarrow[Pt]{H_2} CH_3CH_2\underset{NO_2}{CH}CH_2CH_3$$

3-*Nitropentanol* was prepared by the lit. method,[38] b.p. 74–76°/1·5 mm, n_D^{25} 1·4410; lit.[39] b.p. 78°/2 mm, n_D^{25} 1·4410.

2-*Acethyl-3-nitropentane*. A 5–6 fold volume excess of freshly distilled CH_3COCl was added to 3-nitropentanol-2. The reaction mixture was refluxed for 2 hr. Unreacted acetyl chloride was removed on a rotary evaporator and the product was used without further purification.

3-*Nitropentene-2*. A mixture of 0·06 mole of 2-acetyl-3-nitropentane, 6 ml anhyd benzene and 0·03 mole anhyd Na_2CO_3 was refluxed for 4 hr, then filtered and distilled under vacuum. Fraction gave material b.p. 72°/22 mm lit[40] b.p. 57·8°/10 mm.

3-*Nitropentane*.[41] 3-Nitropentene-2 was hydrogenated on Pt black in anhyd THF. The catalyst was filtered off and the 3-nitropentane isolated by distillation, b.p. 150–6°/746 mm (66–69/40 mm); n_D^{25} 1·4118; lit.[42] b.p. 152–155°/746 mm; n_D^{25} 1·4091.[39]

1-*Dimethylamino-2-ethyl-2-nitrobutane* (VII) was synthesized analogously to I, b.p. 103–6°/19 mm (97–98°/16 mm), n_D^{20} 1·4470. (Found: C, 55·18, 55·45; H, 10·57, 10·51. Calc for $C_7H_{18}N_2O_2$: C, 55·17; H, 10·34).

The NMR spectrum (solvent CCl_4; internal reference—hexamethyldisiloxane) showed: singlet $\delta = 2·7$ (methylene group); singlet $\delta = 2·1$ (N-Me groups); quadruplet $\delta = 1·8$ (methylene groups of Et substituents); triplet $\delta = 0·8$ ppm (Me groups of Et substituents).

1-*Diethylamino-2-ethyl-2-nitrobutane* (VIII) was synthesized analogously to I, b.p. 120°/17 mm, n_D^{20} 1·4480. (Found: C, 59·19, 59·37; H, 10·74, 10·83; N, 14·03, 13·94. Calc for $C_9H_{22}N_2O_2$: C, 59·40; H, 10·89; N, 13·86).

1-*Piperidyl-2-methyl-2-nitropropane* (IX) was synthesized analogously to I, b.p. 119–120/8 mm, n_D^{20} 1·4649. (Found: C, 57·50, 57·65; H, 9·70, 9·70; N, 15·47, 15·55. Calc for $C_9H_{18}N_2O_2$: C, 58·04; H, 9·74; N, 15·04).

Kinetic measurements

Polarographic measurements were carried out using an automatic electronic polarograph LP-60 with a forced dropping mercury cathode. The characteristics of the capillary were: m = 0·925 mg/sec, $t = 0·26$ sec; anode—calomel electrode. The test soln was placed in a cell having 10 ml useful volume. O_2 was removed by a N_2 stream and the kinetic curve was recorded at a constant potential.

Spectrophotometric measurements were recorded on a "Hitachi" EPS-3 instrument using 1 cm cells placed in a thermostating cell-holder.

Kinetic curves were treated using the Guggenheim's method:[43] a simple first-order equation:

$$k_{obs} = \frac{2,3}{t} \log \frac{D_\infty - D_0}{D_\infty - D_x}$$

where D_∞ is an absorbance of solution at t_∞ (at least eight half-times); D_0—absorbance of soln at arbitrary zero time, t_0: D_x—absorbance of soln at time t.

Activation energies were estimated by the least square procedure.[44] Entropy and enthalpy of activation were evaluated using the equation:[45]

$$k_{obs} = \frac{kT}{h} \exp(\Delta S^{\ddagger}/R) \cdot \exp(-\Delta H^{\ddagger}/RT)$$

where

$$\Delta H^{\ddagger} = E_a - RT$$

Kinetics of 3-nitropentane dissociation in the presence of $OH^{\ominus}$

The spectrophotometric method was employed in a kinetic study of the 3-nitropentane dissociation. The UV absorption of the derived anion had ($\int^{1}_{\max}$ = 235·5 mμ; $\varepsilon_{\max}$ = 10·410). The 3-Nitropentane concentrations used were 10^{-4}–10^{-5}M.

At the investigated KOH concentration, 3-nitropentane is quantitatively converted into its anion. The observed constants are given in Table 5.

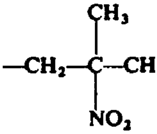
TABLE 5. HYDROXYL ION CATALYZED DISSOCIATION OF 3-NITROPENTANE IN WATER AT 25°

Normality of KOH	Average values of k_{obs} (sec^{-1})	
0·0780	$(5·08 \pm 0·22)\,10^{-3}$	$6·51\,10^{-2}$
0·1143	$(7·53 \pm 0·24)\,10^{-3}$	$6·59\,10^{-2}$
0·1796	$(11·96 \pm 0·34)\,10^{-3}$	$6·66\,10^{-2}$

Average value $(6·59 \pm 0·08)\,10^{-2}$ sec^{-1}

Dissociation constant of 1-*diisopropylamino-2-methyl-2-nitropropane* (V) *conjugated acid.* The value of K_a^{V} was obtained from the correlation for tertiary amines.[22]

$$pK_a = 9·61 - 3·3\,\Sigma\,\sigma_R^{*}$$



A σ_R^{*} value for $-CH_2-\overset{CH_3}{\underset{NO_2}{C}}-CH_3$ is unknown but this substituent is present in II and III. The value 9·61–3·3 $\sigma^{*}_{CH_2C(CH_3)_2NO_2}$ should be the same for all three Mannich bases. Our values for II and III were 6·64 and 6·48 respectively which is within the experimental error. pKa^{V} was estimated using an average σ^{*} = 6·56.

The dissociation constant for 1-*di-n-propyl-amino-2-methyl-2-nitropropane* was determined in the same way.

Dissociation constant of 1-*diethylamino-2-ethyl-2-nitrobutane* (VIII) conjugated acid. The K_a^{VIII} determination was based on the following conclusion. The acidity constant of VII is almost equal to that of II. Hence one may expect that the corresponding constant of VIII should be close to that of III. Thus, i.e.

$$k_r^{VIII} = \frac{K_a^{VIII} \cdot k_r^{VIII}}{k_a^{III}}$$

Dissociation constants of β-*nitroamines in acetonitrile.* General principles of determination are based on the fact that, either for tertiary amines, or picric acid the homoconjugation constant is very low in acetonitrile,[46, 47] and that the picrate ion does not combine with the conjugate acids of the tertiary amines.[46]

TABLE 6. IONIZATION CONSTANTS OF β-NITROAMINE CONJUGATE ACIDS IN ACETONITRILE AT 25°

Compound	K_a mole/l
1-N-Dimethylamino-2-methyl-2-nitropropane	$1{\cdot}1 \cdot 10^{-13} \pm 0{\cdot}2 \cdot 10^{-13}$[a]
1-N-Diethylamino-2-methyl-2-nitropropane	$1{\cdot}3 \cdot 10^{-13} \pm 0{\cdot}7 \cdot 10^{-13}$[a]
1-N-Diisopropylamino-2-methyl-2-nitropropane	$2{\cdot}0 \cdot 10^{-13} \pm 1{\cdot}0 \cdot 10^{-13}$[a]
1-N-Diethylamino-2,2-dinitropropane	$6{\cdot}3 \cdot 10^{-11} \pm 2{\cdot}2 \cdot 10^{-11}$[a]

[a] Standard deviation.

Spectrophotometric techniques was used, the absorbance of picric acid anion being recorded at 415 mμ (ε 1·36 10^4),[49] where other components do not absorb. Two methods have been used. Method I: *Ka* of conjugated acids of II, III, V and VI were estimated from the position of equilibrium in the reaction $Pi^{\ominus} + HB^{\oplus} \rightleftarrows PiH + B$ (where $Pi^{\ominus}$ is picric acid anion, $HB^{\oplus}$—β-nitroamine conjugate acid) by recording the absorbance of picric acid tetraethyl ammonate ($1 \cdot 10^{-3}$M) and chlorohydrates of II, III, V, VI ($1 \cdot 10^{-4}$M) at 415 mμ mixed in the 1 cm quartz cells placed into a cell-holder thermostated at 25 ± 0·1°. Dissociation constants were calculated from the equation:

$$Ka = \frac{[B][HPi]\,Ka^{HPi}}{[HB^{\oplus}][Pi^{\ominus}]\,f^2}$$

where Ka^{HPi} is the dissociation constant of picric acid (equal to $1 \cdot 10^{-11}$);[47] f is the ion activity coefficient from the Debye–Hückel limiting law.[49] K_a^{III} and K_a^{V} were estimated by the second method where the pH of the buffer (free bases III and V neutralized with chloric acid in acetonitrile) was determined spectrophotometrically with picric acid. Subsequent procedure and calculations were similar to those used in the first method.

Ionization constants of β-nitroamine conjugate acids are listed in Table 6.

Dissociation constant of 1-diethylamino-2,2-dinitropropane (VI) *conjugate acid in water.* K_a^{VI} value in water was estimated from the approximate correlation between amine dissociation constants in acetonitrile ($pK_a^{CH_3CN}$) and in water ($pK_a^{H_2O}$).

A plot of $pK_a^{CH_3CN}$ *vs* $pK_a^{H_2O}$ is given in Fig. 4. The values of the dissociation constants are taken from the lit.[46, 48]

Least square treatment gives the equation:

$$pK_a^{CH_3CN} = (1{\cdot}28 \pm 0{\cdot}11)\,pK_a^{H_2O} + 4{\cdot}7$$

As expected[46] the greatest deviation from the plot is observed for the most sterically hindered β-nitroamines. It may be assumed that the deviations are the same for the two equally hindered β-nitroamines II and VI. Using the value of $pK_a^{CH_3CN}$ for VI its ionization constant in water can be approximated to 5.

That value was determined at 25°, whereas k_{obs} for the decomposition of VI in water was determined at 10°.

In order to obtain k_{obs} at 25° we studied its temperature dependency in H_2SO_4 soln at $H_o = 0{\cdot}61$. Data are listed in Table 2. For 25° product $K_a \cdot k_r$ is 5·85 $10^{-3} \pm 0{\cdot}02$ 10^{-3} sec^{-1} mole/l, thus k_r is about 6·0 10^2 sec^{-1}.

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