Intra- and Inter-molecular Catalysis in the Iodination of 4-Diethylaminobutan-2-one and 5-Diethylaminopentan-2-one

By **Ronald P. Bell** * and **Bakir A. Timimi**, University of Stirling, Stirling, Scotland

Measurements are reported of the p*K* values of 4-diethylaminobutan-2-one and 5-diethylaminopentan-2-one and of their rates of iodination in aqueous buffer solutions at 25 °C. Rates of proton-transfer processes are derived by extrapolating rates of iodination to infinite concentration of tri-iodide ion. Velocity constants are obtained for intramolecular proton transfer to the diethylamino-group, and for intermolecular transfer to ethanolamine and to tris-(2-hydroxyethyl)methylamine. The mechanism of the intramolecular process is discussed, and its efficiency compared with that of similar processes.

SEVERAL instances have been reported[1-3] in which the removal of a proton from a carbon atom adjacent to a carbonyl group is facilitated by the presence of a suitably placed carboxylate group in the same molecule, and the same effect should be observable for other basic groups, such as dialkylamino. Kinetic observations attributable to intramolecular catalysis have been reported by Coward and Bruice,[4] but these are not of high accuracy, and no direct comparison was attempted between intramolecular and intermolecular catalysis. The present paper reports such a comparison for 4-diethylaminobutan-2-one and 5-diethylaminopentan-2-one: as in the investigations quoted above, the rates of proton transfer were derived from the rates of iodination, since iodine acts as a scavenger by reacting rapidly with the enolate species formed.

EXPERIMENTAL

Commercial specimens of the amino-ketones were dark red, but on fractionation *in vacuo* gave colourless liquids with boiling points agreeing with literature values (4-diethylaminobutan-2-one, 52 °C at 4—5 mmHg; 5-diethylaminopentan-2-one, 75·5—76 °C at 9—10 mmHg). Other materials were of AnalaR quality.

The pK values for the two amino-ketones were determined by measuring pH at 25 °C (glass electrode) in buffer solutions of total concentration *ca.* 3×10^{-3}M, made up to an ionic strength $I = 0{\cdot}1$ with sodium chloride. The usual corrections were made for hydrolysis, and in calculating the thermodynamic value of pK it was assumed that $\lg \gamma_{\pm} = -0{\cdot}100$ at $I = 0{\cdot}10$. The values obtained were pK (4-diethylaminobutan-2-one) = 10·14 ± 0·01 (mean of five determinations), pK (5-diethylaminopentan-2-one) = 10·01 ± 0·01 (mean of eight determinations).

In the kinetic measurements it was not found possible to prepare self-buffered solutions which were sufficiently resistant to pH changes and at the same time gave conveniently measurable rates of iodination. All kinetic measurements were therefore made in buffer solutions prepared from tris-(2-hydroxyethyl)methylamine (tris; pK = 8·07) or ethanolamine (pK = 9·50). The rate of iodination was measured by following the decrease in tri-iodide absorption at 353 nm in a Gilford 2400 spectrophotometer with the cell compartment at 25 ± 0·05 °C. The initial concentration of tri-iodide was in the range 3×10^{-5}—1×10^{-4}M; all solutions contained 0·1M-iodide ions and had a total ionic strength of $I = 0{\cdot}12$. In these solutions the effective molar absorption coefficient of iodine at 353 nm (allowing for a small extent of dissociation of I_3^- to give $I_2 + I^-$) is $2{\cdot}57 \times 10^5$ mol^{-1} dm^2. The concentration of amino-ketone was in the range 1×10^{-3}—1×10^{-2}M; it was always at least 20 times the initial tri-iodide concentration, and therefore remained effectively constant during an experiment.

The plots of absorbance against time are not strictly linear over the whole of their course. They show a short initial acceleration (probably due to the build-up of a monoiodo-derivative which then rapidly undergoes further iodination), followed by an effectively linear section covering about two-thirds of the reaction, and finally by a decrease of slope in the final stages. Moreover, the slope of the linear portion increases somewhat with increasing $[I_3^-]$. These observations show that the halogenation step is not fast enough to render the proton-transfer reaction wholly rate determinating, and to obtain a value for the rate of the latter reaction it is necessary to extrapolate the rate of iodination to infinite tri-iodide concentration. The form of this extrapolation depends to some extent upon the reaction mechanism assumed, and we shall anticipate here the arguments given in the Discussion section.

For 4-diethylaminobutan-2-one in a buffer solution of B and BH^+ a probable reaction process is as in the Scheme (with an analogous process for 5-diethylaminopentan-2-one). This Scheme assumes that the two species HS and

---

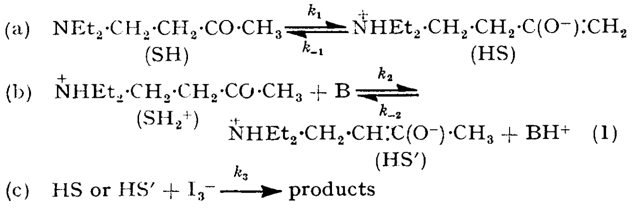
[1] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, 1963, **59**, 1623.

[2] E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, 1965, **87**, 5625.

[3] R. P. Bell, B. G. Cox, and J. B. Henshall, *J.C.S. Perkin II*, 1972, 1232.

[4] J. K. Coward and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969 **91**, 5339.

HS′ have the same reactivity towards halogen. The species HS will be in mobile equilibrium with $NEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}C(O^-){:}CH_2$, $NEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}C(OH){:}CH_2$ and $\overset{+}{N}HEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}C(OH){:}CH_2$ (and similarly for HS′): thus the constant k_3 is a weighted average, whose value in general depends upon pH.



$$\text{(a)}\quad \underset{\text{(SH)}}{NEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{(HS)}}{\overset{+}{N}HEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}C(O^-){:}CH_2}$$

$$\text{(b)}\quad \underset{(SH_2^+)}{\overset{+}{N}HEt_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3} + B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\text{(HS′)}}{\overset{+}{N}HEt_2{\cdot}CH_2{\cdot}CH{:}C(O^-){\cdot}CH_3} + BH^+ \qquad (1)$$

$$\text{(c)}\quad \text{HS or HS′} + I_3^- \xrightarrow{k_3} \text{products}$$

SCHEME

Previous treatment of a similar reaction process [5] showed that in a series of experiments in which only the halogen concentration is varied the reciprocal of the observed reaction velocity (defined as $v = -d[\text{halogen}]/dt$) is a linear function of the reciprocal of the halogen concentration, thus permitting a simple extrapolation to obtain v_∞, the value of v at infinite concentration of halogen. In the present case the analogous equation is (2) with the

$$v^{-1} = v_\infty^{-1} + A[I_3^-]^{-1} \qquad (2)$$

definitions (3) where $K_e = ([HS]_e + [HS']_e)/[SH]_e$, the

$$v_\infty = k_1[SH] + k_2[SH_2^+][B],$$
$$A = (K_e k_3[SH])^{-1} \qquad (3)$$

suffix e indicating the equilibrium concentrations which would be reached in the absence of halogen.* The value of v_∞ can thus be derived from the intercept of a linear plot of v^{-1} against $[I_3^-]^{-1}$. Equation (2) can be re-written as (4)

$$v = v_\infty - Av_\infty(v/[I_3^-]) \qquad (4)$$

so that an alternative procedure is to plot v against $v/[I_3^-]$.

Equations (2) and (4) should strictly be applied to relate the slope of the spectrophotometer traces at a given time to the value of $[I_3^-]$ at the same time. However, as already stated, these traces are effectively linear over a large part of their course, and we have therefore taken v as the slope of the linear portion, and $[I_3^-]$ as the average value relating to this portion. The Figure shows a series of such plots according to equation (4) for the first six reaction mixtures listed in Table 3. Similar extrapolation plots were obtained for all the solutions studied.

The treatment given above implies that one molecule of the active enolate species HS and HS′ reacts with one molecule of iodine [equation (1c)]. Under conditions of basic catalysis it is likely that the monoiodo-derivative first formed will enolise or ionise rapidly and will react with a further molecule of iodine: for the derivative formed from HS this process might be repeated a second time. Further evidence for such multiple halogenation stems from the short period of initial acceleration observed in the spectrophotometer traces. The values of v_∞ derived are therefore greater than the rates of the initial proton transfers by a factor which probably lies between 2 and 3, and the same is true of the velocity constants k_1 and k_2. However, the exact value of this factor is not known, and since our object is to make semi-quantitative comparisons between the rates of intermolecular and intramolecular processes, we have used the uncorrected values of v_∞, k_1, and k_2 in the subsequent discussion.

RESULTS

In Tables 2 and 3 the observed values of v_∞ for the two amino-ketones are compared with those calculated from equation (3) with the values of k_1 and k_2 listed in Table 1.

TABLE 1

Collected velocity constants (25 °C)

(a) 4-diethylaminobutan-2-one (b) 5-diethylaminopentan-2-one

k_1/s^{-1}	k_2 (tris)	k_2 (ethanolamine)
	dm^3 mol^{-1} s^{-1}	
$3{\cdot}35 \times 10^{-2}$ (a)	$1{\cdot}33 \times 10^{-2}$ (a)	$1{\cdot}61 \times 10^{-1}$ (a)
$7{\cdot}80 \times 10^{-3}$ (b)	$2{\cdot}60 \times 10^{-3}$ (b)	$4{\cdot}25 \times 10^{-2}$ (b)

TABLE 2

Rate of iodination of 4-diethylaminobutan-2-one at 25 °C, (v in mol dm^{-3} s^{-1}, all concentrations in mol dm^{-3})

pH	$10^5[SH_2^+]$	$10^8[SH]$	$10^5[B]$	10^8v_∞(obs)	10^8v_∞(calc)
		Tris buffers			
7·90	446	1998	1387	145	149
7·90	268	1200	1387	87	90
7·90	223	999	1387	72	75
7·90	179	799	1387	60	60
7·90	134	600	1387	45	45
7·90	89	400	1387	30	30
7·90	134	600	1110	42	40
7·90	134	600	832	37	35
7·90	134	600	416	28	28
8·29	233	2546	435	99	101
8·32	233	2694	989	121	121
		Ethanolamine buffers			
8·56	82	2040	493	118	120
8·56	82	2040	405	111	109
8·56	82	2040	329	101	99
8·56	82	2040	270	91	93
8·56	82	2040	99	66	68

TABLE 3

Rate of iodination of 5-diethylaminopenta-2-one at 25 °C (v in mol dm^{-3} s^{-1}, all concentrations in mol dm^{-3})

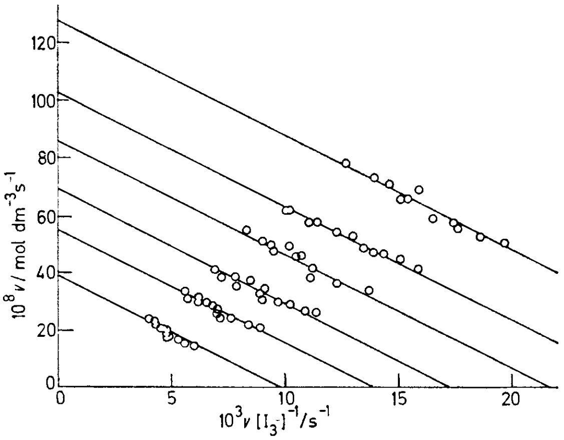
pH	$10^5[SH_2^+]$	$10^7[SH]$	$10^5[B]$	10^8v_∞(obs)	10^8v_∞(calc)
		Tris buffers			
8·39	202	383	1000	39	35
8·39	302	566	994	56	52
8·39	403	754	994	69	69
8·39	504	943	994	86	86
8·39	605	1131	994	103	104
8·39	706	1365	1007	123	125
8·39	504	943	497	81	80
8·39	504	943	1491	93	93
8·39	504	943	2000	100	100
8·23	493	627	841	61	60
7·70	190	493	400	20	20
		Ethanolamine buffers			
8·77	202	874	141	83	80
8·82	202	987	236	102	97
8·79	202	924	296	100	98
8·81	202	959	383	107	108
8·79	202	911	476	112	112
9·06	202	1650	444	172	167
8·46	329	720	224	84	87

---

* A strict treatment of the Scheme, allowing for the fact that HS and HS′ have different stabilities, leads to a much more complicated expression. However, numerical calculations show that the extrapolation plot of v^{-1} against $[I_3^-]^{-1}$ deviates very little from linearity even when these stabilities differ considerably.

[5] R. P. Bell and B. G. Cox, *J. Chem. Soc.* (*B*), 1971, 652.

The latter constants were derived from the intercept and slope of plots of v_∞(obs) against [B] in a series of experiments at constant pH and constant concentration of amino-

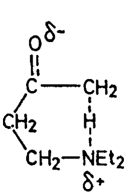


Extrapolation of rates of iodination to infinite concentration of tri-iodide.

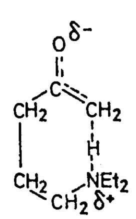
ketone and buffer together with the measured pH, due allowance being made for hydrolysis and for activity coefficients.

DISCUSSION

For many purposes the results for the two amino-ketones can be considered together. Thus both values of k_1 are much too high to be attributed to proton abstraction by a water molecule, since this process has a rate constant of *ca.* 10^{-10} s^{-1} for simple aliphatic ketones, and reaches only *ca.* 10^{-6} s^{-1} even for a strongly activated ketone such as $(CH_2Cl)_2CO$.[6] Moreover, such a process would take place more readily for the protonated form SH_2^+ than for SH, while the agreement with equation (6) observed over a range of pH values shows that only SH is involved. The high rates observed thus point to some form of intramolecular catalysis, and the most obvious suggestion is the abstraction of a proton from carbon by the basic NEt_2 group, as shown in equation (1a). The transition states for the two amino-ketones can then be written as (A) and (B). These transition states involve rings containing respectively five and six atoms in addition to the proton being transferred. Since the proton is small and has no strict angular valency requirements they could reasonably be described as 5½- and 6½-membered cyclic transition states. The values of k_1 found for the two amino-ketones suggest that the 5½-ring is more favourable to intramolecular catalysis than is the 6½-ring, as previously concluded[1] for a series of aliphatic keto-carboxylic acids.

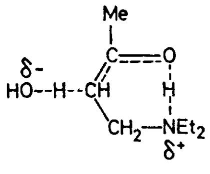


(A)

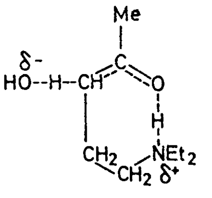


(B)

There is, however, an alternative explanation for the high values of k_1, since the term k_1[SH] is kinetically indistinguishable from $k_{\text{OH}}[\text{OH}^-][\text{SH}_2^+]$. If the observed values are interpreted in terms of this expression by using the known values of K_s [equation (3)] and K_w, we find k_{OH} = 250 and 76 dm^3 mol^{-1} s^{-1} for 4-diethylaminobutan-2-one and 5-diethylaminopentan-2-one respectively. It is again unlikely that these velocity constants could refer to simple proton abstraction from carbon by hydroxide ion, without any assistance from intramolecular processes, since the value of k_{OH} for acetone[6] is only 0·25 dm^3 mol^{-1} s^{-1}, though this would be increased somewhat by the presence of the group $\overset{+}{\text{N}}\text{HEt}_2$.* A likely form of such internal assistance is represented by the transition states (C) and (D), in which the timing of the two proton transfers must remain an open question. These processes produce enols, rather than the enolates given by (A) and (B). However, the various species which differ only by protonation or de-protonation at oxygen or nitrogen will be in mobile equilibrium with one another, and the rate of halogenation at sufficiently high halogen concentrations will be unaffected.



(C)



(D)

It is difficult to distinguish experimentally between the two possibilities, represented by (A) and (B) on the one hand, and (C) and (D) on the other. In principle a distinction should be possible in terms of the nature of the iodination products, since the two possibilities correspond to ionisation or enolisation of the methyl and methylene groups respectively. However, in practice experiments are most conveniently carried out in presence of an added buffer, which would lead to iodination in both positions. Moreover, the iodo-derivatives first formed could readily undergo further hydrolysis or cyclisation reactions, and no product analyses have been attempted.

Some indirect evidence on this point can be adduced from the values of k_2 found for catalysis by tris or ethanolamine (*cf.* Table 1). The relative rates for the two bases are consistent with a Brönsted relation having an exponent β *ca.* 0·8. This term is most simply attributed to proton abstraction by the base from the methylene or methyl groups of SH_2^+, without intramolecular assistance: however, if transition states such

---

* For external attack by hydroxide ion, the presence of this group would favour proton loss from methylene rather than from methyl in the group CH_2COCH_3.

[6] From values collected by R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc.* (*B*), 1967, 827.

as (C) and (D) are important contributors to k_1, k_2 is likely to involve similar concerted processes, with the hydroxide ion replaced by a molecule of base. Feather and Gold[7] have measured the rate of ionisation of a number of aliphatic ketones in the presence of pyridine bases, and find, for example, $k_2 = 5{\cdot}8 \times 10^{-6}$ dm^3 mol^{-1} s^{-1} for acetone + pyridine (p$K = 5{\cdot}22$). By applying the Brönsted relation with $\beta = 0{\cdot}88$, appropriate to acetone,[8] we find for acetone + tris (p$K = 8{\cdot}07$), $k_2 = 1{\cdot}9 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}. This is close to the value $2{\cdot}6 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} found for protonated 5-diethylaminopentan-2-one + tris (Table 1), and the small difference is readily accounted for by the electrostatic effect of the group $\overset{+}{N}HEt_2$: this appears more markedly in the corresponding figure ($1{\cdot}3 \times 10^{-2}$) for 4-diethylaminobutan-2-one, in which the diethylamino-group is closer to the seat of reaction. The evidence is thus against any intramolecular assistance in catalysis by tris, and if this argument is extended to exclude the transition states (C) and (D), we may conclude that k_1 is attributable to (A) and (B).

The efficiency of intramolecular catalysis is conveniently expressed by an 'effective concentration' c_i, defined by $c_i = k_1/k_2^*$, where k_2^* refers to intermolecular catalysis by a (hypothetical) catalyst having the same basic strength as the basic group in the substrate. For the reactions under consideration it is difficult to obtain a direct estimate of c_i, since the intra- and inter-molecular catalyses refer to two different species, SH and SH_2^+ respectively. However, the considerations of the last paragraph suggest that for catalysis by an uncharged base the accelerating effect of a positive charge on the nitrogen atom is not very great, amounting to factors of *ca.* 7 and 1·4 for 4-diethylaminobutan-2-one and 5-diethylaminopentan-2-one respectively. If these figures are accepted, the value of k_2 for SH_2^+ + ethanolamine can be used to estimate k_2^*. Thus for 4-diethylaminobutan-2-one we find $k_2^* = 0{\cdot}161 \times (4{\cdot}4)^{0{\cdot}8}/7 = 7{\cdot}5 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}, where 4·4 is the ratio of the basic strengths of the substrate and ethanolamine, and 0·8 is the observed value of the Brönsted exponent: hence $c_i = 3{\cdot}35 \times 10^{-2}/7{\cdot}5 \times 10^{-2} = 0{\cdot}45$M. Similarly, for 5-diethylaminopentan-2-one we find $k_2^* = 7{\cdot}8 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}, $c_i = 0{\cdot}10$M.

These estimates of c_i can only be approximate, but the values are in the order expected for cyclic transition states with $5\frac{1}{2}$- and $6\frac{1}{2}$-membered rings. They are similar in magnitude to values of c_i previously reported for intramolecular proton transfer in the flexible keto-carboxylic acids,[1] considerably smaller than those for analogous rigid systems,[2,3] and very much smaller than the values of up to 10^8M which have been observed for some intramolecular nucleophilic processes,[9] and which can be interpreted in terms of rotational and vibrational entropies.[10]

We thank the S.R.C. for financial support for this investigation.

[3/251 *Received, 5th February*, 1973]

---

[7] J. A. Feather and V. Gold, *J. Chem. Soc.*, 1965, 1752.

[8] R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.

[9] D. R. Storm and D. E. Koshland, *Proc. Nat. Acad. Sci. U.S.A.*, 1970, **66**, 445; *J. Amer. Chem. Soc.*, 1972, **94**, 5805, 5815.

[10] M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U.S.A.*, 1971, **68**, 1678.