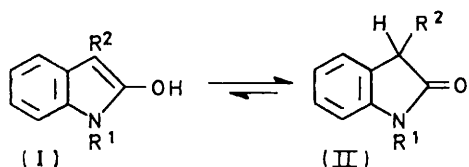


Heteroaromatic Hydrogen Exchange Reactions. Part VIII.¹ The Ionisation of 1,3-Dimethylindolin-2-one

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The kinetics of iodination at the 3-position of 1,3-dimethyl- and [3-²H₁]-1,3-dimethyl-indolin-2-one are reported for buffered mildly alkaline 50% (w/w) aqueous methanol solutions at 25°. Unlike the iodination of many ketones these reactions (even in the presence of excess of substrate and with large amounts of added iodide ion) do not follow a zero-order rate expression, but show behaviour intermediate between a zero- and first-order dependence on [I₂]. This implies that the reactive enolate ion intermediate undergoes protonation as rapidly as reaction with iodine to give 3-iodo-1,3-dimethylindolin-2-one. Analysis of the kinetic data shows that 1,3-dimethylindolin-2-one ionises nearly 100-fold faster than acetone and at least 10⁸ times faster than a simple amide such as acetamide. This makes the substrate one of the most acidic amides known. The deuterium isotope effect associated with the ionisation is 6.3 ± 0.6.

ALTHOUGH electron-withdrawing groups are well known to increase the acidity of α -hydrogen atoms (as in malonates, nitroalkanes, *etc.*), the effect of the carboxamide system in this respect has not been widely investigated, particularly from a quantitative standpoint. Early work demonstrated² that the methyl hydrogens of acetamide were of comparable acidity to those of the parent acid itself, and in 1961 Cram *et al.*³ examined the ionisation of 2-phenylpropionamides in Bu^tOH–Bu^tO⁻–K⁺: here, the *NN*-diethylcarboxamido-group apparently decreased the kinetic acidity of the α -hydrogens by as much as 10⁴ compared with the *t*-butyl ester group, and by a much larger factor relative to a nitrile substituent. In contrast, however, Kowazoe and his colleagues⁴ showed semiquantitatively by n.m.r. measurements that the α -hydrogens of *NN*-diethylpropionamide exchanged



much more rapidly in alkaline deuteriomethanol than those of ethyl propionate. It is not easy to rationalise the apparent conflict in the above results, which may be complicated by concomitant solvolysis of the substrate. In any event, solvolysis is likely to be a problem with simple amides under basic conditions and this may well explain the paucity of hydrogen exchange data for these compounds compared with other carbon pseudo-acids.

Indolin-2-ones are formally the 2-hydroxy-derivatives (I) of indoles, although in solution they exist predominantly in the keto-form (II) and therefore correspond to a cyclic amide. The restoration of aromatic properties on forming (I) suggests that enolisation will be easier than

with most amides and, indeed, qualitative examination has shown that the 3-hydrogen of *N*-methylindolin-2-one exchanges with the solvent on refluxing in mildly alkaline D₂O.⁵ Further, the stability of (II) relative to the acyclic amino-acid⁶ implies that concomitant hydrolysis will not proceed readily and therefore not be a problem in basic media. Indolin-2-ones therefore seem to be ideal substrates with which to start an investigation of the activating influence of the carboxamido-group on carbon basicity. Also, examination of these reactions may provide some understanding of the remarkable differences observed in the magnitudes of primary hydrogen isotope effects for aliphatic and heteroaromatic hydrogen exchange. Recent studies^{1,7} with indolyl compounds show the size of this isotope effect is virtually independent of the transition state symmetry in striking contrast to the results for many aliphatic compounds.⁸ Hydrogen exchange for the 'aliphatic' indolin-2-ones should be closely analogous to that for indoles, the major difference being an exocyclic π -system *versus* an endocyclic one for neutral indoles and their conjugate bases.

RESULTS AND DISCUSSION

One of the most common and satisfactory methods for examining ionisation rates of carbon acids employs rapid and irreversible trapping of the reactive anion intermediate with molecular halogens.⁹ This procedure using iodine was applied to 1,3-dimethylindolin-2-one, where there are no kinetic complications arising from the introduction of more than one iodine atom (Scheme 1). For catalysis by the lyate ion only (where

$$-d[I_2]/dt = \frac{k_1^L[B^-][1,3\text{-dimethylindolin-2-one}]}{1 + k_{-1}^L/k_2[I_2]} \quad (1)$$

HB = solvent in constant excess), assumption of the steady-state approximation for the anion (III) concentration then gives equation (1) for the uptake of iodine

¹ Part VII, B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1625.

² K. F. Bonhoeffer, K. H. Geib, and O. Reitz, *J. Chem. Phys.*, 1939, **7**, 664.

³ D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfeld, *J. Amer. Chem. Soc.*, 1961, **83**, 3678.

⁴ H. Matsuo, Y. Kawazoe, M. Sato, M. Ohnishi, and T. Taksuno, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 391.

⁵ T. Hino, M. Nakagawa, K. Tsuneoka, S. Misawa, and S. Akuboshi, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 1661.

⁶ K. J. S. Arora, M. K. M. Dirania, and J. Hill, *J. Chem. Soc. (C)*, 1971, 2865.

⁷ B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1618.

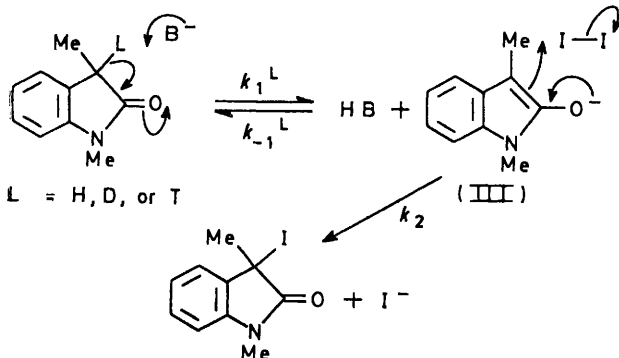
⁸ For example see R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **A**, **294**, 273.

⁹ (a) D. J. Barnes and R. P. Bell, *Proc. Roy. Soc.*, 1970, **A**, **318**, 421; (b) J. R. Jones, 'The Ionisation of Carbon Acids,' Academic Press, London, 1973.

from the reaction solution. Kinetic simplification was effected in the usual manner by adding a relatively high (ca. 0.1M) concentration of KI to the reaction solution so that $[I^-] \gg [I_2]$, and also by ensuring that $[1,3\text{-dimethylindolin-2-one}] \gg [I_2]$. The first condition avoids complications arising from the uptake of I_2 by I^- released on reaction [equation (2)] and, because this



equilibrium lies well to the right $\{K = [I_3^-]/[I^-][I_2] = 715 \text{ l mol}^{-1}\}$,^{9a} it follows that $-d[I_3^-]/dt \propto -d[I_2]/dt$.



SCHEME 1 Base catalysed iodination of 1,3-dimethylindolin-2-one

The second condition gives a pseudo-zero-order dependence on substrate concentration. Under these condi-

$$-d[I_3^-]/dt = \frac{k_0^L}{1 + k_{-1}^L/k_2^* [I_3^-]} \quad (3)$$

tions, the reaction rate follows equation (3) where

by equation (4), and this, depending on whether

$$[I_3^-] = k_0^L t - k_{-1}^L/k_2^* \ln[I_3^-] + \text{const.} \quad (4)$$

$k_{-1}^L/k_2^* [I_3^-]$ is less than or greater than unity, leads to either zero or first-order kinetics, respectively. For the

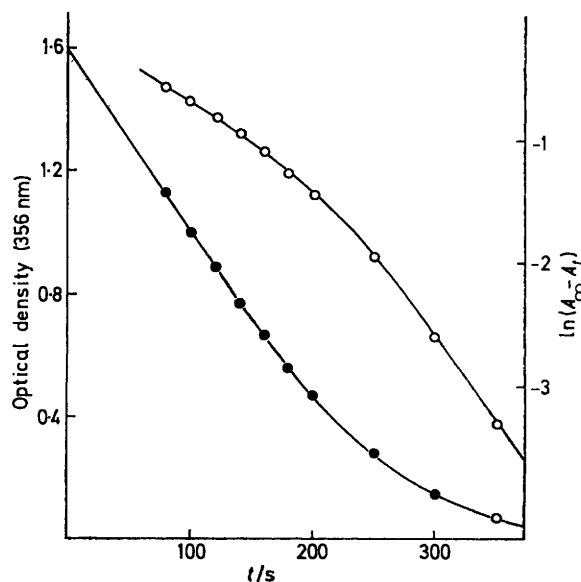


FIGURE 1 Iododeprotonation of 1,3-dimethylindolin-2-one at $\text{pH}_m = 9.118$ and 25° . Initial [Substrate] = $2 \times 10^{-3}\text{M}$, $[I_2] = 6 \times 10^{-5}\text{M}$, $[KI] = 0.12\text{M}$: ●, zero-order plot; ○, first order plot

ionisation of most carbon compounds, zero-order iodination kinetics are frequently observed,^{9b} but recently examples of the first-order reactions have been reported.¹⁰

TABLE I

Iododeprotonation of 1,3-dimethylindolin-2-one in 50% (w/w) aqueous methanol-tetraborate buffer at 25° . Initial $[I_2] = 6 \times 10^{-5}\text{M}$, $[KI] = 0.12\text{M}$

pH_m	$10^6[B^-] \text{ } ^\circ/\text{M}$	$10^3[1,3\text{-Dimethylindolin-2-one}]/\text{M}$	$10^5 k_{-1}^L/k_2^* (\text{mol l}^{-1})$	$10^6 k_0^H/\text{mol l}^{-1} \text{ s}^{-1}$	$k_1^H/\text{l mol}^{-1} \text{ s}^{-1}$
7.910	0.479	10	2.08	10.8	22.6
8.350	1.32	5	2.18	15.5	23.5
8.360	1.35	10	1.96	29.0	21.5
8.582	2.25	5	1.94	25.2	22.4
8.750	3.31	2	2.14	14.9	22.5
8.903	4.71	2	2.26	22.8	24.2
9.108	7.55	2	2.01 (2.01) ^c	35.9 (37.8)	23.8 (25.0)
9.115 ^b	7.67	2	2.23	32.3	21.1
9.118	7.73	1	2.07	18.0	23.3
9.118	7.73	2	2.29	37.2	24.1
9.437	16.1	1	2.28	38.1	23.7
9.648	26.2	1	2.16	58.4	22.3
9.672	27.7	1	2.19	62.2	22.4

Average values $k_{-1}^L/k_2^* = 2.13 \pm 0.12 \times 10^{-5} \text{ mol l}^{-1}$, $k_1^H = 23.0 \pm 1.1 \text{ l mol}^{-1} \text{ s}^{-1}$

^a Calculated from $\log(m_{\text{OH}^-} + m_{\text{MeO}^-}) = \text{pH}_m - 0.13 - 14.097$ (see text). ^b Initial $[I_2] = 2 \times 10^{-4}\text{M}$, followed at 390 nm. ^c Duplicate values in parentheses.

$k_0^L = k_1^L[B^-][1,3\text{-dimethylindolin-2-one}]$ and $k_2^* = k_2/715[I^-] + k_2'$ in which k_2' represents the rate coefficient for reaction between the intermediate (III) and I_3^- . The integrated rate expression is therefore given

¹⁰ R. R. Li and S. I. Miller, *J. Chem. Soc. (B)*, 1971, 2269.

¹¹ R. P. Bell, D. W. Earls, and B. A. Timimi, *J.C.S. Perkin II*,

An intermediate kinetic behaviour is probably more common for these reactions than realised, resulting in curved zero-order plots, and Bell and his colleagues¹¹ have noted these on several occasions.

1971, 811; R. P. Bell and B. A. Timimi, *ibid.*, 1973, 1518; R. P. Bell and B. G. Cox, *J. Chem. Soc. (B)*, 1971, 652.

With a 14-fold excess of 1,3-dimethylindolin-2-one over the initial iodine concentration, iodination proceeded at a convenient rate at 25° in 50% (w/w) aqueous MeOH at pH 8–10 maintained with dilute (*ca.* 0.01M) sodium tetraborate buffers. As shown in Figure 1, however, plots of neither $[I_3^-]$ *versus* time (as required for the zero-order process) nor $\ln[I_3^-]$ *versus* time (for the first-order process) are satisfactorily linear. The observed kinetic behaviour was nonetheless completely reproducible and was unchanged on using zone-refined substrate. Further, the experimental data gave an excellent fit by least squares analysis (see Experimental section) to equation (4) to within ± 0.002 absorbance units and rate coefficients were therefore evaluated in this way. This implies, of course, that reprotonation of (III) is relatively fast compared with its reaction rate with iodine, and that the kinetics are therefore of an intermediate order with respect to $[I_3^-]$.

The validity of this deduction is confirmed satisfactorily by the kinetic analyses applied to reaction in tetraborate buffers and summarised in Table 1, where both k_1^H and k_{-1}^H/k_2^* are sensibly constant for *ca.* 50-fold and 10-fold variations in base and 1,3-dimethylindolin-2-one concentrations, respectively. Further, a three-fold variation in the initial iodine concentration leaves both k_1^H and k_{-1}^H/k_2^* unaffected. Thus k_0^H has a first-order dependence on both $[B^-]$ and $[1,3\text{-dimethylindolin-2-one}]$ and the independence of the k_{-1}^H/k_2^* ratio from both these concentration terms is expected where reprotonation of the enolate ion (III) proceeds solely *via* the solvent. Comparison with rates measured in dilute sodium hydroxide solutions showed no evidence for catalysis of the ionisation step by the tetraborate

$k_0^D/[3\text{-}^2\text{H}_1\text{-}1,3\text{-dimethylindolin-2-one}]$ *versus* $[B^-]$ shown in Figure 2 is also satisfactorily linear, but its lower slope relative to that for the normal 1,3-dimethylindolin-2-one (3.86 *versus* 23.0 $\text{l mol}^{-1} \text{s}^{-1}$) is evidence of

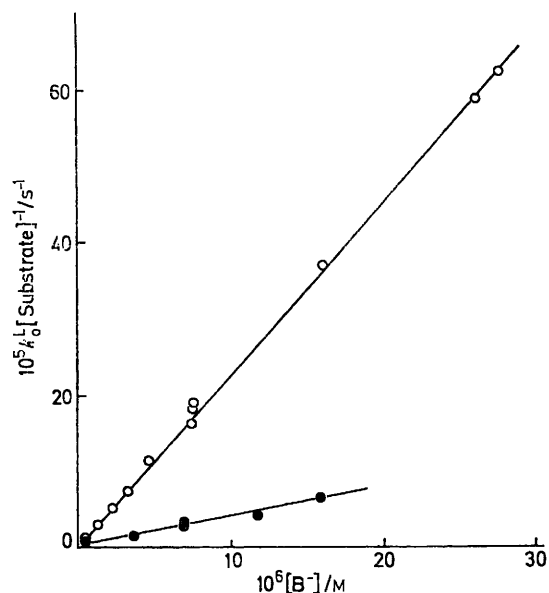


FIGURE 2 Dependence of iododeprotonation (○) and iododeuteriation (●) rates on $[B^-]$ in 50% (w/w) aqueous methanol at 25°

a substantial isotope effect for the ionisation step. When the dedeuteriation rate (k_1^D) is corrected for a 3- $^1\text{H}_1$ content of *ca.* 1% in the deuteriated substrate [partially a consequence of isotopic dilution caused by

TABLE 2

Iododeuteriation of $[3\text{-}^2\text{H}_1\text{-}1,3\text{-dimethylindolin-2-one}]$ in 50% (w/w) aqueous methanol-tetraborate buffer at 25°. Initial $[I_2] = 6 \times 10^{-5}\text{M}$, $[KI] = 0.12\text{M}$, $[\text{Na}_2\text{B}_4\text{O}_7] = 0.01\text{M}$

pH _m	$10^6[B^-] \text{ } ^\circ/\text{M}$	$10^2[\text{Substrate}]/\text{M}$	$10^5 k_{-1}/k_2^* (\text{mol l}^{-1})$	$10^8 k_0^D / \text{mol l}^{-1} \text{s}^{-1}$	$k_1^D / \text{l mol}^{-1} \text{s}^{-1}$
8.050	0.661	2	3.65	5.09	3.86
8.800	3.72	1	2.14	15.2	4.08
9.072	6.95	1	2.13	26.6	3.83
9.075	7.00	1	2.38	28.3	4.04
9.118	7.73	1	2.08	28.6	3.70
9.303	11.8	1	2.51	41.0	3.48
9.432	15.9	0.5	2.06	31.9	4.01

Average values $k_{-1}/k_2^* = 2.23 \pm 0.18 \times 10^{-5}$, $k_1^D = 3.86 \pm 0.21 = 3.66 \pm 0.203 \text{ l mol}^{-1} \text{s}^{-1}$ when corrected for 1% $3\text{-}^1\text{H}_1$ content in substrate

* Calculated from $\log(m_{\text{HO}^-} + m_{\text{MeO}^-}) = \text{pH}_m - 0.13 - 14.097$ (see text).

buffer base, and this is confirmed by the zero intercept for the plot of $k_0^H/[1,3\text{-dimethylindolin-2-one}]$ *versus* $[B^-]$ in Figure 2.

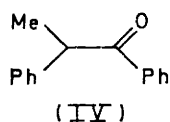
Iodination of $[3\text{-}^2\text{H}_1\text{-}1,3\text{-dimethylindolin-2-one}]$ under similar conditions also gave curved plots for $[I_3^-]$ *versus* time and analysis of the data (Table 2) leads to an identical value of k_{-1}^H/k_2^* to that obtained for the normal substrate. This is expected inasmuch as neither the rate of protonation of the enolate ion (III) nor its iodination rate should be influenced by the *initial* isotopic composition of the substrate. The plot of

¹² J. R. Jones, *Trans. Faraday Soc.*, 1965, **61**, 95.

reprotonation of the enolate ion (III) by the solvent], a primary isotope effect of $k_1^H/k_1^D = 6.3 \pm 0.6$ (standard error propagated rigorously from the rate constants to the ratio) is obtained. Its reasonable value also confirms the validity of the kinetic analysis applied to the experimental results. Remarkably, 1,3-dimethylindolin-2-one ionises nearly 100-fold faster in 50% (w/w) aqueous MeOH than either acetone (k_1^H 0.167 $\text{l mol}^{-1} \text{s}^{-1}$)¹² or α -phenylacetophenone [(IV), k_1^H 0.251 $\text{l mol}^{-1} \text{s}^{-1}$]¹³ in aqueous media at 25°, and at least 10^6 times

¹³ D. W. Earls, J. R. Jones, and T. G. Rumney, *J.C.S. Faraday I*, 1972, 925.

faster than a simple amide such as acetamide.² This rapid ionisation can be rationalised partly in terms of the high stability of the enolate ion (III) in which the negative charge on oxygen can conjugate directly with the aromatic nucleus, but, by comparison with (IV) above, the nearly planar conformation of the substrate must also be an important factor. The high ionisation rate should be reflected in the pK_A for 1,3-dimethylindolin-2-one and although difficulty was experienced in measuring this parameter accurately due to aerial



oxidation, a reasonable value is probably 14–15, compared with *ca.* 22 for acetone^{9b} and 16–17 for cyclopentanone.^{9b} The reasons for rapid reprotonation of the enolate ion (III) relative to its nucleophilic attack on iodine (as evidenced by its non-integral order plots) are much less clear. There is a remote possibility that aerial oxidation (noted earlier by Julian and Pikel¹⁴ during preparative experiments) perturbs the release of iodine from the reaction solutions. This oxidation is base catalysed, but is fairly slow at pH 8–10, and to further minimise its effect the reaction solutions were rigorously degassed. Also, it seems unlikely that a

EXPERIMENTAL

Substrates and Reagents.—1,3-Dimethylindolin-2-one was prepared in the manner described by Julian *et al.*¹⁵ by cyclisation of the appropriate α -bromoanilide with $AlCl_3$, b.p. 84° at 0.3 Torr, m.p. (from hexane or zone refining) 56° (lit.,¹⁵ 55°), δ (CCl_4) 1.35 (3 H, d, J 7 Hz), 3.07 (3 H, s), 3.22 (1 H, m, J 7 Hz), and 6.9 (4 H, m), m/e 161 (M^+), 146, and 118 ν_{max} . (Nujol-hexachlorobutadiene) 3 040, 2 970, 2 940, 2 880, 1 720, 1 700, 1 605, and 765 cm^{-1} .

[3-²H₁]-1,3-Dimethylindolin-2-one was prepared by shaking a solution of the normal compound (1 g) in ether (20 ml) with D₂O (10 ml) containing sodium (0.2 g) for 12 h during which time the aqueous phase was renewed twice. After separation from the aqueous phase, the ether was removed under vacuum and the product, [3-²H₁]-1,3-dimethylindolin-2-one, after recrystallization from hexane contained *ca.* 99% deuterium in the 3-position only as shown by ¹H n.m.r.

AnalaR potassium iodide, sodium tetraborate, sodium chloride, and methanol were used without further purification. Iodine was sublimed before use.

Kinetics.—The ionic strength of reaction solutions was adjusted with either AnalaR sodium chloride or potassium iodide. Their pH was checked on a Radiometer pH 26 meter using a G 202B glass electrode. The measured pH_m was corrected using $pH_m = pA_H^* + 0.13$ for 50% (w/w) aqueous methanol, and the base concentrations were calculated from the expression $\log (m_{OH^-} + m_{MeO^-}) = pH_m - 0.13 - 14.097$.¹⁶ In 50% (w/w) aqueous methanol, $m_{MeO^-}/m_{OH^-} = 1.06$,¹⁶ but since the acid strengths of H₂O and MeOH are very similar¹⁷ catalysis by the two lyate ions

TABLE 3

Iodideprotonation of 1,3-dimethylindolin-2-one in 50% (w/w) aqueous methanol-tetraborate buffer at 25°. Initial [1,3-dimethylindolin-2-one] = $2 \times 10^{-3}M$, $[I_3^-] = 6 \times 10^{-5}M$, $\epsilon_{I_3^-} = 2.54 \times 10^4 l mol^{-1} cm^{-1}$

t/s	Minimisation of $ A_\infty - A_t ^a$				Minimisation of $\ln A_\infty - A_t ^b$		
	$0.5A_t$	$(A_\infty - A_t)$	Calc.	Difference	$-\ln(A_\infty - A_t)$	Calc.	Difference
80	0.156	0.564	0.563	-0.001	0.573	0.576	-0.003
100	0.220	0.500	0.502	0.002	0.693	0.687	0.006
120	0.278	0.442	0.441	-0.001	0.816	0.821	-0.004
140	0.337	0.383	0.386	0.003	0.960	0.951	0.009
160	0.388	0.332	0.330	-0.002	1.103	1.109	-0.007
180	0.439	0.281	0.281	0.000	1.269	1.268	0.001
200	0.484	0.236	0.235	-0.001	1.444	1.448	-0.004
250	0.579	0.141	0.140	-0.001	1.969	1.962	-0.003
300	0.645	0.075	0.078	0.003	2.590	2.581	0.009
350	0.683	0.037	0.036	-0.001	3.297	3.301	-0.004
∞	0.720	0.000					

^a $k_0^H = 37.19 \pm 0.38 \times 10^{-6}$, $k_{-1}/k_2^* = 2.279 \pm 0.038 \times 10^{-5}$. ^b $k_0^H = 37.24 \times 10^{-6} mol l^{-1} s^{-1}$, $k_{-1}/k_2^* = 2.289 \times 10^{-5} mol l^{-1}$.

random effect of this kind would lead to the reproducible deviations from zero-order behaviour as observed.

Our findings show that suitably stabilised amides, such as indolin-2-ones, are sufficiently acidic to be a new class of carbon acid amenable to study by conventional techniques. Experiments to ascertain the effect of substituents remote from the reactive site on kinetic parameters such as primary hydrogen isotope effects are in progress.

¹⁴ P. L. Julian and J. Pikel, *J. Amer. Chem. Soc.*, 1935, **57**, 539.

¹⁵ P. L. Julian, J. Pikel, and D. Boggess, *J. Amer. Chem. Soc.*, 1934, **56**, 1797.

¹⁶ C. H. Rochester, *J.C.S. Dalton*, 1972, 5.

¹⁷ P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.

was not differentiated and their sum ($m_{MeO^-} + m_{OH^-}$) is referred to collectively as base concentration.

Duplicate degassed reaction solutions containing aqueous sodium tetraborate (5 ml, 0.05M) and MeOH (14.4 ml) were prepared in volumetric flasks (25 ml) and to each was added a degassed aqueous solution of iodine (3 ml, $5 \times 10^{-4}M$) containing potassium iodide (1M). The pH of both solutions was adjusted to the desired value by addition of either NaOH or HCl and the reaction was initiated by adding the appropriate volume of stock 1,3-

dimethylindolin-2-one ($2.5 \times 10^{-2}\text{M}$) in degassed methanol to one volumetric flask. The other 'control' solution, with an equivalent amount of degassed methanol added, was adjusted to 25 ml with H_2O and then placed in the sample cell (10 mm path length) of a Unicam SP1800 spectrophotometer. The reaction solution, similarly adjusted to 25 ml with H_2O , was placed in the reference cell and the apparent difference in optical density between the two solutions was monitored at 356 nm with respect to time. This differential procedure helps to minimise errors arising from slight spontaneous decomposition of I_3^- in solution.

The u.v. data obtained was fitted to equation (5) [cf. equation (4)] where A_t and A_∞ = absorbance at time t and ∞ respectively, $a = k_1^{\text{H}}$ [Substrate][HO^-] ϵl , $b = k_{-1} \epsilon l/k_2^*$,

$$(A_\infty - A_t) = at - b \ln(A_\infty - A_t) + \text{const.} \quad (5)$$

ϵ = extinction coefficient at 356 nm for $\text{I}_3^- = 2.54 \times 10^4 \text{ l mol}^{-1} \text{ cm}^{-1}$, and l = optical path length in cm. Equ-

ation (5) was approximated to a linear function in three (independent) variables and solved by linear multiple regression analysis using a weighting $w_i = 1/(A_t + 0.2)^2 (1 + b^2/A_t^2)$ which corresponds to an error of $\sigma_{A_t} = 0.005A_t + 0.001$ in the absorbance.¹⁸ This procedure was checked by rearranging equation (5) so that residuals in the term $\ln(A_\infty - A_t)$, rather than $(A_\infty - A_t)$ as above, were minimised. The two methods gave consistent results and an excellent fit of the experimental data to equation (5) was obtained (see Table 3) with deviations of the same order as the spectrophotometric accuracy.

We thank the S.R.C. for an equipment grant and the Salters Company for a Scholarship to H. S. R.

[5/507 Received, 14th March, 1975]

¹⁸ W. E. Deming, 'Statistical Adjustment of Data,' Wiley, New York, 1943.