Elimination–Addition Mechanisms of Acyl-group Transfer: the Neutral and Alkaline Decomposition of 1-(*N*-Methylcarbamoyl)imidazoles

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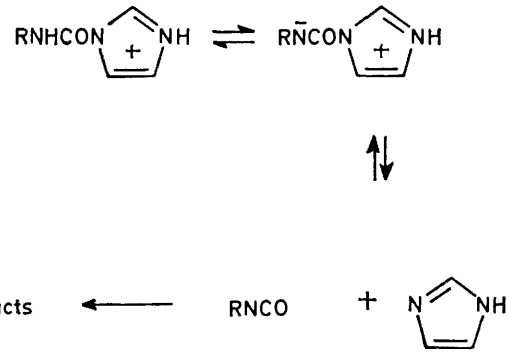
Aqueous hydrolysis of 1-(*N*-methylcarbamoyl)imidazoles exhibits a pH-dependence consistent with *E*1cB pathways through neutral and cationic forms of the substrate. The derivatives of the most basic imidazoles have the greatest overall hydrolytic reactivity. There is little steric requirement for decomposition *via* either mechanism despite the relatively high crowding in the most hindered species studied; the slight enhancement of the hydrolysis rate for 1-(*N*-methylcarbamoyl)-2,4,5-trimethylimidazole is judged to be due to a gain in rotational entropy during departure of the leaving imidazolyl group. The ionisation of imidazoles and of their conjugate acids have nearly identical selectivities to substituent change.

1-CARBAMOYLIMIDAZOLE and 1-(*N*-phenylcarbamoyl)-imidazole decompose *via* the isocyanate species in an elimination–addition pathway.[1–3] At low buffer con-



(1)

centrations the proton-transfer steps are rate-limiting for the *N*-phenyl case [2] but at higher levels the decomposition of the zwitterion is rate determining. The reverse reaction, namely attack of isocyanate on imidazole, has also been studied to provide equilibrium data.[1,3]

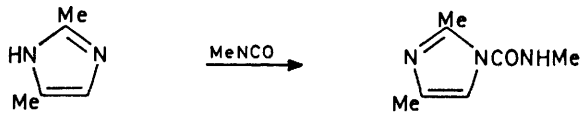
Previous data from this laboratory [4] indicate that the steric requirement on the leaving group in substituted phenyl carbamate hydrolyses is negligible; it is the purpose of the present work to examine a leaving-group system where the requirements are more stringent. Such a system is the carbamoylimidazole series where the substituents flanking the leaving nitrogen will have a far greater influence than those flanking the oxyanion in a leaving phenol. We decided to study the *N*-methylcarbamoyl derivatives for two reasons: although 1-carbamoylimidazole is easily synthesised from potassium cyanate and imidazole this is not true of the other imidazolyl species. There is a greater steric requirement at the reactive carbamoyl group for the *N*-methyl derivatives compared with the parent making any test of the steric effect more stringent.

EXPERIMENTAL

Materials.—Imidazole, 2-methylimidazole, benzimidazole, and 2-methylbenzimidazole were purchased from Aldrich. Other substituted imidazoles were obtained by synthesis *via* standard routes: 2,4(5)-dimethylimidazole was prepared from hydroxyacetone, ammonia, and acetaldehyde *via* cupric acetate oxidation; decomposition of the cuprous imidazolide by H_2S yielded the free imidazole which was purified as its hydrochloride.[5] 4,5-Dimethylimidazole was prepared from 3-hydroxybutan-2-one, ammonia, and formaldehyde by the above method. 2,4,5-Trimethylimidazole was prepared from acetoin, ammonia, and acetaldehyde by the above method [5] but it was also prepared in good yield by the simpler process of mixing acetaldehyde (0.5 mol) and diacetyl (0.5 mol) with ammonia (80 ml, 28%) and ethanol (100 ml) at *ca.* 0 °C. The mixture was kept overnight, refluxed for 1 h, and evaporated. The imidazole was isolated as its hydrochloride.

The 1-(*N*-methylcarbamoyl)imidazoles were prepared by the following general procedure: the free imidazole (5 mmol) in benzene (10 ml) was warmed to effect dissolution and then cooled. Methyl isocyanate (0.89 g, 5 mmol) was added to the ice-cold mixture over *ca.* 2 min. After a few minutes the carbamoylimidazole was precipitated; further material was recovered by the addition of light petroleum (b.p. 40—60 °C). The product was recrystallised from benzene and analytical and melting point data are recorded in Table 1.

All the species have i.r. and n.m.r. spectra which are consistent with the proposed structures. The structure of the 1-(*N*-methylcarbamoyl)-2,4(5)-dimethylimidazole is



5 - Isomer 4 - Isomer

probably the 2,4-dimethyl isomer because the parent nucleophile with an electron-donating 4(5)-substituent is probably the 5-isomer according to Ridd's observation that electron-withdrawing groups favour the N^{τ}–H tautomer.[6] Neither the i.r. or the ^1H n.m.r. spectral data are diagnostic of the isomeric form of the carbamate but the latter together with the sharp melting point indicate a single compound.

Buffer species were of analytical reagent grade and water used throughout this investigation was twice distilled from glass.

Methods.—The hydrolysis of the carbamoylimidazoles was carried out in a series of buffers at 1M-ionic strength. The stock solution of substrate (*ca.* 10 mM) in acetonitrile (50λ) was added on the tip of a glass plunger to buffer (2.5 ml) in a cuvette (1 cm path length in a thermostatted cell

TABLE 1

Analytical and melting point data for 1-(*N*-methylcarbamoyl)imidazole substrates [a]

Imidazole	M.p. (°C)	Analyses (%) Found C	H	N	Formula	Calculated C	H	N
Parent	113—115	48.1	6.1	33.4	$C_5H_7N_3O$	48.0	5.6	33.6
2-Me	88—90	51.8	7.0	30.0	$C_6H_9N_3O$	51.8	6.5	30.2
2,4-Me_2 [c]	92—94	54.7	7.7	27.0	$C_7H_{11}N_3O$	54.9	7.2	27.4
2,4,5-Me_3	98—99	57.4	8.2	25.3	$C_8H_{13}N_3O$	57.5	7.8	25.1
4,5-Me_2 [b]	90—92	58.1	7.1	25.0	$C_7H_{11}N_3O$	54.9	7.2	27.4
Benzimidazole	114—116	61.5	5.0	24.1	$C_9H_9N_3O$	61.7	5.2	24.0
2-Methylbenzimidazole	85—86	63.3	6.2	22.1	$C_{10}H_{11}N_3O$	63.5	5.9	22.2

[a] Analyses were by Mr. G. Powell using a Hewlett–Packard model 185 CHN analyser; melting points were determined with a Kofler Thermospan instrument. [b] This compound gave consistently poor analyses but n.m.r. data indicate the presence of no impurities and an impurity level equal to the other carbamoylimidazoles. [c] The n.m.r. data and sharp melting point indicate only one isomer.

TABLE 2

Kinetic and thermodynamic data for the hydrolysis of 1-(*N*-methylcarbamoyl)imidazoles [a,f]

Imidazole	k_{H_2O}/s^{-1} $\times 10^5$	$k_{OH}/$ mol l^{-1} s^{-1} $\times 10^3$	$k_2/$ mol l^{-1} s^{-1} $\times 10^{-5}$	pK_a [b]	pK_k [c]	pK_1 [d]	pK_2 [d]
(1) Parent	8.3	2.3	2.6	4.5	4.68	7.30	14.52
(2) 2-Me	79	1.4	1.6	5.7	5.72	8.26	15.13
(3) 2,4,5-Me_3	370	3.7 [e]	0.93	6.6	6.61	9.3	16.06
(4) 2,4-Me_2	30	36	0.17	6.25		8.9	15.71
(5) 4,5-Me_2	50	0.68	1.1	5.65		8.55	15.39
(6) Benzimidazole	2.5	24	79	2.5		5.8	12.78
(7) 2-Methylbenzimidazole	87	79	14	4.8		6.65	13.70

[a] Conditions: 25 °C, ionic strength made up to 1M with KCl, acetonitrile concentration (from stock) <2%. [b] Thermodynamic pK_a of the 1-(*N*-methylcarbamoyl)imidazoles determined by titration. [c] The kinetic pK_a of 1-(*N*-methylcarbamoyl)-imidazoles. [d] The pK_1 and pK_2 refer to ionisation of cationic and neutral imidazole species respectively; the latter is calculated (except in the case of imidazole and benzimidazole) from the linear free-energy relationship of Table 3. [e] Estimated upper limit from the observed value of k_{obs} at pH 13.89. [f] Values of k_{H_2O}/s^{-1} at different temperatures are:

T/°C	$k \times 10^3$	$\Delta H^{\ddagger}_{25°}/$ kcal mol^{-1} [g]	$\Delta S^{\ddagger}_{25°}/$ J K^{-1} mol^{-1} [g]
Imidazole			
36.3	0.197	23	−1
39.0	0.376		
48.0	1.01		
57.5	2.80		
2,4,5-Trimethylimidazole			
21.0	2.16	23	+7
30.0	6.92		
34.8	11.6		
40.0	22.8		
2,4-Dimethylimidazole			
30.0	0.581	25	+7
40.0	2.26		
50.0	6.50		
60.0	18.3		

[g] The enthalpies and entropies of activation are accurate to ±1 kcal mol^{-1} and ±4 J K^{-1} mol^{-1} respectively.

holder of a Unicam SP 800 spectrophotometer) and the spectrum scanned repetitively. This procedure gave an indication as to the stoicheiometry of the reaction and the best wavelength for its study. The procedure was repeated and the reaction followed at a fixed wavelength using either a Unicam SP 800 or Beckman DBG instrument. Pseudo-first-order rate constants were determined from plots of $A_t - A_\infty$ *versus* time on semilogarithmic two-cycle graph paper. Buffer species employed were acetate, phosphate, trishydroxymethylaminomethane, carbonate, and hydroxide. Previous studies indicated that provided the buffer concentration was relatively high (*ca.* 0.1M) there was no effect on the hydrolysis rate constant and the present studies indicate no buffer effect in this range. See results given in the Supplementary Publication [SUP No. 22516 (3 pp.)].*

Measurement of pH was carried out using either a Pye-Dynacap expanded scale instrument or a Radiometer pH-meter PHM 26 calibrated with E.I.L. buffers to ±0.02 pH-units.

The pK_a values of *N*-methylcarbamoyl and free imidazoles were determined at 1M-ionic strength with a Radiometer titration set: PHM 26, REC 61/REA 160 recording titration system, and autoburette ABU 11.

The data for hydrolysis were fitted to a theoretical equation [see equation (2)] relating rate constant to pH using a BASIC computer program. In some cases sufficient data were available to obtain kinetic values for the ionisation constant (corresponding to pK_k) and for k_{H_2O} and k_{OH}. Where data was insufficient to estimate pK_k the thermodynamic value (pK_a see Table 2) was employed as a constant in the computations.†

* For details of the Supplementary publications scheme see Notice to Authors No. 7, *J.C.S. Perkin II*, 1978, Index issue.

† We are grateful to Mr. C. R. Farrar for help with the program; the computations were run on the Kent On-line System from the University of Kent Computer Centre.

RESULTS AND DISCUSSION

The hydrolysis rates for the carbamoylimidazoles were accurately pseudo-first order over at least 90% of the total reaction. The data are tabulated in the Supplementary Publication for a pH-range and are illustrated in

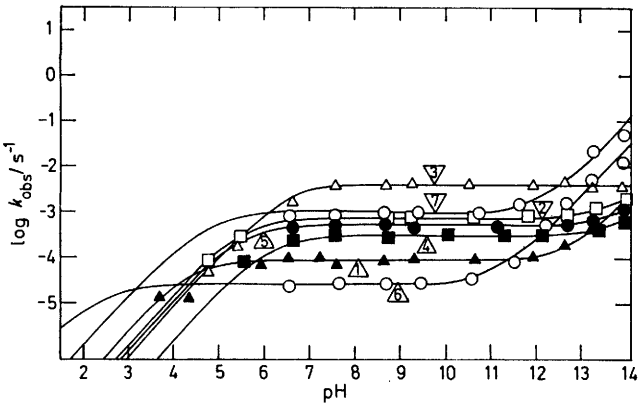


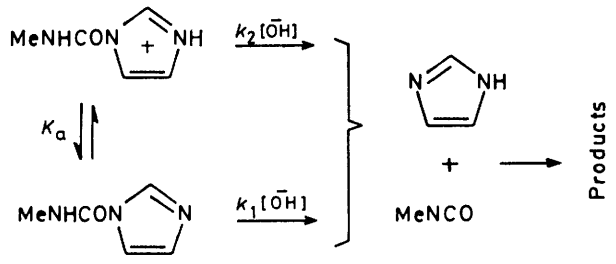
FIGURE 1 Dependence of k_{obs} on pH for the decomposition of 1-(*N*-methylcarbamoyl)-imidazoles. Lines are calculated from values of pK_a, k_{OH}, and k_{H_2O} given in Table 2; identification numbers are from Table 2. Conditions: 25 °C, 1M ionic strength made up with KCl, less than 2% acetonitrile

Figure 1; the pseudo-first order rate constants obey the general rate law [equation (2)] and the parameters k_{H_2O} and k_{OH} are recorded in Table 2.

$$k_{obs} = (k_{H_2O} + k_{OH}[OH^-])/(1 + a_H/K_a) \qquad (2)$$

The pH-profile (Figure 1) indicates that at least two mechanisms are participating and the simplest scheme consistent with the rate equation (2) is shown in equation (3).

It is clear from earlier work [1-3] that the plateau region of the pH-profile corresponds to the mechanism of equation (1) and the top pathway of equation (3); the attack of the hydroxide ion on the conjugate acid of the carbamoylimidazole (k_2) is, in reality, a composite reaction involving ionisation followed by *E*1 decomposition. Paradoxically the carbamoylimidazoles of the most basic imidazolyl species are the most reactive in the plateau region (k_{H_2O}); this phenomenon may be



(3)

explained in terms of the proposed mechanism and values of k_2 (= $k_{H_2O} \cdot K_a/K_w$) have a normal selectivity towards basicity of the leaving group. The Brønsted β_{LG} for k_2 (see Figure 2) is *ca.* −0.7 in agreement with an *E*1cB mechanism; reaction of hydroxide ion with substituted phenyl *NN*-methylphenylcarbamates is an addition–elimination reaction and possesses a β_{LG} −0.24 consistent with rate-limiting addition of nucleophile.[7]

TABLE 3

Correlation between the first and second ionisation constants of substituted imidazoles

Imidazole	pK_1 [a]	pK_2 [b]	pK_2(calc.) [c]	Refs.
Parent	7.05	14.52	14.05	*d*
4(5)-carbamoyl	3.7	11.8	11.07	*e*
2,4(5)-Ph$_2$	5.64	12.53	13.80	*f*
4,5-Ph$_2$	5.90	12.8	13.03	*f*
2-Ph	6.48	13.32	13.55	*f*, *g*
4(5)-Ph	6.1	13.42	13.21	*f*, *g*
4(5)-NO$_2$	1.5	9.1	9.12	*h*
Benzimidazoles				
Parent	5.4	12.78	12.59	*f*, *j*
5(6)-NO$_2$	3.05	10.6	10.49	*f*, *h*
2-PhCH$_2$	5.1	12.7	12.32	*i*
5,6-Me$_2$	6.09	12.52	13.20	*i*
2-Cl	2.6	9.6	10.09	*i*
2-MeO·CO·CH$_2$	4.6	11.7	11.87	*i*

[a] Ionisation of the cation. [b] Ionisation of the neutral species. [c] pK_2 = 0.89 pK_1 + 7.78 (r = 0.966). [d] H. Walba and R. W. Isensee, *J. Org. Chem.*, 1956, **21**, 702. [e] E. F. Rogers, W. J. Leanza, H. J. Becker, A. R. Matzuk, R. C. O'Neill, A. J. Basso, G. A. Stein, M. Solotorovsky, F. J. Gregory, and K. Pfister, *Science*, 1952, **116**, 253. [f] H. Walba and R. W. Isensee, *J. Org. Chem.*, 1961, **26**, 2789. [g] A. H. M. Kirby and A. Neuberger, *Biochem. J.*, 1938, **32**, 1146. [h] T. C. Bruice and G. L. Schmir, *J. Amer. Chem. Soc.*, 1958, **80**, 148. [i] L. S. Efros and B. A. Porai-Koshits, *Zhur. obschchei Khim.*, 1953, **23**, 697 (*Chem. Abs.*, 1954, **48**, 7603h).

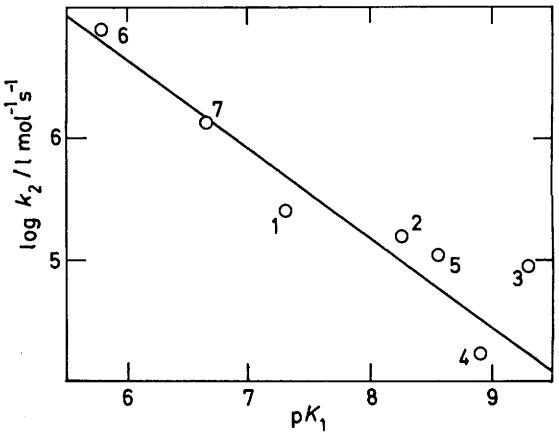
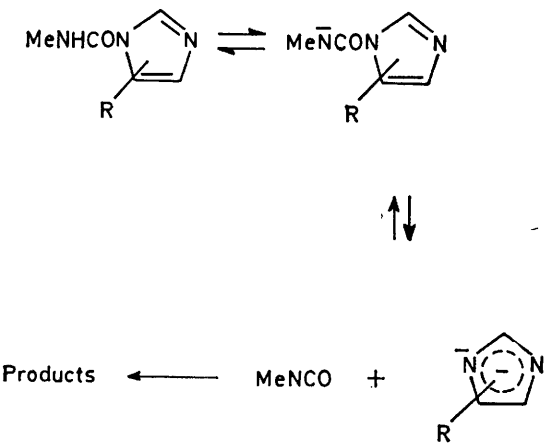


FIGURE 2 Dependence on pK_1 of the parameter k_2; line is theoretical from the equation: log k_2 = −0.74 pK_1 + 11.1

This paper records the first observation of alkaline hydrolysis of a 1-carbamoylimidazole. The imidazolide leaving group is poor because the pK_a of its conjugate acid is in the region 12—14 (Table 3); the usually very rapid *E*1cB hydrolysis giving rise to the plateau rate constant therefore tends to compete successfully with the alkaline pathway. The effective competition is also seen in this series for the trimethylimidazolyl species where the neutral mechanism through the zwitterion takes the major part of the reaction flux even up to 1M-hydroxide ion concentration.[8] The Brønsted plot (Figure 3) *versus* the pK_a of the imidazole (pK_2) has a β_{LG} of

ca. −0.7 consistent with an *E*1cB mechanism [equation (4)].



A negative deviation is observed in the rate constant below the theoretical line in the extreme alkaline region of pH for the hydrolysis of the 2-methylbenzimidazolyl and benzimidazolyl species (Figure 1). This depression

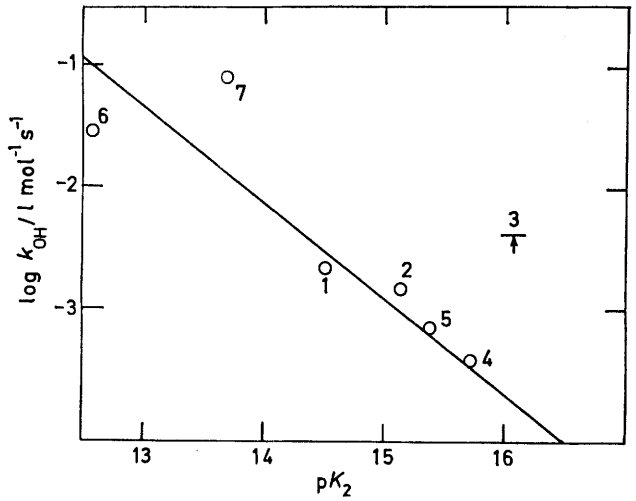


FIGURE 3 Brønsted plot for k_{OH} *versus* pK_a; line is theoretical from the equation: log k_{OH} = −0.68 pK_a + 7.38; the arrow indicates the upper limit for the alkaline hydrolysis of the 2,4,5-trimethylimidazolyl species

amounts to about two-fold even when the theoretical line for equation (2) is derived from values including these deviant points. We believe this depression represents a change in rate-controlling step in the decomposition of the neutral 1-carbamoylimidazole from the formation of the conjugate base at low pH to its decomposition at higher pH [see equation (4)].

Methyl isocyanate resulting from alkaline reaction of 1-(*N*-methylcarbamoyl)benzimidazole in the elimination–addition mechanism has been trapped as the urea with piperidine. This provides unequivocal evidence supporting the pathway of equation (4); reaction of piperidine at 1M concentration and pH 12.67 in a preparative-scale experiment using 2 g of the substrate gave benzimidazole and *N*-methyl-*N'N'*-pentamethyleneurea * in equimolar amounts as judged from proton n.m.r. spectroscopy on the product mixture (evaporated to remove excess of piperidine). No effective change in rate constant for decomposition of the substrate was observed in the presence or absence of piperidine indicating that the urea product does not arise *via* direct attack of the amine on the substrate.†

Both alkaline and neutral paths for the decomposition of the 1-carbamoylimidazoles [k_1 and k_2 respectively in equation (3)[6] are more reactive than that for decomposition of the substituted phenylcarbamate with corresponding pK_a for leaving phenol (*ca.* 13 and *ca.* 7 respectively)]. This enhancement amounts to *ca.* 100-fold for k_1 and 200-fold for k_2. The parent 1-carbamoylimidazole and 1-carbamoyl-3-methylimidazole react with hydroxide ion some 300 to 400-fold faster than does 4-nitrophenylcarbamate.[1,4] These observations are consistent with recent work on leaving-group ability of species from tetrahedral intermediates where the imidazolyl group is found to depart faster than an oxyanion of corresponding pK_a.[9] We propose, for this reason, that the effect lies in the reactivity of the *E*1 reaction rather than in the ionisation step.

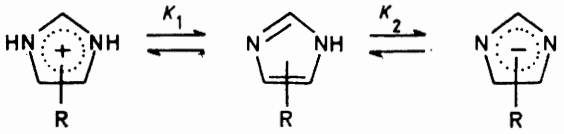
The linear free-energy relationships of Figures 2 and 3 are remarkably good considering the steric constraints built into the system. We can use this linearity as further evidence for *E*1cB mechanisms because ionisation is not likely to involve large steric requirements and the *E*1 decomposition of the conjugate base represents a decrease in co-ordination at the carbamoyl carbon. An addition–elimination process would not give a good correlation and this has been found for attack of phenolate and water on 1-acetyl derivatives of the imidazoles used in this work.[10] A slight enhancement of the trimethylimidazole substrate is observed in the neutral reaction [k_2, equation (3)] and the upper limit for the alkaline reactivity (k_1) could also encompass an enhancement. Study of Corey–Pauling–Koltun models of the substrates indicates that the carbamoyl group of 1-(*N*-methylcarbamoyl)-2,4,5-trimethylimidazole cannot be coplanar with the imidazolyl function unless there is severe steric strain. The steric hindrance requires that there is no rotational degree of freedom about the carbamoyl–nitrogen bond and other rotations are also somewhat restricted. We suggest that the enhancement is due to a gain in rotational entropy in the *E*1 reaction. The transition state for this step is far advanced as judged

* *N*-Methyl-*N'N'*-pentamethyleneurea was synthesised from methyl isocyanate and piperidine using benzene as solvent. The product was recrystallised from cyclohexane and had m.p. 72—74 °C (Found: C, 59.2; H, 9.7; N, 19.9. $C_7H_{14}N_2O$ requires C, 59.2; H, 9.9; N, 19.7%). The n.m.r. spectrum of this species was consistent with the proposed structure and with benzimidazole provided standards for product analysis. All the n.m.r. spectra were recorded with $(CD_3)_2SO$ solutions using $SiMe_4$ as reference.

† The rate constant for reaction of 1-(*N*-methylcarbamoyl)-benzimidazole ($\times 10^3$/s^{-1}) = 1.43 at zero molarity piperidine and 1.4 at 1M-piperidine (when the yield is 100% urea). The rate-controlling step for the reaction must, therefore, be prior to amine attack and hence the trapping results are inconsistent with direct attack on the substrate.

from previous work on attack of nucleophiles at isocyanates and it is, therefore, reasonable to suppose that rotational movement is possible at this level. Values of entropies of activation given in Table 2 do not throw much light on the deviation. Indeed, it appears that the enhancement of the trimethylimidazole species over the imidazole species of similar pK_a resides in an enthalpy difference. We are loathe to interpret such small enthalpy and entropy differences in a system of such high solvation.

Acidity of Imidazoles.—The second pK_a of imidazoles (K_2) is usually not easily accessible for water solutions for those species with electron-donating substituents and the Brønsted relationship of Figure 3 utilises estimated values. A survey of the literature (Table 3) reveals that, for those imidazoles where pK_2 is known, there exists a good correlation between pK_1 and pK_2 even though the data are from a variety of sources and are for different solvent media. The difference of *ca.* 10^8 between first and second ionisations is a result of the cationic nature of the acid for K_1. The nearly identical selectivity of the ionisations to substituents is expected because the change in charge is identical and the electronic structure changes are the same in K_1 and K_2 [equation (5)].



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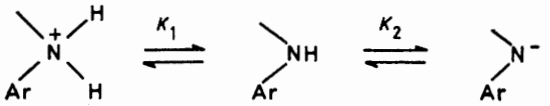
In the aniline dibasic system the first and second ionisations do not have similar selectivities to structure.[11] We interpret this as due to a large change in electronic structure in K_1 compared with that in K_2. This predicts a larger selectivity for K_1 in agreement with the experimental results [11] where a plot of pK_2 *versus* pK_1 has a slope of only +0.6. Equation (6) illustrates the



(6)

large structural differences between the changes corresponding to first and second ionisations.

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