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THE RELATION BETWEEN STRUCTURE AND REACTIVITY IN FIVE-MEMBERED HETEROAROMATIC COMPOUNDS–II

CNDO/2 CALCULATIONS ON AZOLIUM CATIONS AND ON THE ZWITTERIONS RESULTING FROM THEIR DEPROTONATION[1]

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Abstract—Olofson's group and Norris and Henry have reported proton exchange rates for a variety of azolium cations in aqueous solution. They found that ring protons in positions located α- to pyrrole-type N atoms exchange much faster than those located β- to such nitrogens, and that addition of pyridine-type nitrogen to the ring also caused a large increase in rate of exchange. This report describes the results of CNDO/2 calculations on azolium cations representative of those studied experimentally, and on the zwitterions resulting from the deprotonation of these cations. The calculated vapor-phase energies of deprotonation are in agreement with the structure-reactivity trends summarized above, but the calculated effect of added nitrogen is unexpectedly small relative to the effect of interchanging α- and β- pyrrole-type N atoms. The calculated charge distributions and one- and two-atom contributions to the calculated energies of deprotonation are analyzed in terms of classical organic mechanisms for transmission of substituent effects. The results of this analysis suggest that the relative reactivities of isomeric tetrazolium cations are determined primarily by coulombic effects, but that relative reactivities of isomeric positions in the imidazolium and pyrazolium series are apparently determined primarily by inductive and hybridization effects. π-Electron resonance (contributions from carbenoid resonance forms) is apparently not of overriding importance. When nitrogen is added to the ring in an α-position relative to the CH group undergoing exchange, the resulting increase in CH acidity seems to be due to inductive and hybridization effects, partially offset by a coulombic effect due to the negative charge on the added nitrogen. If classical σ-inductive and hybridization effects from an added β-nitrogen are at all influential, they seem much less so than from an added α-nitrogen; thus according to CNDO/2 these effects alone apparently cannot explain the observed large rate increase due to added β-nitrogen. The possible importance of solvent effects, delocalization of the added negative charge into the σ-framework and coulombic effects due to the added nitrogen are discussed.

INTRODUCTION

We have recently begun a study of the relation between structure and reactivity in azole derivatives.[1a,3–5] Our publications to date are concerned primarily with CNDO/2 calculations on heteroaromatic compounds. These include reports describing the results of CNDO/2 calculations on pyrrole and its aza derivatives, and on the substituent effects exerted by these ring systems,[4] and an examination of the effect of assumed molecular geometry on CNDO/2 electron distributions for some tetrazole derivatives.[1] Preliminary presentations describing experimental and theoretical work on substituent effects exerted by tetrazole rings[3,5] have already been delivered. Manuscripts describing this work are being prepared for publication.

Several years ago, Olofson's group,[6a–g] and Norris and Henry[6h] reported the kinetics of H-D exchange of some azoles and azolium cations; the reaction is illustrated (Scheme 1) for the 1,3-dimethylimidazolium cation, and the results for diazolium, triazolium and tetrazolium cations are summarized in Table 1.

Interchanging α- and β-pyridine and pyrrole-type N atoms causes an increase of *ca* 10^4 in exchange rate when the pyrrole-type nitrogen atoms are moved to the α-position relative to the C-H group undergoing exchange. Addition of extra pyridine-type N atoms also causes a rate increase of *ca* 10^4 per added nitrogen. While this manuscript was in preparation, Vaughan *et al.*

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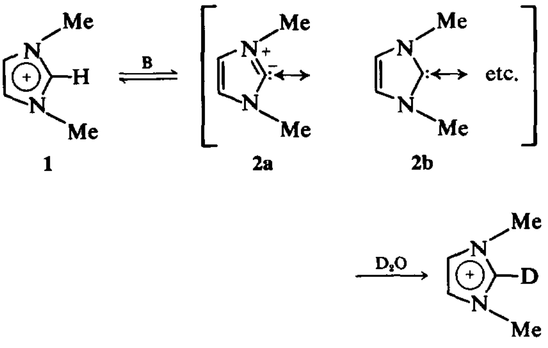
Table 1. Measured rates of hydrogen-deuterium exchange for azolium cations in aqueous buffers at 31°

Cation	Anion	Position	$k^{a,b,c}$ (1 Mol^{-1} sec^{-1})	Δ log k	−RTΔ log k (kcal/mole)
1,2-Dimethylpyrazolium	I^-	3(5)	$5{\cdot}8\times10^{-3}$	−4·5	−6·3
		4	$< 5{\cdot}8\times10^{-3}$	<−4·5	<−6·3
1,3-Dimethylimidazolium	I^-	2	$2{\cdot}0\times10^{2}$	0	0
		4(5)	$< 2{\cdot}0\times10^{2}$	<0	<0
1,3-Dimethylbenzimidazolium	Cl^-	2	$4{\cdot}3\times10^{4d}$	2·3	3·2
1-Ethyl-2-phenyl-1,2,3-triazolium	Cl^-	4	$\sim 10^{-2}$	∼−4·3	∼−6·0
		5	$9{\cdot}7\times10^{2}$	0·7	1·0
1-Ethyl-3-phenyl-1,2,3-triazolium	Cl^-	4	$2{\cdot}4\times10^{2}$	0·1	0·1
		5	$1{\cdot}0\times10^{2}$	−0·3	−0·4
1,4-Dimethyl-1.2,4-triazolium	BF_4^-	3	$1{\cdot}0\times10^{7d}$	4·7	6·5
		5			
1-Ethyl-4-phenyl-1,2,4-triazolium	Cl^-	3	$1{\cdot}9\times10^{3}$	1·0	1·4
		5	$8{\cdot}6\times10^{7}$	5·6	7·8
2,3-Diphenyltetrazolium	Cl^-	5	$1{\cdot}7\times10^{2}$	−0·1	−0·1
1,3-Dimethyltetrazolium	Cl^-	5	$7{\cdot}6\times10^{5e}$	3·6	5·0
1,3-Diethyltetrazolium		5	$7{\cdot}7\times10^{5}$	3·6	5·0
1,4-Diethyltetrazolium	OTos$^-$	5	$2{\cdot}9\times10^{11}$	9·2	12·8

[a] R. A. Olofson, W. R. Thompson and J. S. Michelman, *J Am. Chem. Soc.* **86**, 1865 (1964).
[b] W. P. Norris and R. A. Henry, *Tetrahedron Letters* 1213 (1965).
[c] R. A. Olofson, private communication.
[d] Preliminary value.
[e] At 25°.



SCHEME 1

reported CNDO/2 energy differences for deprotonation of imidazole and oxazole, and for some pyridinium, oxazolium and imidazolium cations; they concluded that CNDO/2 zwitterion and anion stabilities might be useful indices of exchange reactivity, especially for large reactivity differences.[7]

The present paper describes CNDO/2 calculations aimed at reaching a better understanding of the factors affecting the relative CH acidities of these azolium cations. The correlation between calculated deprotonation energies and observed deprotonation rates will be examined, and the calculated charge distributions will be studied in an effort to understand the nature of the important factors affecting relative deprotonation rates in this series. This use of our charge distributions seems justified because the CNDO/2 method successfully calculates dipole moments;[4a,b, 8a,b] because CNDO/2 charge densities correlate with ^{13}C chemical shifts;[8b] and because CNDO/2 charge distributions show trends similar to those in *ab initio* (STO-3G) charge distributions, provided the *ab initio* orbital exponents are optimized for the particular molecular environment under consideration.[8c] Further evidence for the validity of CNDO/2 trends in resonance and field effects is provided by the results of Brownlee and Taft,[8d,e] who carried out CNDO/2 calculations on substituted benzenes, ethylenes and acetylenes; they found reasonable correlations of σ_R and σ_R^0 values with various calculated indices of π-electron distribution. σ-Electron densities on fluorine in substituted fluorobenzenes and [2.2.2] bicyclooctyl 1-fluorides corresponded well in general to the σ_I scale; this was attributed to a field effect. Finally, it has been found that when C_{1s} and N_{1s} binding energies (corrected for Madelung potential) for azines and their perchloro and perfluoro derivatives are plotted against CNDO/2 atomic charges, good correlations are obtained;[8f] although details were not given, it was also stated[8g] that a similar procedure for some 5-membered heteroaromatics gave a good straight line with a slope of 25·4 eV/unit charge.

Evidence as to the reliability of substituent effects on CNDO/2 energy differences is provided by, for example, a recent finding[8h] that CNDO/2 proton affinities for a series of 4-substituted pyridines exhibit substituent effects that are in reasonable agreement with those obtained from vapor-phase measurements on the same series of compounds; the agreement was held to support the predictive value of the CNDO/2 method in this application.

CALCULATIONS

The CNDO/2 calculations[8a, 9a–d] were carried out using a program described previously.[1,4] The assumed molecular geometries are detailed in the footnotes to the tables.

Orbital electron densities q_a and bond orders fl_{ab} were calculated from the following equations:

$$P_{ab} = \sum_{i}^{M} n_i C_{ia} C_{ib}$$

$$P_{aa} = q_a = \sum_{i}^{M} n_i C_{ia}^2$$

where a and b are two different atomic orbitals, i is a molecular orbital, n_i is the occupation number of orbital i, the C's are components of the CNDO eigenvector matrix and M is the number of occupied molecular orbitals.

The bond index W_{ab} between orbitals a and b is defined[9d] by

$$W_{ab} = P_{ab}^2$$

RESULTS

Cation-zwitterion energy differences are given in Tables 2 and 3; trends and approximate magnitudes are relatively independent of assumed molecular geometry. These numbers may be converted to kcal/mole by multiplying them by 627·71.

Calculated charge distributions for azolium cations and azoliumyl zwitterions are given in Tables 4–10. The species for which charge distributions are presented include di-H azolium cations (Table 4) and azoliumyl zwitterions (Table 5) for which ring geometry is represented by regular pentagons 1·33 Å on a side; and dimethylazolium cations and zwitterions for which ring geometry is represented by regular pentagons 1·33 Å (Tables 6 and 7) on a side.

A further set of calculated charge distributions for the 1,3-dimethylimidazolium cation and corresponding zwitterions is given in Table 8; the assumed geometries for these calculations were taken from experimental data, as detailed in the footnotes to the table. Trends and approximate magnitudes are relatively independent of assumed molecular geometry. This is in agreement with our conclusion in Part I of this series,[1a] which was reached on the basis of CNDO/2 calculations on aminotetrazole derivatives and the tetrazolate anion.

Table 9 shows CNDO/2 bond indices and s character in the CH bonds of some of the cations under consideration. The experimental-geometry calculation on 1,3-dimethylimidazolium cations shows the same trends as the regular-pentagon calculation on the same cation.

Table 10 shows changes on deprotonation in calculated coulombic energies of interaction between the atoms of the dimethylazolium cations.

Table 2. Calculated (CNDO/2) total energy values for azolium cations and zwitterions[a]

Cation	Position	Total energy of cation E_T (a.u.)	Total energy of zwitterion E_T (a.u.)	ΔE_T (a.u.)
1,2(Di-H) Pyrazolium	3(5)	−48·118	−47·452	0·666
	4	−48·118	−47·411	0·707
1,3(Di-H) Imidazolium	2	−48·092	−47·458	0·634
	4(5)	−48·092	−47·398	0·694
1,2(Di-H) 1,2,3-Triazolium	4	−51·946	−51·257	0·689
	5	−51·946	−51·289	0·657
1,3(Di-H) 1,2,3-Triazolium	4(5)	−51·963	−51·288	0·675
1,2(Di-H) 1,2,4-Triazolium	3(5)	−51·921	−51·271	0·650
1,4(Di-H) 1,2,4-Triazolium	3	−51·933	−51·266	0·667
	5	−51·933	−51·307	0·626
1H-4-Vinyl-1,2,4-Triazolium[b]	3	−67·599	−66·925	0·674
	5	−67·599	−66·964	0·635
2,3(Di-H) Tetrazolium	5	−55·778	−55·110	0·668
2H-3-Vinyl Tetrazolium[c]	5	−71·459	−70·774	0·685
1,3(Di-H) Tetrazolium	5	−55·802	−55·152	0·650
1,2(Di-H) Tetrazolium	5	−55·792	−55·143	0·649
1,4(Di-H) Tetrazolium	5	−55·815	−55·201	0·614

[a] Azole rings taken as regular pentagons 1·33 Å on a side; other bond lengths and angles as suggested by J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967).

[b] Vinyl group oriented *syn* to position 3.

[c] Vinyl group oriented *syn* to position 4.

Table 3. Calculated (CNDO/2) total energy differences for deprotonation of dimethylazolium cations

Cation	Position	ΔE (Zwitterion-cation) (a.u.)		
		1·33 Å[a]	1·45 Å[b]	Exp.[c]
1,2-Dimethylpyrazolium	3(5)	0·685	0·673	
	4	0·727	0·721	
1,3-Dimethylimidazolium	2	0·652	0·642	0·651
	4(5)	0·710	0·704	0·708
2,3-Dimethyltetrazolium	5	0·697	0·679	
2-Vinyl-3-methyltetrazolium[d]	5	0·698		
1,3-Dimethyltetrazolium	5	0·675	0·661	
1,2-Dimethyltetrazolium	5	0·663	0·645	
1,4-Dimethyltetrazolium	5	0·636[e] 0·637[f]	0·625	
1-Vinyl-4-methyltetrazolium[g]	5	0·636		

[a] Azole rings represented by regular pentagons 1·33 Å on a side; other bond lengths and angles represented as suggested by J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967). Unless otherwise specified the Me groups were taken to be oriented in such a way that each had one CH bond coplanar with the ring; the coplanar C—H bond was oriented in such a way as to allow least interaction with adjacent positions of the ring.

[b] Azole rings represented by regular pentagons 1·45 Å on a side; N—Me bond lengths taken as 1·50 Å. Other bond lengths and angles represented as suggested by J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967). Me groups were assumed to have one C—H bond perpendicular to the plane of the ring; the two perpendicular Me C—H bonds in each cation pointed in the same direction.

[c] Ring geometry and exocyclic angles involving Me groups taken from X-ray crystallographic studies of Beard and Lenhert, *Acta Crystallogr.* **B24**, 1529 (1968) on 1,3-diphosphorylimidazole; ring CH bonds assumed to bisect ring angles; other bonds represented as suggested by J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967).

[d] Vinyl *anti* to position 1.

[e] Coplanar Me CH bonds oriented *syn* to position 5.

[f] Coplanar Me CH bonds oriented *anti* to position 5.

[g] Vinyl *anti* to position 5.

These quantities were calculated using the equation

$$E_q = \frac{1}{2} \sum_{\substack{A,B \\ (A \neq B)}} \frac{Q_A Q_B}{r_{AB}} \qquad (1)$$

where E_q is the classical coulombic interaction energy, Q_A and Q_B are the net atomic charges on atoms A and B respectively and r_{AB} is the distance between atoms A and B. The sum is taken over the atoms indicated in the column headings and footnotes to Table 10, and the cation-zwitterion differences are tabulated in the table. Values of E_q in (electronic charges × 1000)^2/Å were converted[9e] to kcal/mole through the conversion factor $3{\cdot}32 \times 10^{-4}$. The ΔE_q values in Table 10 are not on quite the same scale as the CNDO/2 energy differences, since the use of classical theory as presented in Eq. (1) is equivalent to setting γ_{AB} equal to $1/r_{AB}$ for all (rather than just for large) values of γ_{AB}. However, these ΔE_q values should reflect the trends and approximate magnitudes of the CNDO/2 coulombic effects on the total isolated-molecule energy changes for these deprotonation reactions.

Columns 1–7 of Table 11 show the resolution of the total energies of deprotonation into components due to the following: (1) the change in the one-atom energy term associated with the carbon atom undergoing deprotonation; (2) the one-atom energy term associated with the hydrogen atom involved in the deprotonation; (3) the two-atom energy term associated with the C-H bond involved in the deprotonation; (4) the total change in all one-atom energy terms except those for the C and H atoms directly involved in the deprotonation; (5) the total change in all two-atom terms between atoms considered to be "bonded" in the classical sense, omitting only that term corresponding to the C-H bond directly involved in the deprotonation; and (6) the total change in all two-atom terms between atoms not considered to be "bonded" in the classical sense. Trends similar to those in this table were found when a similar resolution was carried out on the deprotonation energies for the di-H azolium cations. Columns 8–9 of Table 11 list respectively the sums of energy terms (1) and the change in coulombic energy due to the interaction of the carbon and hydrogen atoms involved in the deprotonation with each other and with all other

Table 4. Calculated[a] (CNDO/2) atomic charges for azolium cations

		Atomic charges[b]				
Cation	Position	σ	π	Total	H	Total + H
1,2(Di-H) Pyrazolium	1(2)	−399	+415	+16	+204	+220
	3(5)	+55	+125	+180	+84	+264
	4	+25	−81	−56	+88	+32
1,3(Di-H) Imidazolium	1(3)	−535	+538	+3	+200	+203
	2	+161	+50	+211	+95	+306
	4(5)	+123	−63	+60	+84	+144
1,2(Di-H) 1,2,3-Triazolium	1	−439	+479	+40	+213	+253
	2	−371	+439	+68	+227	+295
	3	+40	+33	+73	—	+73
	4	+83	−49	+34	+102	+136
	5	+50	+99	+149	+94	+243
1,3(Di-H) 1,2,3-Triazolium	1(3)	−518	+589	+71	+222	+293
	2	+206	−126	+80	—	+80
	4(5)	+100	−26	+74	+93	+167
1,2(Di-H) 1,2,4-Triazolium	1(2)	−418	+427	+9	+210	+219
	3(5)	+90	+159	+249	+100	+349
	4	+35	−173	−138	—	−138
1,4(Di-H) 1,2,4-Triazolium	1	−503	+545	+42	+216	+258
	2	+146	−194	−48	—	−48
	3	+141	+29	+170	+102	+272
	4	−549	+537	−12	+209	+197
	5	+138	+84	+222	+100	+322
2,3(Di-H) Tetrazolium	1(4)	+51	0	+51	—	+51
	2(3)	−413	+505	+92	+235	+327
	5	+134	−10	+124	+120	+244
1,3(Di-H) Tetrazolium	1	−520	+573	+53	+231	+284
	2	+170	−68	+102	—	+102
	3	−483	+598	+115	+241	+356
	4	+123	−149	−26	—	−26
	5	+128	+45	+173	+112	+285
1,2(Di-H) Tetrazolium	1	−451	+483	+32	+222	+254
	2	−392	+460	+68	+235	+303
	3	+80	+70	+150	—	+150
	4	+106	−152	−46	—	−46
	5	+87	+140	+227	+112	+339
1,4(Di-H) Tetrazolium	1(4)	−515	+550	+35	+228	+263
	2(3)	+171	−103	+68	—	+68
	5	+122	+106	+228	+109	+337

[a] Assumed molecular geometries detailed in footnote *a*, Table 2.
[b] In units of 0·001 electronic charge.

atoms and the sums of energy term (1) and the change in coulombic energy of deprotonation due to interaction of all atoms with all other atoms; these sums correlate fairly well with the total calculated energy of deprotonation ΔE_T. The last column of Table 11 shows the contribution to ΔE_T due to factors other than the one-atom terms from the C and H atoms involved in the deprotonation.

DISCUSSION

A. *Applicability of these calculations to the study of observed chemical reactivities*

In reading the discussion section of this paper, the following points should be kept in mind.

1. The energies and charge distribution given are not those of the equilibrium geometrical configurations for the species under study, but rather those

Table 5. Calculated[a] (CNDO/2) atomic charges, for azoliumyl zwitterions

		Atomic charges[b]				
Zwitterion	Position	σ	π	Total	H	Total + H
1,2(Di-H) Pyrazoliumyl(5)	1	−370	+317	−53	+100	+47
	2	−348	+365	+17	+100	+117
	3	−573	+352	−221	—	−221
	4	+54	−113	−59	−15	−74
	5	+62	+79	+141	−10	+131
1,2(Di-H) Pyrazoliumyl(4)	1(2)	−382	+355	−27	+103	+76
	3(5)	+90	+86	+176	−22	+154
	4	−577	+117	−460	—	−460
1,3(Di-H) Imidazoliumyl(2)	1(3)	−475	+447	−28	+94	+66
	2	−476	+320	−156	—	−156
	4(5)	+129	−107	+22	−10	+12
1,3(Di-H) Imidazoliumyl(4)	1	−529	+530	+1	+99	+100
	2	+188	−71	+117	+3	+120
	3	−511	+552	+41	+94	+135
	4	−512	+179	−333	—	−333
	5	+184	−189	−5	−18	−23
1,2(Di-H)-1,2,3-Triazoliumyl(4)	1	−423	+421	−2	+109	+107
	2	−358	+370	+12	+116	+128
	3	+1	−3	−2	—	−2
	4	−513	+152	−361	—	−361
	5	+80	+60	+140	−12	+128
1,2(Di-H)-1,2,3-Triazoliumyl(5)	1	−389	+429	+40	+104	+144
	2	−336	+329	−7	+117	+110
	3	−23	−7	−30	—	−30
	4	+110	−78	+32	−7	+25
	5	−575	+327	−248	—	−248
1,3(Di-H)-1,2,3-Triazoliumyl(4)	1	−525	+585	+60	+115	+175
	2	+193	−277	−84	—	−84
	3	−488	+584	+96	+111	+207
	4	−532	+210	−322	—	−322
	5	+149	−102	+47	−12	+35
1,2(Di-H)-1,2,4-Triazoliumyl(3)	1	−392	+341	−51	+104	+53
	2	−366	+365	−1	+101	+100
	3	−517	+376	−141	—	−141
	4	−17	−195	−212	—	−212
	5	+91	+113	+204	−2	+202
1,4(Di-H)-1,2,4-Triazoliumyl(3)	1	−506	+536	+30	+106	+136
	2	+143	−320	−177	—	−177
	3	−480	+263	−217	—	−217
	4	−518	+528	+10	+102	+112
	5	+152	−8	+144	+3	+147
1,4(Di-H)-1,2,4-Triazoliumyl(5)	1	−432	+443	+11	+103	+114
	2	+78	−233	−155	—	−155
	3	+141	−14	+127	+2	+129
	4	−501	+470	−31	+100	+69
	5	−492	+334	−158	—	−158
2,3(Di-H)-Tetrazoliumyl(5)	1	0	−31	−31	—	−31
	2	−398	+436	+38	+122	+160
	5	−450	+189	−261	—	−261

Table 5 – *Continued*

Zwitterion	Position	Atomic charges[b] σ	π	Total	H	Total + H
1,3(Di-H)-Tetrazoliumyl(5)	1	−485	+551	+66	+117	+183
	2	+133	−185	−52	—	−52
	3	−497	+593	+96	+126	+222
	4	+88	−226	−138	—	−138
	5	−483	+268	−215	—	−215
1,2(Di-H)-Tetrazoliumyl(5)	1	−400	+420	+20	+109	+129
	2	−364	+362	−2	+121	+119
	3	+5	+33	+38	—	+38
	4	+47	−172	−125	—	−125
	5	−518	+357	−161	—	−161
1,4(Di-H)-Tetrazoliumyl(5)	1	−456	+470	+14	+112	+126
	2	+93	−140	−47	—	−47
	5	−498	+339	−159	—	−159

[a] Assumed molecular geometries detailed in footnote *a*, Table 2.
[b] In units of 0·001 electronic charge.

of the particular configuration chosen for the calculation. In order to obtain results for the equilibrium configuration, it would be necessary to minimize calculated total energy against molecular geometry, a prohibitively expensive process. In the present work, the azole rings were represented by regular pentagons. Since a set of crystallographic bond lengths and angles is available for a compound closely analogous to the 1,3-dimethylimidazolium cation,[10] it was also possible to carry out a set of "experimental-geometry" calculations on this system. Further details concerning our assumed geometries are given in the section on "Results" and in the footnotes to the tables. Our reasons for this choice of geometrical models are given in the preceding report of this series.[1a] Briefly, the experimental-geometry calculations give the most accurate results in an absolute sense; but the regular-pentagon calculations have the advantage that use of a constant geometry throughout the series facilitates the separation of effects due to electronegativity alone from those due to experimental uncertainties in atomic positions or to small substitution-induced changes in bond lengths and angles. The use of both regular-pentagon and experimental-geometry calculations side-by-side combines these advantages and in addition provides a check for the effect on the results of small variations in assumed molecular geometry. However, the regular-pentagon calculations have the disadvantage that they ignore the difference in bond lengths between, for example, pure single C-C and C-N bonds.

Pople and Gordon[8a] have discussed the advantages of using standardized bond angles and lengths for each type of bond (C—C, C—N, N—N etc) in open-chain systems; and in addition to ourselves, a number of other authors have also represented azole rings by regular pentagons; for references see the preceding report of this series.[1a]

2. The calculated results are those for an isolated molecule; solvation, polarization of the cations by the approaching nucleophile, and other effects which might play a role in solution are ignored, as are kinetic energy effects. Consequently, the best quantities with which to compare the results of calculations such as these might be vapor-phase values for ΔE_p or $\Delta E_p\ddagger$, where E_p is potential energy. However, comparison with ΔH or ΔH‡ values measured in solution is possible if solvent and kinetic energy effects are assumed negligible or constant throughout the series under consideration. Comparison with equilibrium or kinetic rate constants is possible if entropy effects are assumed negligible or constant throughout the series.

It has been pointed out[11] that the enthalpy and entropy contributions to the free energy of solvation should tend to cancel each other, and hence that rate or equilibrium constants measured in solution are actually a better basis for comparison with calculated energy differences than are energies or enthalpies of reaction or activation measured in solution, since it is difficult to separate these last into components due to internal and solvent effects. Reactions influenced by steric effects would be exceptions to this argument; note that we present arguments below which suggest that steric effects are not the dominant factor in determining relative H-D exchange rates for these compounds.

3. In the present paper, we will employ an approach which combines some features of both the "localization" and "isolated molecule"

Table 6. Calculated (CNDO/2) atomic charges for dimethylazolium cations, representing azole rings by regular pentagons 1·33 Å on a side[a]

Cation	Position	Atomic charges[b]			
		σ	π	Total	H
1,2-Dimethylpyrazolium	1(2)	−411	+471	+60	—
	3(5)	+66	+74	+140	+70
	4	+22	−75	−53	+74
	Me	+87	−37	+50	+53[c], +63
1,3-Dimethylimidazolium	1(3)	−535	+587	+52	—
	2	+172	−14	+158	+78
	4(5)	+119	−75	+44	+70
	Me	+91	−37	+54	+53[d], +56
2,3-Dimethyltetrazolium	1(4)	+61	−74	−13	—
	2(3)	−427	+570	+143	—
	5	+122	+4	+126	+100
	Me	+87	−44	+43	+66[e], +83
1,3-Dimethyltetrazolium	1	−519	+628	+109	—
	2	+174	−150	+24	—
	3	−480	+659	+179	—
	4	+101	−162	−61	—
	5	+126	+19	+145	+94
	Me(1)	+96	−46	+50	+65[f], +67
	Me(3)	+94	−49	+45	+71[f], +76
1,2-Dimethyltetrazolium	1	−464	+539	+75	—
	2	−407	+531	+124	—
	3	+93	−6	+87	—
	4	+82	−139	−57	—
	5	+102	+79	+181	+95
	Me(1)	+97	−50	+47	+68[g], +51
	Me(2)	+89	−44	+45	+64[g], +82
1,4-Dimethyltetrazolium	1(4)	−514	+611	+97	—
	2(3)	+155	−125	+30	—
	5	+133	+31	+164	+92
	Me	+93	−43	+50	+61[h], +72
1,4-Dimethyltetrazolium	1(4)	−514	+610	+96	—
	2(3)	+155	−125	+30	—
	5	+134	+31	+165	+92
	Me	+102	−51	+51	+69[i], +55

[a] Other bond lengths and angles used are given in footnote *a*, Table 3.
[b] In units of 0·001 electronic charge.
[c] Two equivalent hydrogens, out of plane of ring and *syn* to the remaining Me group in the cation.
[d] Two equivalent protons, out of plane of ring and *syn* to position 2.
[e] Two equivalent hydrogen atoms, oriented *syn* to the remaining methyl group in the cation.
[f] Two equivalent hydrogen atoms oriented *syn* to position 2 or 5.
[g] Two equivalent hydrogen atoms oriented *syn* to position 5 or 1.
[h] Two equivalent hydrogens oriented *syn* to position 5.
[i] Two equivalent hydrogen atoms *anti* to position 5.

approaches[12] in classical π-electron theory. We will report calculations on the reactants (cations) and products (zwitterions) throughout the series; from comparison between calculated trends in energy difference and electron distribution, we will then seek to draw conclusions concerning the reasons for observed trends in CH proton exchange rates among the compounds under consideration. Our discussion will be primarily in terms of the resonance, inductive, hybridization and field or coulombic effects which are already familiar to modern organic chemists. In many ways, the approach employed will resemble that commonly encountered in classical discussions of

Table 7. Calculated (CNDO/2) atomic charges for dimethylazoliumyl zwitterions, representing azole rings by regular pentagons 1·33 Å on a side[a]

			Atomic charges[b]		
Zwitterion	Position	σ	π	Total	H
1,2-Dimethylpyrazoliumyl(3)	1	−370	+352	−18	—
	2	−349	+401	+52	—
	3	−573	+336	−237	—
	4	+49	−108	−59	−18
	5	+65	+61	+126	−13
	Me(1)	+51	+8	+59	6[c], 14[c]
	Me(2)	+44	+15	+59	0[c], 25[c]
1,2-Dimethylpyrazoliumyl(4)	1(2)	−387	+393	+6	—
	3(5)	+95	+64	+159	−25
	4	−586	+124	−462	—
	Me	+49	+6	+55	+7[c], +22[c]
1,3-Dimethylimidazoliumyl(2)	1(3)	−472	+482	+10	—
	2	−467	+297	−170	—
	4(5)	+126	−112	+14	−11
	Me	+53	+13	+66	+3[c], 0[c]
1,3-Dimethylimidazoliumyl(4)	1	−529	+565	+36	—
	2	+196	−107	+89	+2
	3	−509	+585	+76	—
	4	−519	+175	−344	—
	5	+179	−190	−11	−22
	Me(1)	+49	+6	+55	+9[c], +19[c]
	Me(3)	+43	+13	+56	+2[c], +22[c]
2,3-Dimethyltetrazoliumyl(5)	1(4)	+6	−66	−60	—
	2(3)	−400	+478	+78	—
	5	−466	+201	−265	—
	Me	+46	+2	+48	+16[c], +35[c]
1,3-Dimethyltetrazoliumyl(5)	1	−478	+585	+107	—
	2	+142	−232	−90	—
	3	−491	+635	+144	—
	4	+77	−230	−153	—
	5	−488	+258	−230	—
	Me(1)	+50	+6	+56	+10[c], +25[c]
	Me(3)	+43	−3	+45	+24[c], +32[c]
1,2-Dimethyltetrazoliumyl(5)	1	−399	+454	+55	—
	2	−363	+404	+41	—
	3	+8	+5	+13	—
	4	+37	−167	−130	—
	5	−517	+337	−180	—
	Me(1)	+56	+1	+57	+16[c], +4[c]
	Me(2)	+51	+3	+54	+14[c], +26[c]
1,4-Dimethyltetrazoliumyl(5)[d]	1(4)	−451	+511	+60	—
	2(3)	+90	−152	−62	—
	5	−493	+312	−181	—
	Me	+55	+7	+62	+10[c], +10[c]
1,4-Dimethyltetrazoliumyl(5)[e]	1(4)	−451	+511	+60	—
	2(3)	+89	−151	−62	—
	5	−492	+310	−182	—
	Me	+54	+8	+62	+7[c], +17[c]

[a] Other bond lengths and angles given in footnote *a*, Table 3.

[b] In units of 0·001 electronic charge.

[c] Calculated charges for two kinds of non-equivalent hydrogen; for further information see Table 6 and footnotes thereto.

[d] Me C—H bond coplanar with ring, oriented *anti* to position 5.

[e] Me C—H bond coplanar with ring, oriented *syn* to position 5

Table 8. Calculated (CNDO/2) atomic charges for dimethylimidazolium cation and dimethylimidazoliumyl zwitterions, representing imidazole ring by experimentally-determined ring geometry for 1,3-diphosphorylimidazole[a]

		Atomic charges[b]			
	Position	σ	π	Total	H
1,3-Dimethylimidazolium cation	1	−529	+564	+35	—
	2	+151	+28	+179	+80
	3	−527	+563	+36	
	4	+113	−67	+46	+77
	5	+116	−76	+40	+78
	Me(1)	+92	−35	+57	+51[c], +55
	Me(3)	+92	−35	+57	+51[c], +55
1,3-Dimethylimidazoliumyl 2-zwitterion	1	−465	+458	−7	—
	2	−483	+331	−152	—
	3	−464	+458	−6	—
	4	+112	−98	+14	−2
	5	+116	−110	+6	−1
	Me(1)	+58	+13	+71	+2[c], 0
	Me(3)	+57	+13	+70	+2[c], 0
1,3-Dimethylimidazoliumyl 4-zwitterion	1	−528	+543	+15	—
	2	+173	−56	+117	+2
	3	−513	+563	+50	—
	4	−517	+195	−322	—
	5	+185	−217	−32	−11
	Me(1)	+52	+8	+60	+7[c], +19
	Me(3)	+47	+14	+61	+2[c], +22
1,3-Dimethylimidazoliumyl 5-zwitterion	1	−518	+564	+46	—
	2	+177	−59	+118	+2
	3	−524	+542	+18	—
	4	+179	−209	−30	−12
	5	−512	+190	−322	—
	Me(1)	+47	+14	+61	+2[c], +21
	Me(3)	+52	+7	+59	+7[c], +19

[a] For details of assumed geometry for these calculations, see footnote *c*, Table 3.

[b] In units of 0·001 electronic charge.

[c] Two equivalent hydrogens *syn* to position 2.

Table 9. Carbon-hydrogen bond indices and percent s character in ring C—H bonds of dimethylazolium cations

		Bond indices[a]		Percent s
Cation	Position	Total C—H	C_{2s}—H	Character
1,2-Dimethylpyrazolium[c]	4	0·955	0·297	31·1
	3(5)	0·956	0·325	34 0
1,3-Dimethylimidazolium[c]	4(5)	0·962	0·328	34·1
	2	0·960	0 363	37·8
1,3-Dimethylimidazolium[d]	4(5)	0·964	0·340, 0·342	35·3, 35·5
	2	0 961	0·361	37·5
2,3-Dimethyltetrazolium[c]	5	0·955	0·375	39·3
1,3-Dimethyltetrazolium[c]	5	0·9585	0·368	38·4
1,2-Dimethyltetrazolium[c]	5	0·958	0 368	38·4
1,4-Dimethyltetrazolium[c]	5	0 9595	0·363	37 8

[a] Wiberg bond index; see K. B. Wiberg, *Tetrahedron* **24**, 1083 (1968).

[b] 100 × (C_{2s}—H bond index)/(Total C—H bond index).

[c] Assumed molecular geometries for these calculations are detailed in footnote *a*, Table 3.

[d] Experimental-geometry calculation; for details see footnote *c*, Table 3.

Table 10. Estimated electrostatic energies of deprotonation for dimethylazolium cations[a]

Cation		ΔE_q (CH, α)[b]	ΔE_q (CH, all)[c]	ΔE_q (all)[d]	$-\Delta E_q$ (H)[e]
1,2-Dimethylpyrazolium	(4)	−31	−40	−91	+6·4
	(3)	−12	−29	−64	+8·3
1,3-Dimethylimidazolium	(4)	−15	−22	−71	+7·3
	(2)	−26	−32	−65	+10·6
2,3-Dimethyltetrazolium	(5)	+5	−24	−60	+9·9
1,3-Dimethyltetrazolium	(5)	−13	−29	−67	+11·0
1,2-Dimethyltetrazolium	(5)	−12	−29	−63	+11·7
1,4-Dimethyltetrazolium	(5)	−39	−38	−70	+12·7

[a] All values in kcal/mole, calculated from results of 1·33 Å pentagon calculations summarized in Tables 3, 6 and 7; see also section on "Results".

[b] Change on deprotonation in estimated Coulombic energy of interaction between C and H atoms involved in the exchange reaction and the atoms in the α-positions of the ring with respect to them.

[c] Change on deprotonation in estimated Coulombic interaction energy of C and H atoms involved in the exchange reaction with each other and with all other atoms.

[d] Change on deprotonation in estimated Coulombic interaction energy among all atoms

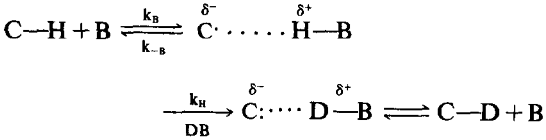
[e] Estimated Coulombic interaction energy of exchanging H atom with all other atoms in the cation.

organic problems; the principal difference will be that instead of arrows, dotted lines, plus and minus signs and so on, we will employ CNDO/2 charge densities, bond indices and energies.

4. We calculated only the initial and final states; we made no attempt to determine the location of the transition state along the reaction coordinate. Consequently, our conclusions actually relate primarily to equilibrium properties such as energies or heats of deprotonation, or to the pK_a values associated with the CH bonds in the azolium cations.

In order to apply our conclusions to the *rates* of deprotonation, we must consider the question of whether the transition state for the reaction resembles either the cation or the zwitterion sufficiently for a change in relative stabilities of reactants and products to be reflected by a corresponding change in activation energy. We feel that the transition state probably resembles the zwitterion sufficiently to allow this; we base this feeling on several considerations. First, in any reaction in which a proton is exchanged between a strong base (in the present case, an azoliumyl zwitterion) and a weaker base (H_2O, OH^-, etc.), the transition state would be expected to resemble the strong base more than the weaker one.[13a] Second, a recent consideration[13b] of this point for the case of proton exchange in imidazolium, oxazolium and thiazolium cations led the authors to express the opinion that, although the barrier to reprotonation of azoliumyl ylids is probably *ca* 7–9 kcal/mole greater than for a diffusion-controlled reaction, the C—H bond is probably fairly well broken in the transition state. Furthermore, it has recently been noted[6d] that $\Delta H\ddagger$ for proton exchange of 1,4-dimethyltetrazolium cation in 9·0N CF_4CO_2D-D_2O is 25·6 kcal/mole; a reaction this endothermic should have a fairly product-like transition state.[14] Because of these considerations, we feel that it is reasonable to assume that any factor which stabilizes the zwitterion relative to the starting cation should also stabilize the transition state relative to the cations.

It has also been pointed out[15] that the available evidence is consistent with the operation of an internal return mechanism in the deprotonation of these and related compounds; such a mechanism could be written as follows (Scheme 2)



$$\mathrm{C{-}H + B} \underset{k_{-B}}{\overset{k_B}{\rightleftharpoons}} \overset{\delta^-}{\mathrm{C}}\cdot\cdots\cdots\overset{\delta^+}{\mathrm{H}}\mathrm{{-}B} \xrightarrow[\mathrm{DB}]{k_H} \overset{\delta^-}{\mathrm{C}}\!:\cdots\cdot\overset{\delta^+}{\mathrm{D}}\mathrm{{-}B} \rightleftharpoons \mathrm{C{-}D + B}$$

Scheme 2

where the step denoted by k_H is the slowest step; the protonation of the zwitterion is diffusion-controlled. If this is the case, the transition state must be very zwitterion-like. The rate constants k_2 for proton exchange of two azolium CH acids G and H should then be related by $k_2^G/k_2^H = (K_A^G/K_A^H)$, and log ($k_2$) will be linearly related to pK_A. This situation would be most favorable to our present use of the calculated results since it removes the need for assumptions concerning the transition state; the calculated energy differences and electron distributions can be related directly to equilibrium constants.

5. Another justification for attempting to correlate features of our calculated electron distributions with proton exchange rates emerges

Table 11. One- and two-atom components of CNDO/2 deprotonation energies for dimethylazolium cations (kcal/mole).

Cation		ΔE_T[a]	ΔE_C[b]	ΔE_H[c]	ΔE_{CH}[d]	$\Sigma\Delta E_1$[e]	$\Sigma\Delta E_2$[f] (Bonded)	$\Sigma\Delta E_2$[g] (Nonbonded)	ΔE_q (CH, all) + ΔE_C	ΔE_q (all) + ΔE_C	$\Delta E_T - \Delta E_C - \Delta E_H$
1,2-Dimethylpyrazolium	(4) (3)	+456 +430	−158 −213	+270 +271	+473 +473	−112 −111	+36 +77	−53 −67	−198 −242	−249 −277	+344 +372
1,3-Dimethylimidazolium	(4) (2)	+446 +409	−195 −229	+271 +269	+476 +476	−97 −100	+59 +60	−68 −68	−217 −261	−266 −294	+370 +369
2,3-Dimethyltetrazolium	(5)	+438	−213	+266	+475	−130	+114	−74	−237	−273	+385
1,3-Dimethyltetrazolium	(5)	+424	−221	+267	+476	−104	+72	−66	−250	−288	+378
1,2-Dimethyltetrazolium	(5)	+416	−228	+267	+474	−121	+90	−67	−257	−291	+377
1,4-Dimethyltetrazolium	(5)	+400	−228	+267	+475	−100	+40	−54	−266	−298	+361

[a] Total energy change on deprotonation (from Table 3, column 2).

[b] Change on deprotonation in one-atom contribution to total energy associated with C atom involved in the deprotonation.

[c] One-atom energy term associated with H atom involved in the deprotonation.

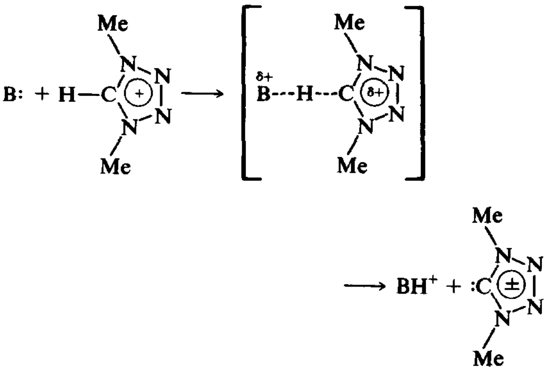
[d] Two-atom energy term associated with the C—H bond broken during deprotonation.

[e] Change on deprotonation in contribution to total energy of one-atom energies other than ΔE_C and ΔE_H.

[f] Change on deprotonation in two-atom energy terms from bonded atom-pairs omitting ΔE_{CH}.

[g] Change on deprotonation in two-atom energy terms from atoms not directly bonded to each other

from examination of the transition state for deprotonation:



In addition to changes in solvation, the principal changes taking place during the formation of the transition state are the approach of B: to the cation, and the shift of the proton from the ring to B:. There are no gross changes in hybridization and no disruption of the π-electron structure of the ring: in this respect deprotonation stands in contrast to reactions like nucleophilic or electrophilic substitution, which do involve such gross disruptions. Because the gross structure of the ring is largely unchanged during the reaction, it seems more reasonable to seek correlations between observed reactivities and features of calculated electron distribution for deprotonation than for reactions which do involve changes in the gross structure of the ring.

B. *Energy differences*

Our CNDO/2 cation-zwitterion energy differences are summarized in Tables 2 and 3. Comparison of these energy differences with the experimentally measured rates of exchange[6] (Table 1) allows the following comments: (1) The relative ordering of kinetic acidities of CH bonds in isomeric positions is predicted correctly. (2) the calculations correctly predict some increase in rate (lower energy difference) on adding nitrogen to the ring. However, this increase is often too small relative to the increase caused by interchanging α and β pyrrole-type nitrogens, especially when the added nitrogen is in a β-position. For example, the calculated energy differences for position 2 of the 1,3-dimethylimidazolium cation and position 5 of the 1,3- and 1,4-dimethyltetrazolium cations (Table 3) are respectively 0·642, 0·661 and 0·625 a.u., as opposed to relative rates of 1, $10^{3\cdot 6}$ and $10^{9\cdot 2}$ for the same positions (Table 1). (3) Replacement of methyl by phenyl generally causes rate of exchange to increase by a factor of *ca* 10 for each phenyl group;[6] vinyl might be expected to have somewhat the same effect. However, our calculations predict little if any change in acidity on replacing methyl by vinyl (Table 3), although it is true that vinyl might exert a different electron-withdrawing effect than phenyl. (4) The calculated proton affinities predict a larger range of reactivities than is observed in solution; for example the values for the tetrazolium cations cover a range of 38 kcal/mole (Table 11, column 1) corresponding to a factor of *ca* 10^{27} in reactivity, whereas the observed rates of exchange in aqueous solution cover a range of only about 10^{10}. There is reason to believe that this discrepancy may in fact reflect reality, rather than being an artifact of the CNDO/2 method. This follows from a very recent communication[8h] describing CNDO/2 calculations, experimentally-measured pK_a's and gas phase proton affinities for some 4-substituted pyridine derivatives; the ΔG values in aqueous solution covered a range of *ca* 7 kcal/mole, the CNDO/2 proton affinities covered a range of *ca* 28 kcal/mole and the experimental gas-phase proton affinities covered a range of about 25 kcal/mole. The extent of agreement was said to support the predictive value of the CNDO/2 method, and the attenuation on going from the vapor phase to solution was rationalized in terms of dielectric constant and H-bonding effects.

In summary, the *trends* in CH acidity resulting from major structural modifications such as addition of nitrogen to the ring or interchange of α- and β-pyrrole-type nitrogens are separately reproduced. Possibly the underestimation of the relative effect of added nitrogen is due to a solvent effect such as protonation or H-bonding involving the lone pairs of pyridine-type nitrogens in aqueous solution; for example, evidence supporting the operation of such an effect in the deprotonation of the Me groups in, e.g., quinaldine has been summarized,[16a,b] and the inclusion of H-bonded water molecules improved the correlation between observed dissociation constants and CNDO/2 deprotonation energies for a series of 4-substituted bicyclooctanecarboxylic acids.[16c]

We now attempt to evaluate this effect for proton exchange of the azolium cations; we begin by assuming that H-bonding involving solvent molecules is unimportant in the case of the cations. This seems reasonable, since the cations should be surrounded by a "shell" of water molecules oriented with the negative (oxygen) end of their molecular dipole toward the cation, and the positive charge on the cation should strongly inhibit the approach of the positive end of the OH dipole of a water molecule. The effect of H-bonding on the relative stabilities of the zwitterions compared to the cations will then be given by the difference in proton-acceptor strengths of aromatic CH groupings on the one hand and pyridine-type N atoms on the other. Because of the amount of information available, we will use the systems methanol-benzene and methanol-pyridine as models. On the basis of data on related systems,[16d] we will take ΔH for the methanol-benzene H-bond to be between $-1\cdot0$ and $-1\cdot5$ kcal. ΔH for the pyridine-methanol H-bond is known to be of the order of $-3\cdot5$ to $-4\cdot0$ kcal.[16e–g] If the ΔS values for the two systems are taken to be similar, ΔΔG for the two systems is between $-2\cdot0$ and $-3\cdot0$ kcal, corresponding to a rate enhancement by a factor of $10^{1\cdot5}-10^{2\cdot0}$ on replacing CH by pyridine-type nitrogen. This enhancement would have been larger had we used the value of $-5\cdot0$ kcal given[16h] for the pyridine-water H-bond in moist pyridine. Data on benzene- and azine-phenol H-bonding supports the idea of similar entropies for H-bonds to CH and to pyridine-type nitrogen[16i,j,k][*] and suggests that addition of nitrogen to the ring may reduce the interaction somewhat but should not eliminate it altogether.[16i,j] H—D isotope effects shouldn't affect this result too much, since it has been found[16l] that the equilibrium constant ratio K_H/K_D (and hence $\Delta G_H-\Delta G_D$) for phenol association with neutral-molecule bases in CCl_4 is relatively independent of the nature of the base; the values 1·2 for pyridine-phenol and 0·7 for acetonitrile were given. We feel that these values should bracket the range covered by the azoliumyl zwitterions.

A CNDO/2 calculation[16m] on the pyridine-methanol system gave a H-bond energy of 7·6 kcal/mole, and a value of 4·4 kcal was calculated for acetonitrile-methanol; these average out to 6·0 kcal or *ca* 0·01 a.u. Application of the treatment described in the preceding paragraph suggests that this value should lead to a substantial improvement in the correlation between the calculated deprotonation energies in Tables 2, 3 and 10 and the experimental results[6] in Table 1.

C. *Electron distributions*

The CNDO/2 method gives a better account of eigenvector-related quantities than of eigenvalue-related quantities.[8b,9a–d] Furthermore, it appears that CNDO/2 energy differences do not scale resonance and electrostatic effects on the same basis.[17a] Consequently, the remainder of the present paper will consist primarily of a discussion of the calculated electron-distributions, and changes therein on deprotonation, in terms of the classical organic effects mentioned above. Unless stated to the contrary, we will be primarily concerned with effects on the relative stabilities of cation and zwitterion; we will assume that any factor which stabilizes zwitterion relative to cation will also accelerate the kinetic process by stabilizing the transition state for deprotonation relative to the starting cation. The factors which may affect the relative CH acidities of these compounds have been discussed by other authors.[6] These include the following: (1) Steric effects; (2) Delocalization of the forming sp^2 carbanion into the aromatic system (contributions from carbenoid structures such as **2b**); (3) Inductive effects; (4) Hybridization effects (the amount of s character in the C—H bond); and (5) Coulombic effects. In the present discussion, solvent effects will also be considered when necessary.

Steric effects (1) are apparently not of overriding importance; if they were, positions α- to pyrrole-type nitrogens should exchange more slowly than isomeric positions β- to the Me or other group attached to these nitrogens. Experimentally, however, the relative reactivities run several orders of magnitude in the opposite direction.[6] If the reaction is considered to proceed by the mechanism of Scheme 2, further support for the unimportance of steric effects on these deprotonation rates is afforded by data[17b] for the protonation-deprotonation equilibria of pyridine-type nitrogens; steric effects in this series should be almost identical with those in the isoelectronic carbon series presently under consideration. For example, the p*Ka* values for 2-, 3- and 4-methylpyridine are respectively 5·97, 5·68 and 6·02 in water;[17b] since steric effects should be appreciable only for the 2-isomer, it follows that these effects are much smaller than the ten-thousandfold difference generally observed between azolium cations having NCH_3 groups α- and β- to the exchanging CH grouping (Table 1).

Our conclusion about resonance (2) is that, while it may be of some small importance, it probably is not the determining factor in the relative deprotonation rates of these cations. The reasoning behind this conclusion is as follows:

In the deprotonation step of the exchange reaction, the σ-charge on the C atom undergoing deprotonation changes (compare Tables 4, 6 with 5, 7; see also Table 8) by *ca* 0·6 electronic charge in the negative direction; CH acidity will be increased by anything that stabilizes this negative charge. It is quite possible that low π-electron density on this C atom could stabilize the added negative charge due to decreased interelectronic repulsion; a higher positive π-charge should thus lead to more stabilization of zwitterion CH acidity.

According to classical valence-bond resonance theory, the 1,2- and 1,4-dimethyltetrazolium cations, for example, should have more positive π-electron charge at the 5-position than the 2,3- and 1,3-isomers due to the existence of resonance forms with positive π-charge at position 5, such as **3** and **4**, which are not possible for the 1,3- and 2,3-

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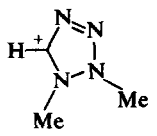
[*] Bhowmik states that "No comparison of the data between the azaaromatic- -naphthol and aromatic hydrocarbon- -naphtol series is attempted; each series is treated separately". However it seems to us that our comparison should be valid to a first approximation.



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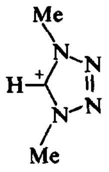

4

isomers. Examination of Tables 4–10 reveals that our calculations are in agreement with this idea; 1,2- and 1,4-isomers are calculated to have more positive π-charge at position 5 than 1,3- and 2,3-isomers throughout the series, both for the cations and the zwitterions.

Consequently, if resonance were the determining factor for the deprotonation rates, one would expect the 1,2-isomers to deprotonate just as fast as the 1,4-isomers (if not faster) and much faster than the 2,3- and 1,3-isomers. Experimentally, this is not so[6] (Table 1); the 3-position of the pyrazolium cation deprotonates *ca* $10^{4\cdot5}$ slower than the 2-position of the imidazolium cation, and the 5-position of the 1,2-disubstituted 1,2,3-triazolium cation exchanges only *ca* 10 times faster than the 1,3-disubstituted isomer. The energy differences (Tables 2 and 3) make much the same prediction, although in many cases they predict somewhat faster exchange for the 1,2- than the 1,3-isomers; possibly this is another example of the apparent tendency[17a] of CNDO/2 energy differences to give different weighting to delocalization and electrostatic effects.

As our criterion of sigma-inductive effects (3) we will adopt the sigma-electron charges on the carbon atom to which the exchanging proton is attached. A high positive sigma-charge on this atom, due to electron withdrawal by other atoms in the molecule, should correspond to increased ability to accept electron density during deprotonation.

Examination of the calculated electron distributions reveals that the sigma-charges on carbon vary considerably with the number of nitrogen atoms in the α-position; σ-charge on carbon becomes more positive (or less negative) with increasing number of nitrogens in the α-positions. Thus, the 4-positions of the pyrazoliumyl 4- and 1,2(di-H)-1,2,3-triazoliumyl 4-zwitterions have calculated σ-charges of −577 and −513 respectively, while the 5-position of the 2,3-(di-H)-tetrazoliumyl zwitterion has a calculated σ-charge of −450 (Table 5). However, compounds such as **3**, which have the 1,2-substitution pattern, have unexpectedly low electron densities on carbon; for example the 2,3-, 1,3-, 1,2- and 1,4-dimethyltetrazolium cations have calculated σ-charges at position 5 of +122, +126, +102 and +133 when the ring is represented by a regular pentagon 1·33 Å on a side (Table 6). Possibly this is due to σ–π electron repulsion, since the 1,2-substitution pattern seems to give rise to higher positive π-charges than the 2,3-, 1,3- and 1,4-patterns. For example, the cations mentioned in the previous sentence have π-charges at carbon of +4, +19, +79 and +31 respectively. Finally, addition of pyridine-type nitrogen in the β-position causes an *increase* in electron density on the C atom under consideration. For example, the σ-charges at position 2 of the 1,3-dimethylimidazolium cation and position 5 of the 1,4-dimethyltetrazolium cation are respectively +172 and +133 (1·33 Å a pentagon calculations-Table 6): this is in accord with the charge alternation noted by Pople and Gordon[8a] for aliphatic systems.

We conclude that σ-inductive effects may be partially responsible for the observed increase in rate of exchange when nitrogen is added to the ring α- to the position of exchange but that if anything they work against the observed increase when nitrogen is added β- to the position of exchange. Furthermore, interchanging α- and β-pyridine- and pyrrole-type nitrogen causes only small changes in σ-charge at carbon; for example consider the numbers given in the preceding paragraph for the tetrazolium cations. Consequently, it seems unlikely that differing inductive effects between pyridine- and pyrrole-type nitrogens can account entirely for the large differences in rate exchange observed when such atoms are interchanged in otherwise isomeric compounds.[6]

The acidity of a compound X—H increases with increasing s character in the X—H bond; thus acetylene is a stronger acid than ethane. For this reason, it seemed possible that hybridization differences (4) might be at least partially responsible for the observed trends in rate of exchange.

In order to obtain information on this point, we calculated "percent s characters" for the C—H bonds, using Wiberg's bond indices[18] as a criterion of bond strength between two orbitals. The results are summarized in Table 9 which also gives details of the computations.

The trends are apparent; addition of a N atom in the α-position relative to a C—H bond causes an increase of *ca* 3–4% in the s character of that bond, while addition of a nitrogen in the β-position causes no increase. In the case of dimethylimidazolium cation, the regular-pentagon and experimental-geometry calculations give similar results.

These trends are consistent with the results of CNDO[19] and INDO[20] calculations on aliphatic compounds. INDO calculations on acyclic compounds containing sp^2-hybridized carbon,[20] however, suggest that replacement of carbon by nitrogen in a β-position *trans* to a $C(sp^2)$-H bond can cause a systematic increase of as much as *ca* 0·6% in the s character of that bond; for example compare the values of $P_{s_C s_H}$ given[20] for N-methylformimide and formaldehyde hydrazone. On the other hand, the few INDO $P_{s_C s_H}$ values given for benzene, pyridine and pyrimidine derivatives[20] seem to exhibit trends in reasonable agreement with those found in Table 9.

Further information on the effect of assumed molecular geometry on calculated s character in CH bonds is furnished by CNDO/2 and INDO calculations on pyrrole and on its aza derivatives;[4,21] experimental geometries are now available for several members of this series. The calculated C—H s characters for regular-pentagonal and experimental geometries follow pretty much the same trends as those for the azolium cations summarized in Table 9; the few exceptions which occur in the results of the experimental-geometry calculations are found to correlate with changes in the interior ring angle.[4c]

Experimentally, the s character in a C—H bond is usually estimated from experimentally measured bond angles[22] or from the alleged direct proportionality[23] between percent s character and the carbon-proton coupling constant J_{CH} (Eq. 2).

$$J_{CH} = 500\,(\text{s character of the C—H hybrid orbital}) \tag{2}$$

Lide[22a] has concluded that bond angles do not provide a reliable measure of carbon hybridization, since a number of cases are known in which they give misleading or impossible estimates of carbon hybridization.

Experimental values for J_{CH} are available for two of the azolium cations presently under consideration; the 2- and 4-positions of the 1,3-dimethylimidazolium cation have J_{CH} values of 220 and 201 Hz respectively and positions 3 and 5 of the 1,4-dimethyl-1,2,4-triazolium cation have values of 225·5 and 226·2 Hz.[6g] Application of Eq. (2) shows that, in the order given, these numbers correspond to 44, 40, 45 and 45 per cent s character. These numbers are *ca* 5–10 percent higher than the calculated values given in Table 9.

The measured values of J_{CH} are in agreement with the prediction that addition of nitrogen should cause an increase in s character in the α-position, since it causes an increase of *ca* 20 Hz in J_{CH} in that position. However, the J_{CH} values disagree with the calculations in that they predict that addition of nitrogen should also cause a smaller increase in s character when nitrogen is added in the β-position. Similar trends are found in the results of J_{CH} measurements on pyrrole and its aza derivatives.[6g]

These discrepancies do not necessarily indicate that the CNDO/2 C-H hybridizations are in error by the indicated amounts; in fact, we feel that there is good reason to believe that J_{CH} values often do not accurately reflect the hybridization of the C atoms in the C—H bonds in the compounds presently under consideration.

The reasons for this are as follows: (a) McFarlane[23] has recently reviewed the literature on C—H coupling constants, and has concluded that variations in J_{CH} can be accounted for by changes in s character only if the electronegativity of the substituents remains relatively constant; this condition is plainly not obeyed when carbon is replaced by nitrogen in the α-position, and it can be questioned whether it is obeyed when the replacement takes place in the β-position. (b) Recent theoretical work[20,24,25]* has also led to suggestions that variations in J_{CH} are due to factors other than changes in the amount of s character in the C—H bond.

We now attempt a quantitative estimate of the influence of C—H bond hybridization on reactivity. The J_{CH} values (Table 10) increase by *ca* 20 Hz when nitrogen is added in the α-position and by *ca* 5 Hz when the addition takes place in the β-position; application of Eq. (2) to these numbers yields increases of 4% and 1% respectively in the s character of the C—H bonds. The calculations (Table 10) suggest an increase of *ca* 3% in the α position and little if any increase in the β-position.

Now, the pK_a values[27] for acetylene, ethylene, and ethane are respectively 25, 42 and 48; in other words, an increase of 1% in the s character of a C—H causes its pK_a to decrease by about 1 pK unit. Assuming that the same or a similar relationship holds for azolic C—H bonds, it follows that addition of nitrogen to an azole ring should cause the acidity of a C—H bond in the α-position to increase by a factor of 1000 or more, while the acidity of a C—H bond in the β-position should not increase by more than a factor of about 10 or so. Among isomeric compounds, changes in C—H hybridization caused by interchanging α- and β-pyrrole and pyridine type nitrogens should also have comparatively little influence on C—H acidity; for example compare the calculated s characters[4c] and J_{CH} values[6g] given for the C—H bonds in the tetrazoles.

In a recent paper on proton-exchange in the azabenzene series,[26] the interesting possibility was raised that addition of nitrogen α- to a C—H bond might cause bond angle changes resulting in decreased s character in that bond; this suggestion was based on the available geometrical data for the azabenzenes. However, on the basis of the calculated s characters and the above discussion, we suggest that the dominant effect of added nitrogen is in fact probably an *increase* in s character due to the electronegativity of the added α-nitrogen. Further support for our suggestion is furnished by a recent experimental-geometry

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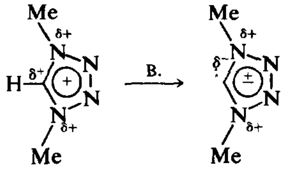
*Gil and Teixeira-Dias[25] argue that the description of CH bonds in terms of localized MO's is not valid, and hence that no physical meaning can be rigorously attached to concepts such as "rehybridization".

INDO calculation on pyridine.[20] This calculation yielded $P_{s_C s_H}$ values of 0·5327, 0·5260 and 0·5229 for the C—H bonds in the 2,3 and 4-positions of pyridine, corresponding to approximately 28·4, 27·7 and 27·3 percent s character respectively. The corresponding values for benzene are 0·5213 and 27·2% s character.

Coulombic effects (5) are due to creation and release of favorable and unfavorable charge distributions in going from the reactants to products or transition states. An example of coulombic effects is provided by the following reactions:



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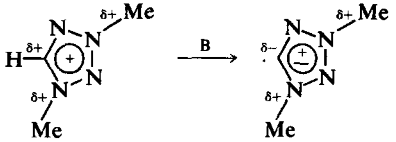
In going from cation **5** to ylid **6**, the positive charge on carbon between two positively charged groupings is transformed to a negative charge between two positively charged groupings; this process could well be energetically more favored than the reaction **7** → **8**, in which the disappearing positive charge has only one positively charged N-Me grouping adjacent to it.



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Classically, it might be expected that coulombic effects provide the best explanation for the observed variations in proton-exchange reactivity among isomeric azolium salts containing only carbon and nitrogen. The importance of these effects seems reasonable in view of the fact that, according to valence-bond resonance theory, the pyrrole-type N atoms carry net positive charges, which would be expected to destabilize the positive charges on the cationic carbon atom and stabilize the developing negative charge in the transition state.

In the present work, we estimated coulombic effects by applying Eq. (1) to the calculated net charges and assumed interatomic distances for the dimethylazolium cations. Certain contributions to the total changes in E_q on deprotonation are summarized in Table 10.

The first column shows the calculated change on deprotonation in the electrostatic interaction energy between the CH grouping undergoing deprotonation and the atoms in the positions located *α* to it; the interaction of the C and H atoms involved in the deprotonation is also included. The predicted reactivity order among isomeric compounds is quite good, except for the pyrazolium 4-position. This position is predicted to react much too fast; experimentally[6a] (Table 1) it does not undergo proton exchange under the stated conditions, but its ΔE_q value is predicted to be more negative than those for most of the dimethyltetrazolium cations.

The second column of Table 10 shows the change on deprotonation in calculated coulombic interaction of the reacting C and H atoms with each other and with all other atoms in the molecule; again, the correct ordering of isomeric compounds is predicted except for the 4-position of the dimethylpyrazolium cation, although the variations in ΔE_q are smaller.

However, examination of Tables 4–8 shows that only 30–40% of the positive charge lost from the cation during deprotonation is lost from the CH group undergoing deprotonation; the remainder of the added electron density is spread among the remaining positions of the ring. Consequently it seemed appropriate to evaluate the coulombic effects among *all* the atoms. The numbers in the third column of Table 12 are the changes on deprotonation in the calculated electrostatic interaction energy among all atoms in the species under consideration. These numbers do not correlate with the observed deprotonation rates (Table 1) of the diazolium cations, although the reactivity order of the 2,3-, 1,3- and 1,4-dimethyltetrazolium cations is reproduced correctly.

The fourth column of Table 10 shows the calculated coulombic interaction energies between the protons under consideration and all other atoms in the respective cations. The proper ordering is reproduced for all compounds under consideration, but the calculated $\Delta\Delta E_q(H)$ values are much too small. For example the $\Delta E_q(H)$ values of 1,3-dimethyltetrazolium and 1,4-dimethyltetrazolium cations differ by only 1·7 kcal/mole, corresponding to an increase in rate of exchange by a factor of *ca* 10 for the 1,4- over the 1,3-isomer; experimentally, however, the 1,4-isomer exchanges faster than the 1,3-isomer by a factor of $10^{5\cdot5}$ (Table 1), and the calculated difference in deprotonation energies is 24 kcal/mole (Table 11).

So far, our discussion of coulombic effects has been based on the results in Table 10. Confirmation for these results is furnished by the numbers in the last column of Table 11. This column gives the results of another attempt at evaluating coulombic contributions to $\Delta\Delta E_T$; the one-atom contributions to ΔE_T from the C and H atoms involved in deprotonation were subtracted out and variations in the remainder were taken to be due primarily to coulombic effects. These ΔE_T-ΔE_C-ΔE_H values exhibit variations similar to the ΔE_q(CH, all) and ΔE_q (all) values in Table 10; the pyrazolium 4-position is much less positive than the others, and the values for the tetrazolium cations vary in the order 2,3 > 1, 3 ≅ 1, 2 > 1,4. This parallel seems significant, although the ΔE_T-ΔE_C-ΔE_H values are still "contaminated" with those contributions to resonance, inductive and other effects that are due to atoms and bonds not included in the CH grouping actually involved in the deprotonation.

Our conclusion concerning coulombic effects is that they probably are of some importance in determining relative CH acidities among the tetrazolium cations, but they seem less important in the case of the diazolium cations. This follows from a fact that the calculated ΔE_q (CH, all) and ΔE_q (all) values for the tetrazolium protons show much better agreement than the diazolium cations with the experimentally observed fact that a sizable increase in CH acidity is caused by shifting a pyrrole-type nitrogen from a β- to an α-position relative to the exchange proton; furthermore the calculated changes in these ΔE_q values are large enough to lend credence to the idea that coulombic interactions could be important factors in determining CH acidity.

However, in addition to the rather drastic assumptions inherent in CNDO theory itself[8a,b,9a–c] the present calculations take no account of the effect of solvation on coulombic interactions. Consequently, although this factor should not affect the *trends* in coulombic effects, great significance should not be attached to quantitative comparison between the exact ΔE_q values and the experimental rates of exchange in Table 1. The most meaningful comparisons are between the calculated ΔE_q values and the *calculated* acidities ΔE_T (Column 1, Table 11); these comparisons are considered in the next section.

CONCLUSION

In the preceding discussion, we sought to evaluate the role of carbenoid resonance, inductive, hybridization and coulombic effects individually; in the present section we combine these in an effort to understand how they interact to determine relative CH acidities throughout the series. We seek to explain two principal trends: (1) A proton located α- to a pyrrole-type nitrogen exchanges H for D at a rate faster by a factor of *ca* 10^4 than a proton in an isomeric position located β- to pyrrole-type nitrogen; and (2) replacement of a CH grouping in the azole ring by a pyridine-type nitrogen causes the remaining CH groupings to increase in rate of exchange by a factor of *ca* 10^4 for each such replacement.

The results of our calculations suggest that, in the case of the tetrazolium and other high-nitrogen cations, trend (1) is primarily the result of changes in coulombic interactions. In the case of the diazolium cations, however, a more likely explanation of this trend would involve primarily variations in hybridization and inductive effects. In the case of the triazolium cations, both effects are presumably playing a role; inductive and hybridization effects would be expected to be important in determining acidities of protons differing in the number of α-nitrogens, while coulombic effects would probably be dominant among positions with the same number of α-nitrogens. These conclusions are based on the following considerations, developed in the previous section or shown in Table 11: (a) The proper ordering of calculated and observed CH acidities of the tetrazolium cations, but not the diazolium cations, is reproduced by the ΔE_q (CH, all) and the ΔE_q (all) values, and the relative magnitudes of the $\Delta\Delta E_q$ and $\Delta\Delta E_T$ values for the tetrazolium cations are such that $\Delta\Delta E_q$ is a fairly important component of $\Delta\Delta E_T$. (b) Columns 8 and 9 of Table 11 show the sums (ΔE_q (CH, all) + ΔE_C) and (ΔE_q (all) + ΔE_C); these sums reproduce the major portion of the variations in the total calculated CH acidities ΔE_T. Since ΔE_C presumably includes mainly non-field polar (inductive, hybridization and resonance) effects, this suggests that these effects may be the factors controlling relative reactivities in the low-nitrogen cations. Note that ΔE_C seems to depend primarily on the number of nitrogens in the α-position; this constitutes further evidence for the importance of inductive and hybridization effects in determining ΔE_C. Similar variations in ΔE_C were found for the di-H azolium cations.

The ΔE_C values appear to mean that carbenoid resonance (**2a** ↔ **2b**) is important in determining the ΔT_T values; for example calculated values of ΔE_C for the 2,3-, 1,3-, 1,2- and 1,4-dimethyltetrazolium cation deprotonations are respectively −213, −221, −228 and −228 kcal/mole. However, due to the fact that γ_{AA} is taken to be the same for both s and p orbitals,[9a–c] we feel that the CNDO/2 method may be over-estimating the importance of resonance. The assumption of equal values for γ_{AA} is equivalent to assuming that s and p orbitals (and hence the π-electrons and the σ-framework) are congruent; since in fact they are not congruent, it follows that σ–π electron repulsion energy must be overestimated.[29a] Now, the importance of resonance in these deprotonation reactions arises from σ–π repulsion; hence the contribution of resonance to ΔE_C (and hence to ΔE_T) is probably overestimated. Possibly this overestimation of σ–π electron repulsion is also responsible for the unusually low calculated electron densities at carbons with pyrrole-type nitrogens in the 1,2-substitution pattern. A recent paper[17a] on arylmethyltosylate reactivities also describes a tendency for the CNDO/2 method to scale delocalization differently from electrostatic effects. The

INDO procedure[29b,c] takes some account of the difference in shapes of 2s and 2p orbitals; consequently this method might give a better account of the relative contributions of electrostatic and resonance effects to reactant-product energy differences. It is also possible that solvent effects might contribute to this discrepancy.

With regard to trend (2), we consider two separate cases: when the added nitrogen is in an α-position with respect to the exchanging proton, and when it is in a β-position. When the added nitrogen is in an α-position, we suggest that the increase in rate of exchange is due primarily to inductive and hybridization effects; these are to some extent offset by a coulombic effect due to the added nitrogen, but the through-bond effects prevail. This follows from the increase in σ-charge on carbon caused by adding nitrogen in an α-position; from the negative increase in ΔE_C caused by addition of α-nitrogen; from the increase in s character in the CH bond caused by addition of α-nitrogen; and from the fact that the calculated ΔE_q values (Table 10) for the 2,3-dimethyltetrazolium 5-position are less negative than those for the 1,2-dimethylpyrazolium 4-position, while the ΔE_C values (Table 11) for the two positions vary in the opposite sense. It might seem that the ΔE_q values for positions with the 1,3- and 1,2-patterns of pyrrole-type nitrogens do not support this, since for example the ΔE_q values do not become appreciably less negative on going from the 1,2-dimethylpyrazolium 3-position to the 1,2-dimethyltetrazolium 5-position; however see the following paragraph.

One possible reason for the rate increase on adding β-nitrogen might be a coulombic effect resulting from withdrawal of electrons by the added nitrogen from the positions located α to it; since one of these positions will also be located α to the exchanging proton, electron-withdrawal from it should cause electrostatic stabilization of the developing negative charge at the deprotonating position. The ΔE_q values for the dimethylimidazolium-2 and 1,4-dimethyltetrazolium-5 positions are in agreement with this; these values are more negative for the tetrazolium cation, and the magnitude of the change is comparable to $\Delta\Delta E_T$ between these cations. Inductive and hybridization effects of the type discussed for the addition of α-nitrogen are apparently not too important; this follows from the fact that σ-electron density on the carbon atom undergoing deprotonation is increased rather than decreased by replacement of β-carbon with nitrogen, and from the fact that this replacement seems to cause little if any change in s character of the CH bond. Also, the ΔE_C values are almost identical for the dimethylimidazolium-2 and the 1,4-tetrazolium-5 positions.

The dependence of carbon σ-charge and of ΔE_C on the number of α-nitrogens suggests that the increase in rate of exchange caused by replacement of pyrrole-type nitrogen by oxygen[6,13b] is also due to inductive and/or hybridization effects; since oxygen is more electronegative than nitrogen, it should exert these effects to an even greater degree than nitrogen.

There are a number of other possible reasons for the rate increase on addition of nitrogen to the ring; two of these in particular seem worth mentioning. First, as mentioned previously, the negative charge added to the ring during deprotonation does not reside entirely on the deprotonated C atom; rather, about one-third of this charge spreads itself more or less evenly about the ring, with most of it going to the pyridine-type nitrogens or to the remaining H atoms.[30] Now, N is more electronegative than C or H; consequently it is possible that replacement of CH by N might result in better stabilization of that portion of the added negative charge which migrates into the ring. Except when the added nitrogen is in the α position, the calculated $\Sigma\Delta E_1$ values (Table 10) do not show the decrease expected on this basis; but it is possible that a set of parameters could be found which would yield such behavior.

Secondly, it is possible that solvent effects may be important in determining the effect of replacing CH by pyridine-type nitrogen. In particular, since pyridine-type nitrogen differs from a CH group in that it has an unshared pair of electrons, the possibility of interaction between this unshared pair and solvent molecules should be kept in mind. Such interaction could take the form of H-bonding[16] or outright protonation; either of these should be more important for the zwitterion than for the cation and thus should increase the rate of exchange (see discussion under "Energy differences").

If we consider the proton exchange in aqueous solution as a kinetic rather than an equilibrium process, there is another factor which could influence the rate of exchange. This factor is the electrostatic interaction of the approaching base with the exchanging CH and neighboring positions. This could influence the kinetics in two ways. First, electrostatic attraction would make it easier for the base to approach a CH grouping having a large positive charge and located adjacent to positively charged positions. For example, it would be easier for OH^- to approach position 5 of the 1,4- than the 1,3-dimethyltetrazolium cation, and easier to approach the 3- than the 4-position of the 1,2-dimethylpyrazolium cation (Table 6).

The effect described in the preceding paragraph would influence rate of exchange through the enthalpy of activation. In addition to this effect, there could also be a parallel entropy effect. This could arise from the fact that the base (the nature of which is uncertain, but is probably some combination of OH^- and/or buffer anion and water) might tend to associate with the cation due to electrostatic interaction; this association should be strongest around highly positive CH groupings which also have highly positive neighbors, and might lead to an entropy effect parallel to the enthalpy effect, since a position strongly associated with base in this way should require less "ordering" in the course of the reaction than a weakly associated position.

Some notion of the possible importance of the first effect can be obtained from consideration of the numbers in Table 10, and of the effect of placing a unit negative charge *ca* 1–2 Å from the cation along the vector defined by the CH bond axis. This consideration suggests that the magnitude of the enthalpy effect should parallel $\Delta E_q(H)$, and that the magnitudes could easily be sufficient to account for a significant portion of the experimentally-observed[6] (Table 1) rate difference; however, a quantitative estimate was not attempted due to the obvious uncertainties due to such factors as solvent effects, the exact nature of the base, and perturbation of the charge distribution in the cation by the charge or dipole of the approaching base.

After this manuscript was finished, proton exchange rates for a variety of 1,2- and 1,3-disubstituted-1,2,3-triazolium salts were published;[31] these results are in reasonable agreement with the literature values given in Table 1.

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