The Structure and Reactivity of Dipyrido[1,2-*a*:1′,2′-*d*]pyrazinium Cations

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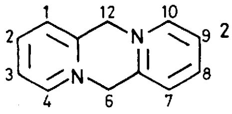
The crystal structure of 6,12-dihydrodipyrido[1,2-*a*:1′,2′-*d*]pyrazinium dibromide (**1**) has been determined by *X*-ray crystallography. In aqueous or methanolic solution (**1**) behaves as a strong acid and is in equilibrium with the monocation (**2**); the proton-transfer kinetics have been studied using stopped-flow methods and the *N*-protonated form of (**2**) has been isolated as the di-iodide. Reduction of (**1**) with borohydride yields a mixture of isomeric octahydro derivatives which do not appear to re-aromatise to compound (**3**). The relative enthalpies of formation of (**1**) and (**3**) have been calculated using MNDO and are compared to related heteroaromatic compounds.



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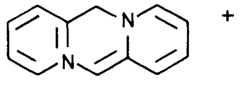

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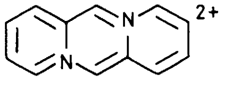

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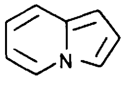


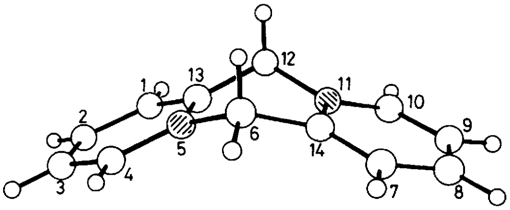
(4)

Condensed heterocyclic systems which incorporate pyridinium cations have attracted considerable attention not only because they are found in many natural product systems[1a] but also because of the potent herbicidal activity of selected derivatives.[1b] More recently, dipyridinium cations have been shown to be components of a novel class of organic metals.[2] It is somewhat surprising that the dipyrido[1,2-*a*:1′,2′-*d*]pyrazinium ring system, although first identified in 1948,[3] has been relatively poorly studied subsequently.[4a–c] Indeed the parent aromatic compound (3) has yet to be characterised.

Structure of Cation (1).—The structure of (1) has been determined by single-crystal *X*-ray diffraction. The molecular diagram is shown in the Figure, with a systematic numbering scheme.† The dication lies across a crystallographic mirror plane with an atom-type disorder among the quaternary sites, C(13) and N(11). The bromide ions lie on this symmetry element, as does the carbon atom of the methanol solvate. The central ring of the dication is non-planar with a dihedral angle of 141°, a similar value to those found in the well studied 9,10-dihydroanthracene systems.[5] Only the values for the unique bond angles are given in Table 1, while the bond distances between atoms in the asymmetric unit and those across the mirror plane are shown in Table 2.

The shorter bond lengths to C(10) [1.336 to C(9) and 1.341 Å to N(11)] compared with those to C(1) [1.412 to C(2) and 1.372 Å to C(13)] may reflect the presence of the nearest bromine anions; one bromine lies 3.55 Å below the C(10) benzo-ring while the other lies approximately in this plane and 3.01 Å from H(9) [and H(8)].

Bond angles in the outer rings are close to 120° and fusion of these rings with the 'boat'-shaped central ring produces the expected effects on bond angles [*viz.* opening at C(1)–C(13)–C(12), decrease from 120° at C(12)–C(13)–N(5), and increase from tetrahedral at C(13)–C(12)–N(11)]. The packing in the crystal is in the form of stacks of cation molecules interspersed with anions. The closest separation between parallel rings of adjacent cations in these stacks is *ca.* 3.4 Å.



Molecular structure of (1) (bond lengths and bond angles are shown in Tables 1 and 2) with crystallographic mirror plane bisecting the vectors C(3)–C(2), C(13)–N(5), C(14)–N(11), and C(8)–C(9)

Solution Kinetics.—In aqueous or methanolic solution (1) behaves as a strong acid. The protons at C(6) and C(12) are exchanged rapidly in D_2O or CD_3OD as deduced by ^1H and ^{13}C n.m.r. Addition of successive amounts of base to a solution of (1) in 0.01M-HCl is accompanied by formation of two intense bands in the visible spectrum at 508 and 386 nm with clean isosbestic points at 256 and 272 nm. Reaction of (1) in dry methanol with triethylamine may also be monitored by ^1H n.m.r. which reveals formation of one equivalent of $Et_3\overset{+}{N}HBr^-$ on addition of excess of base. Such behaviour is consistent with the formation of the monocationic conjugate base (2). The pK_a of (1) has been determined spectrophotometrically in both water and methanol, by observing the 508 nm band of (2) as a function of hydrogen ion concentration. Results are given in Table 3 and the pK_a, corrected for ionic strength, in water is 7.94, while the value in methanol falls to 5.9. It is well known[6] that the solvent dependence of pK_a is very sensitive to charge type, with ionic species being more effectively stabilised by solvents of high dielectric constant. In this system the more effective solvation of the dicationic species by water means that (1) behaves as a stronger acid in methanol than in water [equation (1)].

$$BH_2^{2+} + S \rightleftharpoons BH^+ + SH^+ \qquad (1)$$

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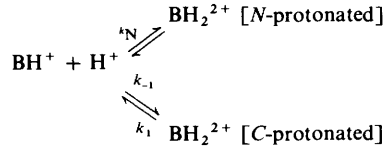
† Tables of atomic co-ordinates and anisotropic thermal parameters are in Supplementary Publication No. SUP 56140 (6 pp.). For details of Supplementary Publications see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1.

The kinetics of proton transfer in this system, measured under first-order conditions, have been studied by stopped-flow spectrophotometry in methanol solution (in H_2O rates of reaction were too fast to be monitored using this technique). Working at constant ionic strength (*I* 0.01) and using dilute solutions of the monocation generated by addition of excess of methoxide, the rate of protonation was measured as a function of acid concentration by monitoring the rate of disappearance of the 508 nm band. Results are given in Table 4.

The data may be interpreted in terms of the Scheme where equilibration with the *N*-protonated form is rapid.

A plot of k_{obs} *versus* $[H^+]$ gave a straight line with a slope of 4×10^4 dm^3 mol^{-1} s^{-1} which represents a value for k_{-1} provided that $K_N[H^+] < 1$. At higher acid concentrations the term $K_N[H^+]$ will become increasingly large and deviation from linearity is expected. The results given in Table 4 are not inconsistent with this interpretation. Given that the pK_a of (**1**) in methanol is 5.9, then k_1 is calculated as 5×10^{-2} s^{-1}. The data also permit an estimation of the p*K* of the postulated *N*-protonated form in methanol. Given that at 3×10^{-3}M-HCl $K_N[H^+] < 1$, then $K_N < 300$ so that the p*K* of the *N*-protonated form must be less than 3. An analogous indolizine (**4**) in water has a pK_a of 3.94[7] and the p*K* in methanol may be expected to be less than this value.



$$k_{obs} = \frac{k_{-1}[H^+]}{1 + K_N[H^+]} + k_1$$

Scheme.

Table 1. Bond angles (°)

C(9)–C(10)–N(11)	119.8(10)	C(10)–C(9)–C(8)	119.5(7)
C(1)–C(2)–C(3)	119.0(6)	C(2)–C(1)–C(13)	120.3(9)
C(13)–C(12)–N(11)	110.9(8)	C(1)–C(13)–C(12)	121.7(9)
C(1)–C(13)–N(5)	120.7(6)	C(12)–C(13)–N(5)	117.6(6)
C(10)–N(11)–C(14)	122.2(9)	C(10)–N(11)–C(14)	120.7(7)
C(12)–N(11)–C(14)	117.1(6)		

Table 2. Bond lengths (Å)

C(10)–C(9)	1.336(17)	C(10)–N(11)	1.341(16)
C(9)–C(8)	1.420(25)	C(2)–C(1)	1.412(16)
C(2)–C(3)	1.399(20)	C(1)–C(13)	1.372(15)
C(12)–C(13)	1.472(16)	C(12)–N(11)	1.498(16)
C(13)–N(5)	1.368(18)	N(11)–C(14)	1.369(19)

Reactions of Cation (**1**).—Reaction of (**1**) with triethylamine in methanol followed by removal of volatiles and addition of excess of methyl iodide in methanol gave purple needles on standing in the dark. The solid-state reflectance spectrum showed two very broad major bands in the visible region at 492 and 375 nm. The ^{1}H n.m.r. spectrum in CD_3OD of a freshly made up solution in the dark showed only a series of four doublets and four triplets shifted upfield (*ca.* 2 p.p.m.) with respect to (**1**) in addition to resonances assigned to the di-iodide of (**1**). Dilute solutions (10^{-5}M) of the purple solid in methanol behaved kinetically identically to (**1**) in basic solution; reaction with acid gave identical rate constants for the proton transfer to regenerate (**1**). Combustion analysis confirmed the molecular formula to be $C_{12}H_{12}I_2N_2$ and the i.r. spectrum (KBr disc) had pyridine ring vibrations (1 622, 1 580 cm^{-1}) and CH out-of-plane deformations (782) distinct from those of the di-iodide of (**1**). This behaviour is consistent with the assignment of an *N*-protonated form of (**2**) for this purple solid. Presumably this chiral dication crystallises out of solution because of its high insolubility in this medium, effectively trapping the kinetic product of protonation of (**2**). In alcoholic or aqueous solvents the dication behaves as a strong acid and the proton on nitrogen dissociates rapidly under diffusion control to generate the monocation (**2**). The *N*-protonated form of (**2**) is a tautomer of (**1**) and is unusual in that both tautomers are isolable. Hardwick

Table 4. Kinetics of protonation of (**2**) in MeOH[a]

$$BH^+ + SH^+ \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} BH_2^{2+} + S$$

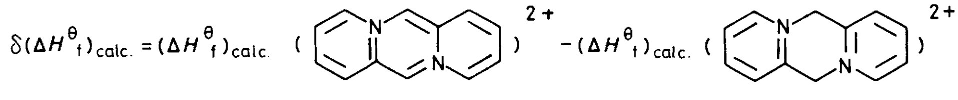
[HCl]/mol dm^{-3}	k_{obs} (±5%)[b]/s^{-1}	10^{-4} k_{obs} [HCl]$^{-1}$/ dm^3 mol^{-1} s^{-1}
2.9×10^{-4}	11.8	4.07
5.8×10^{-4}	22.1	3.86
1.16×10^{-3}	40.3	3.48
2.9×10^{-3}	96	3.33
5.8×10^{-3}	>150	

[a] *I* = 0.01 (NaCl) at 298 K. [b] Measurements of the fading at 508 nm of $[BH^+]$ (1.7×10^{-5}M) on mixing with excess of HCl in methanol.

Table 3. pK_a Determination of (**1**) in H_2O[a] and MeOH

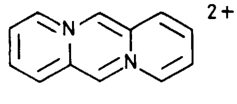
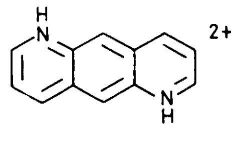
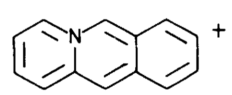
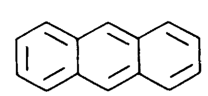
H_2O[e]				MeOH[f]		
pH	Optical density	pK_a[b]	[pK_a[c]]	$-\log_{10}[H^+]$	Optical density	[pK_M[d]]
9.20	0.705	8.23	7.92	4.00	0.03	5.97
7.70	0.250	8.03	7.90	4.60	0.115	5.97
7.51	0.184	8.02	7.89	4.90	0.248	5.91
7.36	0.120	8.10	7.98	5.20	0.39	5.99
7.17	0.083	8.09	7.97	5.80	1.41	5.79
6.94	0.050	8.10	7.98			
6.78	0.038	8.08	7.95		mean	5.93
	mean	8.08	7.94			

[a] At 298 K with freshly prepared solutions with *I* = 0.01M. [b] Determined using the relation pK_a = pH − $\log_{10}\{(OD/OD_\infty)/[1 - (OD/OD_\infty)]\}$ where OD_∞ = 0.78. [c] Corrected for ionic strength. [d] pK_M = $-\log_{10}\{(OD/OD_\infty)[H^+]/[1 - (OD/OD_\infty)]\}$ where OD_∞ = 2.80 [e] Using potassium dihydrogenphosphate buffers. [f] p*K* measurements in methanol are referred to a standard state in methanol and were determined using buffers prepared from 3-chloroaniline, whose p*K* in methanol has the value of 4.60.[6]



(2)

Table 5. MNDO-calculated differences in enthalpies of formation *versus* dihydro analogues

	$\delta(\Delta H_f^{\ominus})_{calc.}$ /kcal mol^{-1}
	38.2
	21.0
	20.7
	21.1

et al. have described a related tautomeric equilibrium involving a benzyl pyridine system in which u.v. spectroscopy was used to characterise the tautomeric structures.[8]

As part of a programme aimed at characterising (**3**), it was necessary to partly reduce the pyridine aromatic rings and then attempt to re-aromatise using standard dehydrogenation procedures. Reduction of (**1**) with aqueous borohydride generates a complex mixture of the isomeric octahydro derivatives with the double bond either in the 8,9- or 9,10-positions according to whether initial hydride attack had occurred at the 10- or 8-position as observed in many related systems.[*,9] These constitutional isomers may exist as *cis–trans* or *trans–trans* diastereoisomers.[4b] Carbon-13 n.m.r. with the aid of the DEPT pulse sequence,[10] revealed at least eight distinct alkane CH resonances centred at δ 125 p.p.m. and three sp^3 CH resonances consistent with this interpretation. Reaction of the mixture of octahydro isomers with bromine followed by treatment with methanolic KOH regenerated (**1**) while reaction with 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) in acetic acid or dioxane afforded a black insoluble solid. When thermolysis with sulphur also did not appear to give evidence of formation of (**3**), the difference in stability of (**3**) with respect to (**1**) was questioned. Accordingly a series of MNDO[11] molecular orbital calculations was performed[†] with the aim of comparing the relative stabilities of (**1**) and (**3**) to a series of related heteroaromatic systems. The data presented in Table 5 refer to the differences in the MNDO-calculated enthalpies of formation for the geometry-optimised ground states of the molecules shown in the table and their dihydro analogues, *i.e.* equation (**2**).

The particularly high $\delta(\Delta H_f^{\ominus})_{calc}$ for the system with two bridgehead nitrogens with respect to all of the other systems is striking, although the reasons for such a large difference are not clear at present.

Experimental

Electronic spectra were recorded in the stated solvent using a Unicam SP800 or a Pye–Unicam SP8-100 spectrometer. Kinetic measurements were made with freshly prepared solutions using a Hi-Tech SF3L stopped-flow spectrophotometer. I.r. spectra were recorded as Nujol mulls or KBr discs using a Perkin-Elmer 297 spectrometer. ^{1}H N.m.r. spectra were recorded using either a Bruker WH360 (360.13 MHz) or a Bruker WB300 (300.13 MHz) instrument; carbon-13 spectra were recorded using the Bruker WB300 (75.5 MHz) instrument.

6,12-Dihydrodipyrido[1,2-*a*:1′,2′-*d*]pyrazinium dibromide was prepared according to the published procedure,[3] δ_H ([$^2H_6$]-DMSO) 9.26 (2 H, d, *J* 6.1 Hz, H-10 + H-4), 8.78 (2 H, td, *J* 7.9 Hz, *J′* 1.3 Hz, H-8 + H-2), 8.39 (2 H, d, H-1 + H-7), 8.28 (2 H, td, H-9 + H-3), and 6.37 (4 H, s, CH_2), $\lambda_{max.}$ (0.01M-HCl) 260 (ε 1.02 × 10^4) and 196 nm (5.92 × 10^4), δ_C(D_2O) 148.2. (C-10, C-4), 145.3 (C-13, C-14), 145.2 (C-8, C-2), 128.8, 127.9 (C-9, C-7, C-3, C-1), and 56.1 p.p.m. (C-6, C-12; exchanged), ν 1 627, 1 570 (ring vibration), 1 494, 1 280, 1 032, 786, and 764 cm^{-1}. Needles of the methanol solvate were obtained from methanol solution for *X*-ray analysis.

Crystal Data.—$C_{12}H_{12}N_2^{2+}\cdot 2Br^-\cdot CH_3OH$, $M = 375.8$. Orthorhombic, $Cmc2_1$, $a = 8.113(4)$, $b = 12.214(6)$, $c = 13.700(7)$ Å, $U = 1\,357(1)$ Å^3, $Z = 4$, $D_x = 1.85$ g cm^{-3}, λ(Mo-K_α) = 0.710 69 Å, $\mu = 59.04$ cm^{-1}, $F(000) = 744$, $T = 200$ K, final $R = 0.048$ for 634 observed data. The central unsaturated ring of the cation adopts an eclipsed boat conformation; the dihedral angle between the outer rings is 141°. The molecules lie on crystallographic mirror planes and there is some atom-type disorder present among the quaternary sites in the cation.

Data Collection, Structure Solution, and Refinement.—Graphite-monochromated Mo-K_α intensity data were collected on a Nicolet P3m four-circle diffractometer at 200 K from a needle crystal (*ca.* 0.2 × 0.25 × 0.7 mm) mounted inside a Lindemann glass capillary and stuck to the wall with some vacuum grease. Cell parameters are based on 25 centred reflections $8 < 2\theta < 27°$. 728 reflection intensities were collected in the bisecting mode by ω–2θ variable scans for one octant of the limiting sphere ($2.9 < 2\theta < 50.0°$), for reflection indices $0 \leqslant h \leqslant 10$, $0 \leqslant k \leqslant 15$, $0 \leqslant l \leqslant 17$. The two standards ($3\bar{1}0$ and $04\bar{4}$), measured every 100 reflections and used to scale the data, showed no significant decay during data collection. Of 678 unique reflections (Lorentz and polarisation-corrected but not corrected for absorption), 44 were considered as unobserved [$F < 5\sigma(F)$].

The structure was solved by Patterson methods for the two bromine atoms and refined by blocked-cascade least-squares using the SHELXTL[12] system of programs. Other non-hydrogen atoms were located in a Fourier calculation based on the bromine atom positions. The disorder in the quaternary C(13) and N(11) sites were refined to 69.4% for C(13) and

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[*] Some additional reduction to the corresponding piperidines was observed for longer reaction times.[9]

[†] Using a CDC 7600 computer at UMRCC and on the NUMAC IBM 370/168 computer at Newcastle. Full details of optimised molecular geometries will be reported subsequently.

subsequently fixed at 70%. All non-hydrogen atoms were given anisotropic thermal parameters except for the carbon and nitrogen atoms at the disordered quaternary sites. Hydrogen atoms were placed geometrically at 0.96 Å (except for the methanol hydroxy at 0.8 Å) and allowed to 'ride' with an isotropic thermal parameter of 1.2 times that of the atom to which they are bonded. Hydrogens and the oxygen in the methanol were given an occupancy of 0.5 to account for disorder across the mirror plane.

84 least-squares parameters were refined to a final R index of 0.048, $R_w = 0.050$ where $w = 1/[\sigma^2(F) + gF^2]$ with g refined to 0.0037 during the final cycles and $\sigma(F)$ as the error in F_0 based on counting statistics. Mean and maximum shifts/e.s.d.s in the last six cycles were 0.1 and 1.4, respectively, the latter all due to solvent atoms. A final difference Fourier had maximum and minimum peak heights of 1.4 and -1.2 e Å^{-3} respectively (the large peaks close to bromine atoms being attributed to the lack of any absorption correction).

N-*Protonated Tautomer of Cation* (**1**).—To a solution of 6,12-dihydrodipyrido[1,2-*a*:1′,2′-*d*]pyrazinium dibromide (344 mg, 1.0 mmol) in methanol (20 cm^3) was added triethylamine (300 mg, 3 mmol) and the solution stirred in the dark (1 h). After removal of solvent and excess of triethylamine *in vacuo*, ^{1}H n.m.r. confirmed the formation of one equivalent of triethylamine hydrobromide. The residue was dissolved in methanol (5 cm^3) and methyl iodide was added (2 cm^3) and the solution left to stand in the dark (24 h), when purple *needles* formed which were filtered off, washed with cold methanol (2 × 3 cm^3), and dried *in vacuo* (260 mg, 50%), (Found: C, 33.3; H, 2.9; N, 6.2. $C_{12}H_{12}I_2N_2$ requires C, 33.0; H, 2.7; N, 6.4%), $\lambda_{max.}$ (diffuse reflectance; diluted in KBr) 492 and 375 nm, $\delta_H(CD_3OD)$ 8.45 (1 H, d, J 5.9 Hz), 7.92 (1 H, t, J 7.3 Hz), 7.72 (1 H + 1 H), 7.45 (1 H, d), 7.25br (1 H, t), 6.86br (1 H, d), and 6.51 (1 H, t), ν 1 622, 1 580 (ring vibration), 1 492, 1 198, 1 174, 1 118, 782 (CH), and 700 cm^{-1}.

Reaction of Cation (**1**) *with Sodium Borohydride.*[9]—To a solution of 6,12-dihydrodipyrido[1,2-*a*:1′,2′-*d*]pyrazinium dibromide (688 mg, 2.0 mmol) in water (20 cm^3) was slowly added a solution of sodium borohydride (1.0 g) in water (10 cm^3). After stirring at room temperature for 1 h, the mixture was refluxed (3 h), when a pale yellow oil separated which was extracted with ether (3 × 20 cm^3) and the solution dried ($MgSO_4$). Removal of solvent under reduced pressure afforded a *solid* which was passed down a short column of alumina (eluted with CH_2Cl_2–MeOH, 100:1) (300 mg, 79%), m/z 190 (M^+), 108, 96, 94, 82, and 80, $\delta_H(CDCl_3)$ 5.75 (4 H, m, CH), 3.2—2.8 (8 H, m, CH_2N), 2.52—2.36 (2 H, m, CH), and 2.05—1.85 (4 H, m, CH_2), δ_C [(major peaks), $CDCl_3$] 126.7, 126.5, 126.0, 124.3, 124.2, 123.9, 123.8, 123.7 (alkene CH); 61.6, 61.2, 60.9 (CH_2N); 59.8, 55.9, 55.7 (CH), 53.5, 53.3, 50.8 (CH_2N); and 29.7 and 29.6 p.p.m. (CH_2) (Found: C, 75.2; H, 9.8; N, 14.7. $C_{12}H_{18}N_2$ requires C, 75.6; H, 9.5; N, 14.4%).

Acknowledgements

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