N-Oxides and Related Compounds. Part XLI.[1] Substituent–Ring Interactions in Methyl- and Chloro-pyrazines and -pyrazine 1-Oxides

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Electric dipole moments show that electronic interactions are greater in methyl- and chloro-pyrazines than in analogous benzene and pyridine compounds.

STUDY of the dipole moments of pyridines[2-4] and of their *N*-oxides[2] and complexes[5] has elucidated the electronic structure and the reactivity of these compounds. Only fragmentary work has appeared on the dipole moments of substituted diazines, although there is considerable interest in the dipole moments of more complex systems such as pteridines and purines[6] which contain fused diazine rings and which require data on these latter ring systems for their interpretation. We have now determined the dipole moments of some mono- and di-substituted pyrazines [see (1)] and their *N*-oxides to supplement the previous work[7,8] in this field.

EXPERIMENTAL

Preparation and Purification of Materials.—AnalaR benzene was dried by refluxing over sodium and was fractionated under nitrogen immediately before use.

2-Methylpyrazine[9] and 2,6-dimethylpyrazine[9] were obtained from Aldrich Chemical Co.; 2,6-dichloropyrazine[10-12] was purchased from Nutritional Biochemicals Corp. 2-Chloro-[10,13] and 2,3-dichloro-pyrazine[12,14] were kindly supplied by Dr. R. G. Shepherd of the Lederle Laboratories, Pearl River, New York. All these samples were recrystallised or redistilled and had m.p.s or b.p.s in agreement with literature values. The following compounds were prepared by methods described in the literature: pyrazine 1-oxide, m.p. 103—104° [lit.,[15] m.p. 113—114°,[16] 104°]; 2,5-dimethylpyrazine 1-oxide, m.p. 104—106° [lit.,[15] 105—106°,[17] 105—108°]; 2,6-dimethylpyrazine 1-oxide, m.p. 54—55° [lit.,[16] 55°]; 3,5-dimethylpyrazine 1-oxide, m.p. 125—127° [lit.,[16] 108—110°] (Found: C, 58·3; H, 6·6; N, 22·6. Calc. for $C_6H_8N_2O$: C, 58·1; H, 6·5; N, 22·6%); 3,5-dichloropyrazine 1-oxide, m.p. 119—120° [lit.,[18] 123—125°] (Found: C, 28·5; H, 1·1; N, 17·0. Calc. for $C_4H_2Cl_2N_2O$: C, 29·1; H, 1·2; N, 17·0%).

3,5-*Bis*(*dimethylamino*)*pyrazine 1-Oxide.*—3,5-Dichloropyrazine 1-oxide (5·0 g) and 25% aqueous dimethylamine (75 ml) were refluxed with stirring for 20 h. The *product*, which crystallised from the reaction mixture upon cooling, was recrystallised from water and, after drying at 90° *in vacuo* over P_2O_5, melted at 170—172° (decomp.); 74·5% yield (Found: C, 53·1; H, 8·1. $C_8H_{14}N_4O$ requires C, 52·7; H, 7·7%); $\lambda_{max.}$ (log ε) 234 (4·32), 294 (3·93), and 376 (3·82) in 1N-HCl.

Physical Measurements.—Dipole moments were calculated by the method of Halverstadt and Kumler[19] from measurements of the dielectric constant (ε) and the specific volume (*v*) of the solvent (benzene) and four different solutions of each compound. The specific volumes were measured with a 5 cm³ pyknometer. Dielectric constants at 25° were derived from measurements with a Wayne–Kerr B641 capacitance bridge, and a glass cell.[20] The electronic polarisation was obtained by summation of bond electronic polarisabilities taken from tables of bond polarisabilities[21] except for C_{Ar}–N_{Ar} and N^+–O^- which are not included therein. C_{Ar}–N_{Ar} Is taken as 2·50, the mean of C–N and C=N, which gives calculated ${}_EP$ values close to those measured by Cumper;[3] further C_{Ar}–C_{Ar} is close to 0·5 (C–C + C=C). For N^+–O^- we have taken the value 5·00 which was estimated from the (fairly wide range of) differences between R_D for pyridines and their *N*-oxides. No allowance was made for atomic polarisation. As before,[22] the dielectric constant and specific volume for benzene were taken as 2·2741 and 1·1446 respectively at 25°. The results are recorded in Tables 1 and 2.

DISCUSSION

The mesomeric moment, μ_m(X.Het), for a substituent in a defined position of a heteroaromatic ring is a measure

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TABLE 1

Dielectric constants and specific volumes in benzene at 25° *

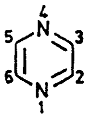
10^6w	$10^6(v_1 - v_{12})$	$10^6(\varepsilon_{12} - \varepsilon_1)$
2-Methylpyrazine		
5056	698	1966
8178	148	3218
10,911	676	4255
13,737	1005	5405
2-Chloropyrazine		
2985	1133	5754
3309	1654	6324
3416	1201	6664
7579	3027	14,877
2,6-Dimethylpyrazine		
4655	489	1136
5620	1029	1342
7663	1267	2191
10,088	905	3160
2,6-Dichloropyrazine		
5337	4986	6786
11,292	6003	9905
14,405	7546	14,108
16,745	9204	18,367
2,3-Dichloropyrazine		
796	291	1359
2504	973	6753
4162	1886	12,115
8483	4124	25,960
Pyrazine 1-oxide		
1806	879	5750
1908	898	6048
3688	1625	11,771
4868	1943	15,869
2,5-Dimethylpyrazine 1-oxide		
2252	568	6076
3367	936	9039
5164	1732	13,865
7665	2291	20,629
3,5-Dichloropyrazine 1-oxide		
2167	1433	937
3486	2985	1467
5381	3757	2264
6864	4340	2848
3,5-Dimethylpyrazine 1-oxide		
2033	793	9261
2825	907	12,271
3703	1478	16,086
4806	1894	20,941
3,5-Bis(dimethylamino)pyrazine 1-oxide		
718	613	9852
1515	685	21,257
2053	626	28,978
2597	582	36,720

* w = Weight fraction. ε_1 and ε_{12} are the dielectric constants for solvent and solution respectively and v_1 and v_{12} are the corresponding specific volumes.

of the transfer of π-electrons between substituent and ring. It may be defined by equation (1), in which measured moments of the substituted heterocycle μ(X.Het), the parent heterocycle μ(Het), and the substituted alkane μ(Alk.X), are summed *vectorially* on the RHS (see ref. 2).†

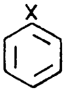
$$\mu_m(\text{X.Het}) = \mu(\text{X.Het}) - [\mu(\text{Het}) + \mu(\text{Alk.X})] \quad (1)$$

Pyrazine itself is centrosymmetric and has zero moment. For pyrazine 1-oxide, our results agree with those reported by Lumbroso and Palamidessi.[7] As these authors point out, the value (1·68 D) [7] is smaller than the vectorial sum (2·23 D) of the pyridine and pyridine 1-oxide moments indicating that the electronic structure of the pyrazine 1-oxide molecule includes an important contribution from canonical form (2).



(1)

(2)



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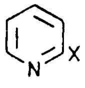

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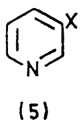

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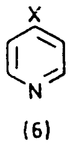

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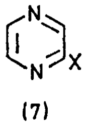
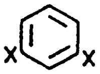


(7)

Values for mesomeric moments of methyl- and chloropyridines (recalculated by the method described above from the data of Cumper *et al.*[3,4]) are compared with those for the corresponding benzenes and pyrazines in Table 3. For both series, the order of the mesomeric moments is 3-pyridine < benzene < 2-pyridine < pyrazine; which is the order expected, since the two nitrogen atoms in pyrazine provide a certain degree of mutual reinforcement. For derivation of values in Table 3, μ(Alk.Cl) was taken as 2·14 D, the moment of t-butyl chloride,[24] and no corrections were made for induced dipole effects; *cf.* ref. 4.



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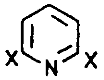

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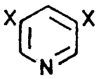

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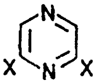

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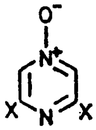

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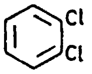

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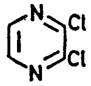

(14)

The dipole moments, and the electronic interactions deduced from them for 2,6-disubstituted pyrazines and 3,5-disubstituted pyrazine 1-oxides are compared with the corresponding data for substituted benzenes and pyridines in Table 4.[3,4] If the rings are assumed to be regular hexagons, then, since vector addition of two equal moments acting at 120° to each other gives a

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† It has been pointed out by a Referee that equation (1) as written appears to neglect inductive effects and C–H bond moments. The full equation is:

$$\mu_{\text{Het.X}} - \mu_{\text{Het.H}} + \mu_{\text{Alk.H}} - \mu_{\text{Alk.X}} = \text{Het.X (mesomeric)} + (\text{Het.X} - \text{Het.H})\ (\text{inductive}) - (\text{Alk.X} - \text{Alk.H})\ (\text{inductive})$$

$\mu_{\text{Alk.H}}$ is zero and the *difference* between the last two terms is also approximately zero.

TABLE 2

Dipole moments of substituted pyrazines in benzene at 25° *

Substituent (s)	dε/dw	−dv/dw	$_TP_{2\infty}$	$_EP$	μ (D)
2-Methyl	0·393 ± 0·002	0·06 ± 0·03	37·4 ± 0·8	26·2	0·74 ± 0·02
2-Chloro	1·97 ± 0·02	0·40 ± 0·04	67·8 ± 1·0	26·4	1·42 ± 0·02
2,6-Dimethyl	0·31 ± 0·03	0·11 ± 0·04	39·7 ± 0·8	30·8	0·66 ± 0·03
2,6-Dichloro	1·0 ± 0·1	0·49 ± 0·08	57·1 ± 0·4	31·1	1·13 ± 0·03
2,3-Dichloro	3·12 ± 0·08	0·49 ± 0·02	116·4 ± 1·0	31·1	2·04 ± 0·01
1-Oxide	3·25 ± 0·03	0·40 ± 0·03	80·0 ± 0·1	26·7	1·62 ± 0·01
2,5-Dimethyl 1-oxide	2·689 ± 0·004	0·31 ± 0·02	93·6 ± 0·7	35·8	1·68 ± 0·01
3,5-Dichloro 1-oxide	0·415 ± 0·004	0·65 ± 0·07	37·2 ± 3·4	36·1	0·23 ± 0·17
3,5-Dimethyl 1-oxide	4·33 ± 0·06	0·39 ± 0·03	129·0 ± 0·3	35·8	2·14 ± 0·01
3,5-Bis(dimethylamino) 1-oxide	14·17 ± 0·07	0·19 ± 0·11	537·2 ± 3·7	52·1	4·87 ± 0·02

* Errors in dε/dw and dv/dw are quoted as ±1 standard deviation based on the least-squares plot. These errors are combined to give the quoted error in μ. Hence, errors are strictly statistical and are not necessarily limits of reliability [see R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1302].

TABLE 3

Mesomeric moments Δμ (D), for monomethyl and monochloro-compounds

	(3)	(4)	(5)	(6)	(7)
Methyl series					
μ(Het)	0	2·22 [a]	2·22 [a]	2·22 [a]	0
μ(Het.Me)	0·43 [b]	1·99 [a]	2·41 [a]	2·62 [a]	0·74
Δμ	+0·43	+0·60	+0·34	+0·40	+0·74
Chloro-series					
μ(Het)	0	2·22 [a]	2·22 [a]	2·22 [a]	0
μ(Het.Cl)	1·61 [c]	3·24 [d]	2·02 [d]	0·82 [d]	1·42
μ(Alk.Cl) [e]	2·14	2·14	2·14	2·14	2·14
Δμ	+0·53	+0·64	+0·41	+0·74	+0·72

[a] Recalculated from data in ref. 3. [b] From ref. 23. [c] From ref. 22. [d] Recalculated from data in ref. 4. [e] From ref. 24; *cf.* ref. 23.

TABLE 4

Interaction moments, Δμ (D), for dimethyl and dichloro-compounds, and differences (ΔΔμ) between these and the mesomeric moments of mono-substituted compounds

	(8)	(9)	(10)	(11)	(12)	(13)	(14)
Dimethyl series							
μ(Het)	0	2·22 [a]	2·22 [a]	0	1·62		
μ(Het.Me$_2$)	0·37 [b]	1·68 [a]	2·59 [a]	0·66	2·14		
Δμ	+0·37	+0·54	+0·37	+0·66	+0·52		
ΔΔμ	−0·06	−0·06	+0·03	−0·08			
Dichloro series							
μ(Het)	0	2·22 [a]	2·22 [a]	0	1·62	0	0
μ(Het.Cl$_2$)	1·54 [c]	3·65 [d]	0·95 [d]	1·13	0·23	2·27	2·04
μ(Alk.Cl) [e]	2·14	2·14	2·14	2·14	2·14	2·14	2·14
Δμ	+0·60	+0·71	+0·87	+1·01	+0·75 (or 0·29)	+0·86	+0·93
ΔΔμ	+0·07	+0·07	+0·46	+0·29		+0·33	+0·21

[a] Recalculated from data in ref. 3. [b] L. Tiganik, *Z. physik. Chem.*, 1931, *B*, **13**, 425. [c] R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, and B. B. Shapiro, *J. Chem. Soc.* (*B*), 1971, 1308. [d] Recalculated from data in ref. 4. [e] From ref. 24; *cf.* ref. 23.

resultant the same as that of one component, the net chlorine σ-moment can again be estimated as 2·14 D. The resulting ' interaction moments,' Δ [equation (2)], show, especially in the case of the methyl compounds, a very close correspondence with the values for the mono-substituted analogues. Two *meta* chlorine atoms appear to increase mutually their interaction moments, especially when they are in the β-positions of the pyridine ring.

$$\Delta = \mu(X_2Het) - [\mu(Het) + \mu(Alk.X)] \qquad (2)$$

The enhancement in the interaction moment observed for two *meta* chlorine atoms is more pronounced when the two chlorine atoms are *ortho*; the measured[23] moment of 2·27 D for *o*-dichlorobenzene implies Δμ of 0·86 D per chlorine, and the measured moment of 2·04 D for 2,3-dichloropyrazine implies Δμ of 0·93 D per chlorine.

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