Correlation of Proton Shifts of Pyrazines with Substituent Constants

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Received June 9, 1971

A study of the ^1H nuclear magnetic resonance spectra of monosubstituted pyrazines in dimethyl sulfoxide revealed that the assigned peak values of the ortho, meta, and para protons correlated quite well with substituent constants. A substituent-ring "second-order" mesomeric interaction is proposed to explain the correlation of the proton meta to electron-donating substituents.

The hope that nuclear magnetic resonance would provide a direct, clear-cut method for measuring the variously hypothesized interactions between the substituent and the ring of substituted benzenes (or other aromatic systems) has never quite materialized.

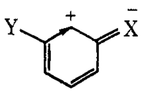
The reason for this is that the significance of chemical shifts in regard to ring-substituent interactions is obscured by the simultaneous action of several mutually opposite effects which determine chemical shifts. In addition to the sometimes overwhelming task of interpreting the complex spectrum of multiproton system (such as substituted benzenes), the difficulty and oftentimes futility in correlating proton nuclear magnetic resonance data with various other data is well documented.

Ring-substituent interactions as described by the Hammett σ constants are generally thought of as the additive effects of mesomeric and inductive interactions.[2] Taft and coworkers have attempted to quantitatively describe the contribution of inductive and mesomeric effects of a substituent to a particular ring position (σ_I is the inductive parameter and $\sigma_R{}^0$ is the resonance parameter).[3]

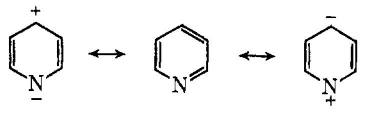
$$\sigma_m{}^0 = \sigma_I + {}^1/_2\sigma_R{}^0$$

$$\sigma_p{}^0 = \sigma_I + \sigma_R{}^0$$

The mixing of both inductive and resonance effects at the meta position may be schematically illustrated by the arrow in the following valence bond resonance form (X-meta substituent, Y-reaction center). The resonance interaction between the meta substituent (X) and the reaction center is called a "second-order" mesomeric effect.



In their analysis of Hammett substituent constants as applied to nitrogen heterocycles, Jaffé and Jones[3b] point out that, while resonance structures **a**, **b**, and **c** all contribute to the ground state of the molecule, structure **c** may not be too important due to the energy requirements of such a resonance form.



a **b** **c**

Another proposed series of substituent constants, designated as σ^+, have been applied to reactions in which strong electrophilic resonance interactions occur between the substituent and the reaction site.[4]

Chemical shifts, as affected by substituents, are postulated to be derived from changes in electron densities, magnetic anisotropy, localized van der Waals forces, and field effects induced by the substituent dipole moments.[5]

In spite of the theoretical and practical difficulties involved in interpreting chemical shifts, empirical attempts to correlate chemical shifts with parameters of electronic interaction have not been entirely unsuccessful. The para ^{13}C and para ^1H shielding of substituted benzenes were found to correlate with Hammett constants. The ^{13}C shifts of several monosubstituted benzenes and para-disubstituted fluorobenzenes were found to correlate with Taft's resonance parameters ($\sigma_R{}^0$).[6]

In a recent series of studies to determine the nature of a possible ortho effect,[7] Charton concluded that significant ortho correlations are obtained using an extended Hammett (Taft–Lewis) equation on a variety of phenomena, including chemical shifts.[7b] The results indicated that in general, no steric effects are exerted by ortho substituents. There was an apparent wide variance in the σ_I and σ_R contributions, evidently precluding the definition of a single set of valid ortho substituent constants.

Previous work on correlating a variety of physical measurements of a family of heterocyclic compounds to Hammett substituent constants[8] has been the subject of a review article by Jaffé and Jones.[2b] In it, they point out that a heteroatom ortho to a substituent might presumably change the substituent's electronic structure, and hence its σ value. They also point out that the heteroatom may affect the transmission of the electronic characteristics of the substituent to the various ring positions.

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[2] (a) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); (b) H. H. Jaffé and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964).

[3] (a) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **82**, 5846 (1960); (b) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960); (c) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963); (d) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, **85**, 3146 (1963).

[4] L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

[5] (a) H. Spiesecke and W. H. Schneider, *J. Chem. Phys.*, **35**, 731 (1961); (b) J. S. Martin and B. P. Dailey, *ibid.*, **39**, 1722 (1963); (c) T. Schaefer, W. P. Reynolds, and T. Yamamoto, *Can. J. Chem.*, **41**, 2969 (1963); (d) A. D. Buchingham, *ibid.*, **38**, 300 (1960); (e) M. J. S. Dewar and Y. Takeuchi, *J. Amer. Chem. Soc.*, **87**, 390 (1969); (f) W. B. Smith and J. L. Roark, *ibid.*, **87**, 5018 (1969).

[6] G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2427 (1965).

[7] (a) M. Charton, *J. Org. Chem.*, **36**, 882 (1971), and references cited therein; (b) M. Charton, *ibid.*, **36**, 266 (1971).

[8] B. M. Lynch, B. C. MacDonald, and J. G. K. Welb, *Tetrahedron*, **24**, 3595 (1968).

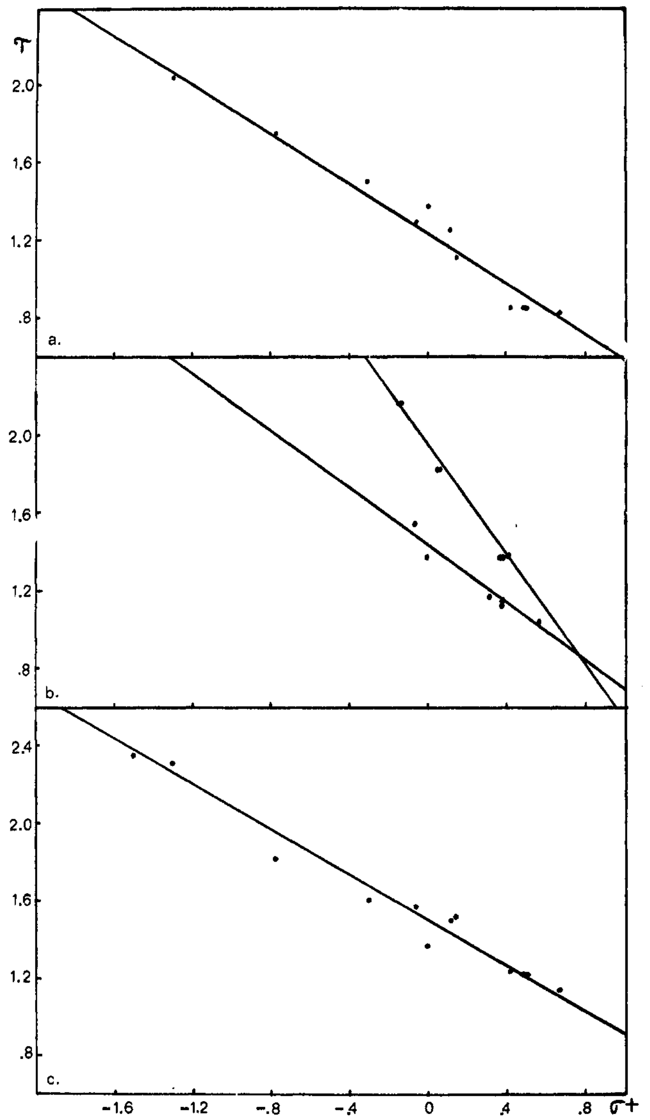
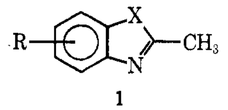


Figure 1.—Least-squares plot of substituent constants σ^+ *vs.* (a) ortho, (b) meta, and (c) para ring proton shifts of monosubstituted pyrazines.

Nevertheless, in a study of substituted benzazoles (**1**), a good correlation was obtained between the chemical shift of the 2-methyl group and the Hammett substituent constants.[9] The correlation of σ constants to the chemical shift of the methyl group was found to be parallel when X was Se, S, and O. It was concluded that the predominant transmission of electronic effects was through the nitrogen atom in all three series. While the heteroatom X plays an important role in establishing the shielding of the 2-methyl protons, it did not seem to influence the transmission of electronic effects.



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X = Se, S, O

Dailey, *et al.*, derived a simple additivity relationship of proton chemical shifts for benzene systems. However, attempts to adapt this method to heterocyclic systems were not successful.[10]

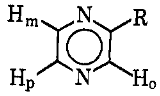
Results and Discussion

In this study, the nuclear magnetic resonance spectra of 13 monosubstituted pyrazines in dimethyl sulfoxide were observed.

The pyrazine system is convenient in that the spectra are not overly complex and are subject to analysis using simple splitting rules. The data are shown in Table I. For the most part, the spectra were found to be quite characteristic for this group of compounds.

TABLE I

CHEMICAL SHIFTS OF SUBSTITUTED PYRAZINES IN DIMETHYL SULFOXIDE[a]



R	Registry no.	H_o	H_m	H_p
CN	19847-12-2	0.82	1.03	1.14
CO_2Et	6924-68-1	0.85	1.14	1.22
CO_2Me	6164-79-0	0.85	1.15	1.22
CO_2H	98-97-5	0.85	1.17	1.24
CHO	5780-66-5	0.97	1.12	1.18
$CONH_2$	98-96-4	0.84	1.19	1.31
I	32111-21-0	1.10	1.36	1.52
Cl	14508-49-7	1.25	1.36	1.50
F	4949-13-7	1.29	1.36	1.57
H	290-37-9	1.37	1.37	1.37
Me	109-08-0	1.50	1.54	1.60
OMe	3149-28-8	1.75	1.82[b]	1.82[b]
NH_2	5049-61-6	2.05	2.14	2.31
NHMe	32111-28-7	2.06[b]	2.06[b]	2.35[b]

[a] Precision ±0.05. [b] Unresolved peak.

The spectra exhibited two doublets and one quartet, the quartet lying upfield. The lowest lying doublet (J = 1.25 cps) was assigned to the ortho proton and the other doublet (J' = 2.50 cps) was assigned to the meta proton. The quartet (J = 1.25 and J' = 2.50 cps) was assigned to the para proton. The assignment of these peaks corresponded to that of substituted benzenes.[2a] The downfield position of the ortho proton, and a larger coupling between the meta and the para proton than between the ortho and the para proton, could be expected.

In three cases, the spectra were not quite so straightforward. The methoxypyrazine showed two unresolved peaks with a relative area of 1:2 (τ_A 1.75, τ_B 1.82). Aminopyrazine showed three doublets (τ_A 2.05, τ_B 2.14, τ_C 2.31; $\Delta\delta_A$ 1.6, $\Delta\delta_B$ 1.6, and $\Delta\delta_C$ 2.1 cps). Methylaminopyrazine exhibited two groups of peaks in a ratio of 2:1 (τ_A 2.06, τ_B 2.35). The downfield peak could not be resolved and the other was a doublet with a coupling constant of $\Delta\delta_B$ 2.50 cps. On the basis of the coupling constants of the peaks and of the expectation that the meta proton does not exhibit greater resonance interaction with the substituent than does the para proton, the highest field peak has been partially assigned to the para proton. While

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[9] G. DiModica, E. Barni, and A. Gasio, *J. Heterocycl. Chem.*, **2**, 457 (1965).

[10] (a) T. K. Wu and B. P. Dailey, *J. Chem. Phys.*, **41**, 2796 (1964); (b) *ibid.*, **41**, 3307 (1964); (c) A. H. Gawer and B. P. Dailey, *ibid.*, **42**, 2658 (1965).

some lack of accuracy might result from the inability to definitely assign the peaks, the error is not greater than $\tau \pm 0.04$.

Using eq 1, the data were analyzed in terms of a least-squares correlation with the three sets of substituent constants forwarded by Hammett (σ), Brown (σ^+), and Taft (σ^0), the latter being calculated from Taft's σ_I and $\sigma_R{}^0$ values in DMSO (Table II).

$$\tau = a\sigma + b \qquad (1)$$

The results indicate that a high degree of linearity exists between the ortho proton shifts and the three sets of (para) substituent constants (see Table III) and compare quite favorably with the results summarized by Charton.[7b]

Table II

Meta and Para Substituent Constants Compiled by Jaffe,[2] Taft,[3] and Brown[4]

	Hammett		Taft		Brown	
R	σ_m	σ_p	$\sigma_m{}^0$	$\sigma_p{}^0$	$\sigma_m{}^+$	$\sigma_p{}^+$
CN	0.56	0.66	0.58	0.70	0.56	0.66
CO_2Et			0.26	0.34	0.37	0.48
CO_2Me	0.32	0.39			0.37	0.49
CO_2H	0.35	0.41			0.32	0.42
CHO	0.25	0.38	0.39	0.53		
$CONH_2$			0.15	0.21		
I	0.35	0.28	0.38	0.27	0.36	0.14
Cl	0.36	0.25	0.38	0.29	0.40	0.11
F	0.34	0.06	0.37	0.22	0.35	−0.07
H	0	0	0	0	0	0
Me	−0.07	−0.17	−0.13	−0.20	−0.07	−0.31
OMe	−0.12	−0.27	−0.03	−0.18	−0.05	−0.78
NH_2	−0.16	−0.66	−0.24	−0.47	−0.16	−1.3
NHMe	−0.18	−0.84	−0.22[a]	−0.46[a]		−1.5

[a] These values are obtained by averaging the amino and the dimethylamino substituent constants.

Table III

Parameters in Correlation of Ortho Proton Shifts with Substituent[a]

	a	b	r	s	n
Hammett	−0.96	1.36	0.980	0.085	12
Brown	−0.64	1.23	0.985	0.075	12
Taft	−1.11	1.44	0.926	0.161	12

[a] See Table IV, footnote *a*.

The correlation of para proton shifts with substituent constants is also high (see Table IV). While the use of Taft's substituent constants gives the poorest results in both the above cases, the same trends are quite apparent. It is noteworthy that the slopes (*a*) for both the ortho and the para correlations have a similar value for each set of substituent constants. This may imply that the nitrogen atom does not appreciably differ from carbon in its ability to transmit the electronic characteristics of substituents.[9]

Table IV

Parameters in Correlation of Para Proton Shifts with Substituent Constants[a]

	a	b	r	s	n
Hammett	−0.86	1.60	0.957	0.115	12
Brown	−0.57	1.50	0.984	0.070	12
Taft	−0.98	1.68	0.897	0.171	12

[a] As applied to eq 1, with correlation coefficient (*r*), root-mean-square deviation (*s*), and the number of points (*n*).

Attempts to correlate the meta shifts with the three sets of substituent constants gave very poor results. However, further analysis indicated that quite good results could be obtained by separately correlating those pyrazines having substituents capable of electron-donating resonance (−R) interaction with the ring. This procedure allowed the substituent constants of both classes of substituents (−R and +R) to correlate very well with the chemical shift data of the meta protons (see Table V).

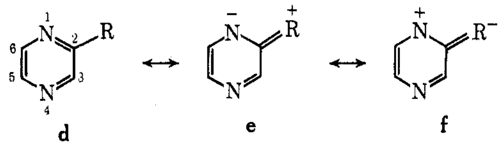
Table V

Parameters in Correlation of Meta Proton Shifts with Substituent Constants[a]

	a	b	r	s	n
Hammett	−1.25	1.66	0.867	0.174	12
Hammett (+R)	−0.76	1.41	0.941	0.058	6
Hammett (−R)	−1.30	1.81	0.973	0.078	6
Brown	−1.14	1.66	0.847	0.166	11
Brown (+R)	−0.75	1.43	0.976	0.037	6
Brown (−R)	−1.34	1.85	0.984	0.058	5
Taft	−1.12	1.65	0.841	0.189	12
Taft (+R)	−0.69	1.38	0.946	0.056	6
Taft (−R)	−1.21	1.81	0.998	0.021	6

[a] As applied to eq 1, with correlation coefficient (*r*), root-mean-square deviation (*s*), and the number of points (*n*).

In attempting to rationalize these results, it can be pointed out that the resonance structure **f** is expected to make a negligible contribution.[2b] Electron-donating substituents (−R) can interact with the ring system as shown in **e**, whereas electron-attracting substituents (+R) would have little recourse to the type of interaction described by **f**.



Adapting the concept of "second-order" mesomeric effect[3,4] to this case, one can see that resonance interaction between the substituent and the nitrogen on position 4 would affect the electronic characteristics on position 6. Depending on the substituent, this takes the form of variably greater electron density on position 6 as reflected by the chemical shift of the proton on that position.

The nmr spectra of two pyrazines were run in a number of solvents. The spectrum of chloropyrazine did not show any changes in going from DMSO to CCl_4. However, methylpyrazine did show some variation with solvent changes but with the overall effect being a convergence of the ring protons. The chemical shift of the methyl group did not exhibit any large solvent dependence (see Table VI).

In conclusion, it appears that the linear correlations of the ortho and para protons of substituted pyrazines with substituent constants indicate that changes in the

TABLE VI

SOLVENT EFFECT ON PROTON SHIFTS OF SUBSTITUTED PYRAZINES

Substituent	H_o	H_m	H_p	H_{CH_3}	Solvent
CH_3	1.52	1.52	1.60	7.47	Neat
CH_3	1.63	1.65	1.68	7.50	CCl_4
CH_3	1.60	1.58	1.62	7.49	$HCCl_3$
CH_3	1.71	1.73	1.75	7.53	CS_2
CH_3	1.50	1.54	1.60	7.50	DMSO
CH_3	1.50	1.54	1.60	7.44	MeOH
Cl	1.25	1.37	1.50		CCl_4
Cl	1.25	1.36	1.50		DMSO

chemical shift of the ring protons of pyrazines parallel changes in substituents. The double linearity of the meta correlation seems to reinforce the view that selective "second-order" mesomeric interaction between some substituents and the meta position is operative.

Experimental Section

2-Pyrazinamide was commercially obtained (Eastman), mp 189-90°.

2-Pyrazinecarboxylic acid was prepared by a basic hydrolysis of 2-pyrazinamide, mp 222-223° dec.

Methyl pyrazinoate[11] was prepared by a sulfuric acid-absolute methanol esterification of 2-pyrazinecarboxylic acid (67% crude) yield). Sublimation at 85° (2.5 mm) gave pure product, mp 57-58°.

2-Hydroxypyrazine was prepared by the method of Yafuso,[12] mp 187-188°.

2-Chloropyrazine[13] was obtained from J. Moshera.

Pyrazinaldehyde was prepared by the method of Rutner and Spoerri,[14] bp 57° (6 mm).

2-Cyanopyrazine,[15] bp 87° (6 mm), was obtained from J. Moshera.

2-Methoxypyrazine, bp 68° (28 mm), was prepared by the method of Albert and Phillips.[13]

2-Fluoropyrazine,[16] bp 107-108°, was obtained from H. Rutner.

2-Iodopyrazine,[17] bp 109-110° (34 mm), was obtained from H. Hertz.

2-Methylpyrazine was commercially obtained (K and K).

Physical Measurements.—All pyrazine nuclear magnetic resonance spectra were run at 37° on a Varian A-60 spectrometer operating at 60 MHz. The peak areas were integrated. Spinning of the samples was always employed. The samples were run five times, once relative to tetramethylsilane as the internal standard, in dimethyl sulfoxide at a rate of 500 cps, and four times relative to benzene as the internal standard in dimethyl sulfoxide, scanning the sample both upfield and downfield.

The least-squares correlations were obtained on a IBM 7040 computer using a program obtained from the Brooklyn Polytechnic Computer Center, and repeated at the computer facility of the Hebrew University.

Acknowledgment.—The authors wish to thank Mr. H. Talz, who ran the nmr spectra, and Mr. J. Moshera for some of the syntheses. Thanks are also due to Dr. A. Meyer for his help in obtaining the use of the computer facility at the Hebrew University.

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[11] W. F. Newell, private communication, 1965.

[12] M. Yafuso, B. S. Thesis, Polytechnic Institute of Brooklyn, June 1964.

[13] A. Albert and J. N. Philips, *J. Chem. Soc.*, 1294 (1956).

[14] H. Rutner and P. E. Spoerri, *J. Org. Chem.*, **28**, 1898 (1963).

[15] M. Robba, *Ann. Chim (Paris)*, **5**, 351 (1960).

[16] H. Rutner and P. E. Spoerri, *J. Heterocycl. Chem.*, **2**, 492 (1965).

[17] A. Hirshberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 1907 (1961).

An Evaluation of Base-Solvent Systems Using Olefin Isomerization as a Probe

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Received June 16, 1971

The base-catalyzed olefin isomerization reaction has been used to probe the efficacy of a wide variety of base-solvent systems. Changes in base type have produced changes in reaction rate that range over eleven powers of ten. The metal alkylamides in hexamethylphosphoramide are the most active. With a given type of anion, both its ligands and the metal cation have pronounced effects. Solvent variation produced a smaller range of reactivity (10^3). Dielectric constant and solvent proticity also play critical roles.

During the past 10 years the use of dipolar aprotic solvents has provided numerous advantages for the organic chemist.[1-3] Perhaps the most significant of these is the discovery of homogeneous base-solvent systems that promote anionic reactions of very weak organic acids under mild conditions. Although the role of the base and solvent are critical to the reaction, a comprehensive study of the relative effectiveness of various combinations is not available. The present work was initiated to provide both practical and theoretical information.

The base-catalyzed olefin isomerization reaction was selected as the probe for this study for several reasons. First, considerable information about the reaction has been obtained and many of the mechanistic details have been elucidated.[4-8] Second, the reaction is experimentally simple since it is homogeneous in both olefin and base. Third, preliminary experiments indicated that the reaction is exceedingly sensitive to variations in the efficacy of the base-solvent system. Fourth, a wide variety of olefin structures are available and, by appropriate selection, olefins of widely varying isomerization capability are obtained easily. Finally, and most important, base-catalyzed olefin isomerization involves the activation of the very weak carbon-hydrogen bond. Accordingly, a broad study of the

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[1] For a comprehensive review see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

[2] A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

[3] H. Normant, *Russ. Chem. Rev.*, **39**, 457 (1970).

[4] S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Org. Chem.*, **33**, 221 (1968).

[5] S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Amer. Chem. Soc.*, **89**, 6897 (1967), and references cited therein.

[6] L. A. Yanovskaya and Kh. Shakhidayatov, *Russ. Chem. Rev.*, **39**, 859 (1970).

[7] H. J. Hubert and H. Reimlinger, *Synthesis*, **1**, 97 (1969).

[8] H. Kloosterziel and J. A. A. van Drunen, *Recl. Trav. Chim. Pays-Bas*, **89**, 37 (1970), and references cited therein.