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The Effect of Methyl Substitution on Ring Proton Chemical Shifts in Thiophene, Furan and Pyrrole

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The total effect of a single methyl substituent on ring proton shifts in thiophene, furan and pyrrole is found to be *ca.* 30 c.p.s., essentially the same as the total for both β -protons in ethylenic derivatives of the structure $\text{CH}_2=\text{CXCH}_3$. There is a small constitutive variation (*ca.* 10%) in the total effect, but on the whole the value appears to be characteristic of the long-range effect produced by methyl attached to unsaturated (sp^2) systems. The distribution of the effect around the ring varies with the heteroatom, and appears in general to parallel the order of aromaticity inferred for these compounds from some other criteria.

Introduction

The effect of methyl substitution upon each of the chemical shifts in a series of ethylenic derivatives of the structure $\text{C}_2\text{H}_3\text{X}$, with $\text{X} = \text{CH}_3, \text{Cl}, \text{Br}$ and CN , has previously been shown to be approximately constant.¹ The methyl substituent effects were determined initially by comparing the chemical shifts for propylene with that of ethylene, with the results: -18 c.p.s. for α , $+17$ c.p.s. for β (*trans* to CH_3) and $+13$ c.p.s. for β (*cis* to CH_3). From these methyl substituent effect values and the chemical shifts of each parent compound, $\text{C}_2\text{H}_3\text{X}$, it was possible to predict the values of the shifts in the methyl derivatives, $\text{C}_2\text{H}_2\text{XMe}$, to within a small deviation which was essentially constant for a given substituent X . This deviation was treated as a constitutive correction, the application of which led to predictions agreeing with experiment within about 1 c.p.s. in most cases.

In order to obtain a uniform and reliable basis for these comparisons, we used as far as possible data obtained from dilute solutions (*ca.* 5%) in tetramethylsilane (TMS) as solvent and internal reference. In the nitrile series the initial assignments necessitated the application of corrections for the diamagnetic anisotropy of the CN group,² but these corrections were not subsequently needed for comparisons within the series.

The downfield displacement of protons α to CH_3 has previously been ascribed to diamagnetic anisotropy of the methyl group,^{3,4} but recently it has been pointed out that the influence of the methyl group on all the protons in propylene is at least qualitatively consistent with the existence in this molecule of a suitably oriented permanent electric dipole.⁵ The effect of various substituents, including the methyl group, on the β -protons has also been shown to be linearly related to the group dipole moments of the substituents.⁶ These correlations do not, however, completely explain the effects of substituents upon the chemical shifts, since the latter will presumably depend upon the detailed nature of the electronic distribution which

gives rise to the electric moment. If, for example, the moment in propylene is considered to be the vector resultant of the various bond moments, whose values depend upon the hybridization of the carbon atoms and are unmodified by induction or mesomerism, the upfield displacement of the protons with methyl substitution is somewhat difficult to rationalize. Such a bond moment approach has recently been proposed by Petro⁷ and has been discussed by Lide,⁸ who has pointed out that the orientation of the moment in propylene, as determined by microwave spectroscopy, appears to favor a hyperconjugative origin for the moment but that other factors may be involved. The upfield displacement of the β -shifts in propylene is also consistent with hyperconjugation, or with an equivalent mechanism which places additional charge on the carbon atom relative to that in ethylene.

When two β -protons are present in an ethylenic compound it was previously found¹ that methyl substitution produced a total upfield displacement for the two protons of *ca.* 30 c.p.s., including the small constitutive correction (*ca.* 10% or less). In light of the foregoing discussion we have reasoned tentatively that this total is a measure of the charge transferred from the substituent methyl group to the ethylenic system by a long-range process, presumably hyperconjugation or an equivalent process. It is tempting to speculate further that replacement of the ethylene structure by a conjugated system should not greatly alter the total amount of charge transferred *via* the long-range process (as measured by the n.m.r. shifts) but would rather lead to its redistribution over the conjugated system.

Some encouragement for this conjecture was obtained by measuring the chemical shift of the slightly structured peak in toluene relative to that of benzene, using dilute solutions (*ca.* 5%) in TMS. This turned out to be approximately 6 c.p.s., or a total of 30 c.p.s. for the five aromatic protons. (In the absence of a detailed analysis, which cannot be carried out because of lack of resolved structure in the toluene spectrum, the value of 6 c.p.s. is to be considered only as an approximate average of the displacements of the five ring proton shifts.)

We have, accordingly, extended the previous investigation by studying the effect upon the ring proton shifts produced by a single methyl substituent at various positions in the heterocyclic compounds furan, thiophene and pyrrole. All of these

(1) G. S. Reddy and J. H. Goldstein, *J. Am. Chem. Soc.*, **83**, 2045 (1961).

(2) G. S. Reddy and J. H. Goldstein, *ibid.*, **83**, 1300 (1961).

(3) P. T. Narasimhan and M. T. Rogers, *J. Chem. Phys.*, **31**, 1303 (1959).

(4) J. Tillien, *Ann. Phys.*, **2**, (71), 631 (1957).

(5) A. A. Bothner-By and C. Koor Collin, *J. Am. Chem. Soc.*, **83**, 231 (1961).

(6) G. S. Reddy, C. E. Boozer and J. H. Goldstein, *J. Chem. Phys.*, **34**, 700 (1961).

(7) A. J. Petro, *J. Am. Chem. Soc.*, **80**, 4230 (1958).

(8) D. R. Lide, Jr., *J. Chem. Phys.*, **33**, 1879 (1960).

TABLE I

CHEMICAL SHIFTS FOR SOME METHYL SUBSTITUTED FURANS, PYRROLES AND THIOPHENES^a

Compound	ω_2	ω_3	ω_4	ω_5	$\omega \text{ Me}(2)$	$\omega \text{ Me}(3)$
Furan	-292.0	-250.0	-250.0	-292.0
2-Methylfuran	-232.5	-244.0	-285.0	-86.9
2,5-Dimethylfuran	-227.5	-227.5	-85.4
Thiophene	-286.0	-279.0	-279.0	-286.0
2-Methylthiophene	-265.0	-270.0	-275.5	-95.2
3-Methylthiophene	-268.5	-270.0	-281.0	-86.9
2,5-Dimethylthiophene	-255.5	-255.5	-92.1
Pyrrrole	-260.2	-246.0	-246.0	-260.2
2-Methylpyrrrole	-230.5	-239.0	-253.5

^a Expressed as c.p.s., at 40 mc./sec., referred to TMS as solvent and internal reference.

systems exhibit partial aromatic character^{9,10} and are accordingly well-suited for testing the hypothesis outlined above. In all, the n.m.r. spectra of nine compounds were studied here under conditions chosen to provide reliable data for the determination of substituent effects. In addition, some relevant published data for thiazole¹¹ have been cited to amplify the discussion.

For all three ring systems (furan, thiophene and pyrrole) the total observed chemical shift effect produced by one methyl substituent is, indeed, about 30 c.p.s., as had been conjectured. In addition, the detailed distribution of the methyl substituent effect around the rings is in generally good agreement with the usual picture of conjugation in these molecules that has been obtained by various other approaches.

Since there can be no protons α to C-methyl substituents in the systems studied here, the present study is necessarily limited to long-range substituent effects. However, it is believed that the α -effects previously observed in ethylenic systems have not yet been entirely clarified by any existing hypothesis, and will require additional investigation and consideration. Further discussion of this point is beyond the scope of the present paper.

Results

All the spectra studied here (furans, thiophenes and pyrroles) were obtained using a Varian Associates model 4300-B high-resolution NMR spectrometer operating at 40 Mc./sec. and equipped with a flux stabilizer. Calibrations were performed by the usual sideband technique using a Krohn-Hite model 440B oscillator. All of the peak measurements were the average of several calibrations, with mean deviations not in excess of about 0.2 c.p.s. Commercially available compounds were used without further purification, and TMS was used throughout as the solvent and internal reference. The furans and thiophenes were all studied at the same concentration, about 5% by volume; the pyrroles were studied in 6% by weight solutions. In addition, from analyses of the pyrrole spectrum at both 6% and 10% concentration in TMS, it was ascertained that neither proton varied by as much

as 1.5 c.p.s. in this concentration range. Since in the comparison between pyrrole and methylpyrrole, at the same concentration, some cancellation of even this small uncertainty is to be expected, the determination of the methyl substituent effect is in all probability not seriously affected by solution effects.

The chemical shifts were obtained by numerically fitting the observed spectra, to within 0.2 c.p.s. or better, or by a first-order treatment of the observed spectrum, whenever this method was applicable. The over-all reliability of the shifts is judged to be about 0.5 c.p.s. These values, designated as ω_1 , are listed in Table I. The effects of the methyl group on each ring proton shift were obtained by subtracting the corresponding values for the parent ring compound, and are summarized in Table II. The

TABLE II
CHANGES OF RING PROTON SHIFTS WITH METHYL SUBSTITUTION IN SOME HETEROCYCLIC SYSTEMS^a

Compound	Ring position				Sum
	2	3	4	5	
2-Methylfuran	..	17.5	6.0	7.0	30.5
2,5-Dimethylfuran	..	22.5	22.5
2-Methylthiophene	..	14.0	9.0	10.5	33.5
3-Methylthiophene	17.5	..	9.0	5.0	31.5
2,5-Dimethylthiophene	..	23.5	23.5
2-Methylpyrrole	..	15.5	7.0	6.7	29.2
2-Methylthiazole ^b	12.0	7.0	19.0
4-Methylthiazole ^b	7.0	19.0	26.0
2,4-Dimethylthiazole ^b	27.0	..

^a All values are in c.p.s. at 40 Mc./sec. and are relative to the corresponding proton values in the unsubstituted parent ring. ^b From ref. 11. Nitrogen is at position 3 in the ring.

substituent effects for the methylthiazoles, also given in Table II, were derived from published data for the pure liquids relative to an external reference,¹¹ and may include contributions from bulk susceptibility effects and solute-solute interactions. These data have been included primarily to provide some possible indications of the effects arising from the presence of a group such as =N— in the ring, and are to be considered only as tentative values.

The substituent effect values for furan and pyrrole shown in Table II are in good agreement with those we have calculated from data recently published by Abraham and Bernstein¹² for a num-

(12) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 905 (1961).

(9) See, for example: Adrien Albert, "Heterocyclic Chemistry," Oxford University Press, Inc., New York, N. Y., 1959.

(10) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 3d Edition, 1960, p. 303.

(11) A. Taurins and W. G. Schneider, *Can. J. Chem.*, **38**, 1237 (1960).

ber of furans and pyrroles studied in 10% acetone solution. The methyl effects at the various positions, as calculated from the two sets of data, differ by at most 1.5 c.p.s. and the total methyl effects agree within about 1.0 c.p.s. Considering the differences in solvent and concentration, this agreement further reinforces the previous judgment that uncertainties due to solution effects are not serious.

Discussion

From the values listed in Table II it is seen that the total methyl substituent effects in 2-methylfuran, 2-methylthiophene, 3-methylthiophene and 2-methylpyrrole are 30.5, 33.5, 31.5, and 29.2 c.p.s., respectively. In the disubstituent compounds the effects on the remaining protons are additive to within *ca.* 1 c.p.s. Thus, the total effect of methyl substitution in these heterocyclic compounds appears to be essentially the same as that previously observed in ethylene and in the one aromatic case cited above (toluene). This does not, of course, establish that the total effect is identical for ethylene and for furan, thiophene and pyrrole, since the effect of the substituent on the heteroatom is not known. However, in ethylenic derivatives of the form $H_2C=C(CH_3)X$ with $X = Cl, Br, CN$ and CH_3 , the methyl substituent effect does not vary by more than ± 3 c.p.s., or $\pm 10\%$. It would appear, therefore, that deviations greater than this—if they occur at all—should be due to the additional factor of conjugation of O or S in the ring system.

The difference in the methyl effect for the two methylthiophenes is small (*ca.* 2 c.p.s.) but probably real. It is reasonable that 2-methyl substitution should produce a greater effect than 3-substitution, since conjugation of the methyl group is less effective at the latter (cross-conjugated) position. The difference between 2-methylthiophene and 2-methylfuran (*ca.* 3 c.p.s.) is comparable to the differences observed in the various α -substituted 2-propenes. This is, perhaps, a hint that the effect of the heteroatom may not vary widely between the two classes of compounds.

It is interesting to compare the distribution of the methyl effect in the monomethyl derivatives. In 2-methylthiophene the effect is much more uniform around the ring than is the case in 2-methylfuran, which is in accord with the common observation that thiophene is the more "aromatic" of the two compounds. However, even in 2-methylthiophene the effect is more pronounced at positions 3 and 5. In 3-methylthiophene, on the other hand, the effect is much less uniform, with the 2-position being much more influenced than the 5-position. From these observations it would seem that the effect of a 2-methyl group in thiophene is at least partially transmitted through the S atom, and that the corresponding transmission in 2-methylfuran is perceptibly less effective.

The relative ease with which substituents at positions 2 and 5 influence one another in thiophene is also indicated by the behavior of the methyl shifts. In 2,5-dimethylthiophene the value of ω (CH_3) is 3 c.p.s. higher than that in 2-methylthiophene, while the corresponding effect in the methylfurans is only half as large. Again, the magnitudes involved are

not large, but they are believed to be well outside the limits of uncertainty and their significance increases when it is considered that these are the effects observed for protons one bond farther from the ring than those previously at the 2-positions.

In pyrrole the total methyl effect is 29.2 c.p.s. The effects at the individual positions resemble those in furan rather than in thiophene. Insofar as the present comparison is reliable, pyrrole can be said to present a situation intermediate between the other two molecules. Rather similar comparisons have been derived from other properties of these heterocyclic compounds.^{9,10}

As mentioned previously, the methylthiazole data were taken under conditions that make reliable comparisons with the other heterocyclics difficult. Some slight indication that environmental effects in the pure thiazole may be somewhat similar is provided by the fact that the total effect in 2,4-dimethylthiazole (27 c.p.s.) is essentially the sum of the individual methyl effects predicted from the two monomethyl derivatives.

Some tentative observations will, therefore, be offered concerning the methyl effect in these compounds. In both monomethylthiazoles the total effect is appreciably less than 30 c.p.s. It is not unreasonable to suppose that the deficiency is due to presence of an additional heteroatom in the ring, the electron attracting $=N-$ linkage, which is expected to participate quite differently from $-S-$, $-O-$ and $-NH-$ in the previously considered compounds. Pullman and Metzger¹³ have reported results of molecular orbital calculations for thiazole and the three methylthiazoles. The changes in charge density with methyl substitution at the various ring positions relative to thiazole, as calculated from their data, are in reasonable agreement with the effects on the corresponding chemical shifts. Thus, in 2-methylthiazole, the shift changes of 12 and 7 c.p.s. correspond to calculated increases in charge of 0.015 and 0.006, while in 4-methylthiazole the shift effect of 19 and 7 c.p.s. correspond to charge increases of 0.029 and 0.014. Moreover, in the former derivative, which exhibits the greater deficiency of total methyl effect, there is a considerably greater total charge increase at the two heteroatoms—0.040 compared with 0.009. Further studies of the methylthiazoles, under appropriate solvent and reference conditions, should be undertaken to test the preliminary observations offered here.

In summary, the n.m.r. data for the series of heterocyclic compounds considered here support the idea that the changes of ring proton shifts produced by a methyl substituent total *ca.* 30 c.p.s. for thiophene, furan and pyrrole. Differences of only about 10% over-all in the total are observed for the three heteroatoms. The total effect and the constitutive variations are quite similar to those observed in substituted ethylenes of the form $H_2C=CXCH_3$. Charge transferred to the heteroatom is, of course, not observable in proton spectra, but the consistency of the effect and its similarity to that in the ethylene series leave open the possibility, at least, that this contribution is relatively small.

(13) A. Pullman and J. Metzger, *Bull. soc. chim.*, **15**, 1021 (1948).

Insofar as the present study is concerned the question of the mechanism of charge transfer (*e.g.*, hyperconjugation) does not enter. However, the transfer is long-range, *i.e.*, to atoms more than one bond removed from the substituent carbon. The distribution of the methyl effect at the various ring positions permits a discussion of conjugation that is in many respects more detailed and possibly less circuitous than those based on composite molecular properties.

Possible effects due to ring currents in the heterocyclic compounds studied here have not been considered in detail. It seems reasonable to suppose that these have been largely cancelled by the use of

shift differences, provided that any existing ring current will not be greatly modified by methyl substitution.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY, BALTIMORE 18, MD.]

The Structure of Dehydrodithizone: A Novel Synthesis of Tetrazolium Salts¹

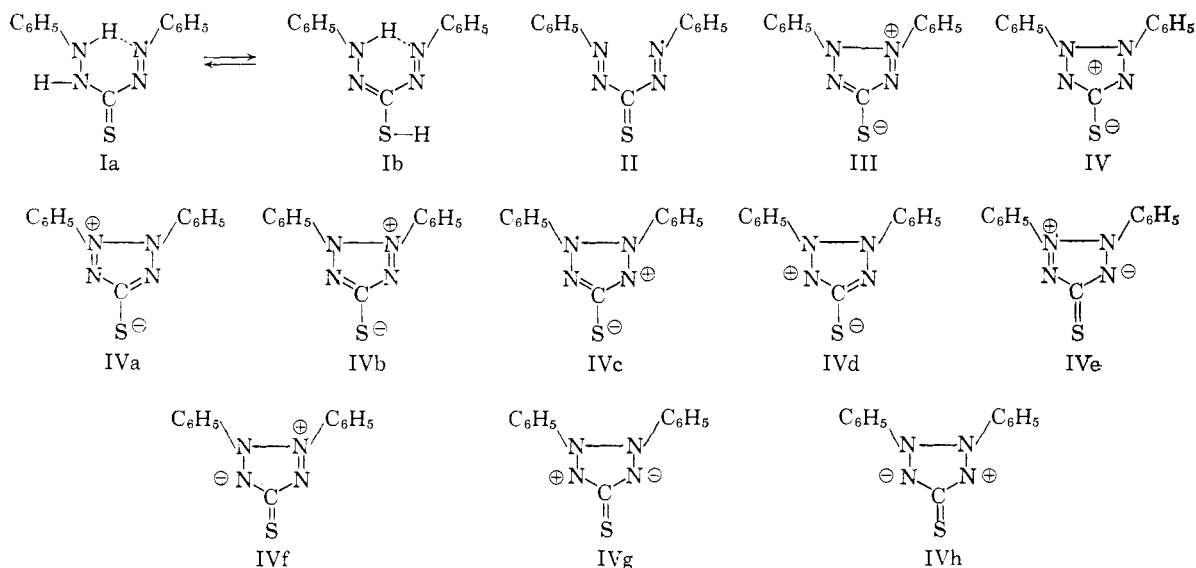
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A nucleophilic displacement of halogens from alkyl halides by dehydrodithizone with concomitant tetrazolium salt formation has been demonstrated. These displacement reactions represent a novel synthesis of a new class of tetrazolium salts, and they also provide chemical evidence in support of the cyclic "meso-ionic" structure proposed for dehydrodithizone in this paper. In addition, the *pK'* values for two of the compounds described have been determined, and these values offer additional support for the cyclic "meso-ionic" structure of dehydrodithizone.

Dithizone, 1,5-diphenylthiocarbazon (Ia,b), is readily oxidized to an orange crystalline dehydroform^{3,4} for which two structures have been proposed. Probably the most commonly accepted structure for dehydrodithizone is the 1,5-diphenyl-

was based predominantly upon the physical properties of the compound. More recently the tetrazolium betaine structure has received support from the ultraviolet spectroscopic studies of Grammaticakis.⁶ Further support for a structure similar



thiocarbonyl structure II which was first proposed by E. Fischer.³ The tetrazolium betaine structure III was later proposed by Bamberger and co-workers.⁵ Their proposal of a betaine structure

to III based on the chemical properties of dehydrodithizone will be presented in this paper. Since, in many respects, dehydrodithizone resembles the sydnone, and the charges may be considered to be delocalized due to contributions from IV(a-h) to the resonance hybrid, it is suggested that IV better represents its structure than III.

(1) Taken in part from the doctoral dissertation of James W. Ogilvie, The Johns Hopkins University, 1955.

(2) (a) Procter and Gamble Fellow, 1953; du Pont Fellow, 1954. (b) Department of Physiological Chemistry, The Johns Hopkins University School of Medicine, Baltimore 5, Md.

(3) E. Fischer and A. Besthorn, *Ann.*, **212**, 316 (1882).

(4) H. Fischer, *Angew. Chem.*, **50**, 919 (1937).

(5) E. Bamberger, R. Padova and E. Ormerod, *Ann.*, **446**, 280 (1926).

(6) P. Grammaticakis, *Compt. rend.*, **234**, 528 (1952).