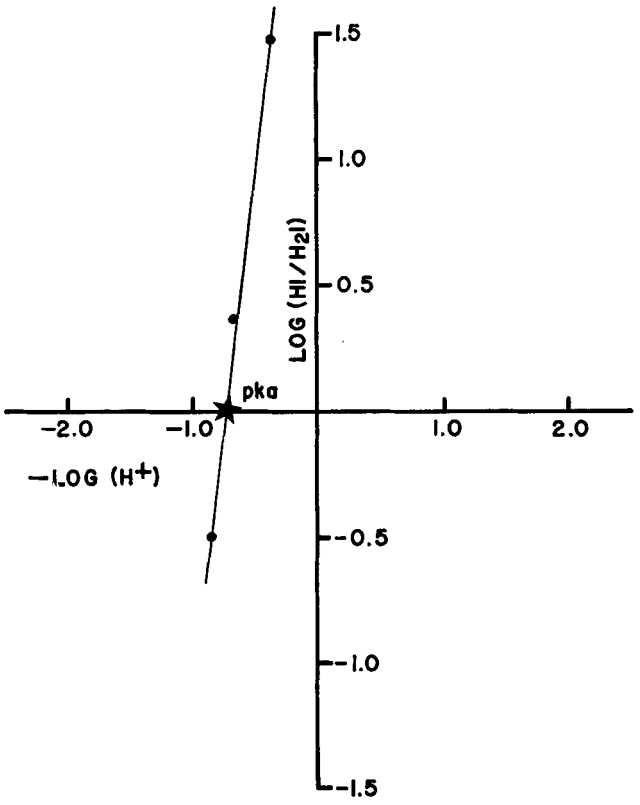

Figure 4—*Determination of the first pKa value of BCP using log* (HI^-/H_2I) *(from Fig. 2)* versus $-\log(H^+)$ *plot.*

Phenol Red—The first pKa value of this dye was estimated to be +1.03 (Table II). The Hammett acidity scale was not used due to reasons previously explained.

It was not possible to take into account the activity coefficients at these higher concentrations of hydrochloric acid. This will, no doubt, cause some error in the determination of the first pKa values of these dyes. Wherever possible, the Hammett acidity scale was also used as explained previously.

Analytical Applications—The information provided is very useful for the determination of the true partition coefficients as reported by Gupta and Cadwallader (10). This information could also be useful to correlate the structural formulas of the dyes.

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Dipole Moment and Structure of Thiophene Derivatives and Benzene Analogs

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Abstract □ The dipole moments of 2-halothiophene, 2,2′-bithiophene, 2-thiophenecarboxylic acid derivatives, and the corresponding benzene analogs have been measured in benzene and in dioxane. Evidence is presented that the conformation in 2-thiophenecarboxylic acid derivatives has the thiophene dipole (which has the sulfur negative) opposed to the resultant dipole of the carboxyl or ester group. The conformation in 2,2′-bisthiophene is shown to be *cis*. In dioxane, there is more resonance interaction between the thiophene ring and the functional groups than between the benzene ring and these groups. The chemical shift and the coupling constant of the NMR spectra of the 2-halothiophenes and 5,5′-dihalo-2,2′-bithiophenes have been assigned.

Keyphrases □ Thiophene derivatives, benzene analogs—dipole moment, structure determination □ NMR spectroscopy—structure

The dipole moment has been shown to be a useful electronic parameter in some structure–activity correlation studies (1), *e.g.*, the insecticidal activity of chlorphenothane (DDT) isomers (2), the cholinesterase inhibitory activity of *N*-alkylsubstituted amides (3), the respiratory stimulation activity of cyclic ureas and thioureas (4), and the inhibition of viral neuraminidase by dihydroisoquinoline derivatives (5).

The usefulness of dipole moments in structure–activity correlation is more restricted than other physico-

Table I—Dipole Moment and Melting Point or Boiling Point of Some Thiophene and Benzene Derivatives

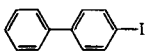
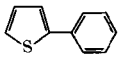
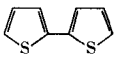
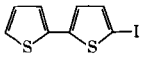
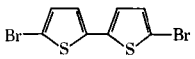
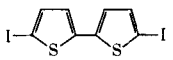
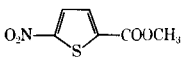
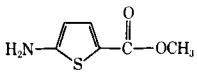
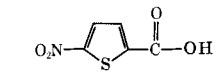
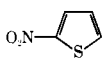
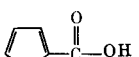
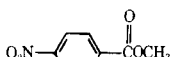
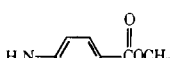
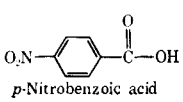
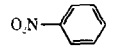
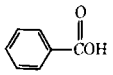
Compound	Dipole Moment, μ (Debye, 25°) Benzene	Dioxane	$\mu_D - \mu_B$	M.p. (corrected)	B.p./(mm. Hg)
 Thiophene	0.52[a]				
 2-Chlorothiophene	1.48 ± 0.01	1.60 ± 0.01	0.12		30°/(5)
 2-Bromothiophene	1.35 ± 0.01	1.41 ± 0.03	0.06		31–32°/(3)
 2-Iodothiophene	1.20 ± 0.01	0.83 ± 0.03	−0.37		57–58°/(3)
 4-Iodobiphenyl	1.55 ± 0.04	0.99 ± 0.02	−0.56	112–114° (113–114°)[b]	
 2-Phenylthiophene	1.04 ± 0.01	—[c]	—	33–35°	
 2,2′-Bithiophene	0.96 ± 0.02	1.15 ± 0.02	0.19	32–33° (32–33°)[b]	
 5-Iodo-2,2′-bithiophene	1.28 ± 0.04	1.79 ± 0.04	0.51		150°/(3.5)
 5,5′-Dibromo-2,2′-bithiophene	1.73 ± 0.09	—[c]	—	144°	
 5,5′-Diiodo-2,2′-bithiophene	0.85 ± 0.04	1.87 ± 0.08	1.02	167–168°	
 Methyl 5-nitro-2-thiophenecarboxylate	3.74 ± 0.01	3.96 ± 0.01	0.22	75–76° (75°)[d]	
 Methyl 5-amino-2-thiophenecarboxylate	3.35 ± 0.01	3.94 ± 0.01	0.58	86–89° (81°)[d]	
 5-Nitro-2-thiophenecarboxylic acid	3.18 ± 0.02	4.43 ± 0.01	1.25	154–157° (157°)[d]	
 2-Nitrothiophene	4.27[a]				
 2-Thiophenecarboxylic acid	1.30[a]				
 Methyl *p*-nitrobenzoate	3.48 ± 0.02	3.74 ± 0.01	0.26	95–96° (96°)[b]	
 Methyl *p*-aminobenzoate	3.41 ± 0.01	3.70 ± 0.01	0.29	112° (114°)[b]	
 *p*-Nitrobenzoic acid	3.42 ± 0.12 (3.5)[a]	4.13 ± 0.03	0.71	240–242° (242°)[b]	

Table I—(*Continued*)

Compound	Dipole Moment, μ (Debye, 25°) Benzene	Dioxane	$\mu_D - \mu_B$	M.p. (corrected)	B.p./(mm. Hg)
 Nitrobenzene	4.01[a]				
 Benzoic acid	1.80[a]				

[a] From A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, 1963. [b] From "Handbook of Chemistry and Physics," 45th ed., R. C. Weast, Ed., The Chemical Rubber Co., Cleveland, Ohio. [c] No measurement because of the limited amount of sample available. [d] From P. Fournari and J. P. Chane, *Bull. Soc. Chim. France*, **1963**, 479.

chemical constants such as Hammett's σ constant or Taft's σ^* constant (6), because the resultant moment of a molecule has to be calculated by vector addition, not by simple addition.

That substitution of a thiophene ring for the benzene ring produces compounds with similar physical and biological properties has long been recognized (7, 8). Based on the concept of "bioisosterism," many thiophene analogs of biologically active compounds containing the benzene ring have been investigated (8).

In considering some of the differences between the two sets of compounds, a knowledge of the conformation of the thiophene compounds and how thiophene transmits resonance effects compared with benzene appeared desirable. It seemed likely that a study of the dipole moments of suitable compounds could give this information.

EXPERIMENTAL

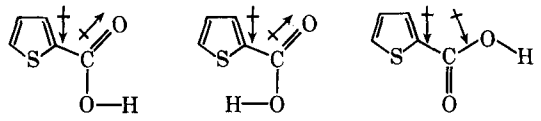
The simple halothiophenes[1] were further purified by vacuum distillation. The other thiophene and benzene derivatives were used as provided.[2] The melting points and the boiling points are given in Table I.

All dipole moments were measured at 25° using a WTW-Dipole Meter model DM01 and a DFL-2 cell. The method of Halverstadt and Kumler (9), programmed for an IBM 1401 by Simpson (10) and converted for an IBM 360/40 computer by the authors, was used to calculate the dipole moments. The solute molar electronic polarization (P_E) was obtained from refractive index measurements. The dipole moments are assembled in Table I.

The NMR spectra of the five compounds examined indicated the samples were of high purity. The NMR spectra were measured on a Varian A-60A spectrometer. The position of the peaks are with reference to that of trimethylsilane (TMS). A complete analysis of the second-order splitting of the ABC pattern for the 2-halothiophenes and the first-order splitting of the AB pattern for the 5,5′-dihalo-2,2′-bithiophenes are summarized in Table II.

RESULTS AND DISCUSSION

The analysis of the dipole moment data is dependent on whether the dipole moment in thiophene has the negative end toward sulfur  or toward the carbons  . The latter might result if there were appreciable contributions from forms with a separation of charges such as  . The literature contains conflicting opinions in regard to the direction of this dipole (8, 11). A consideration of the dipole moments of 2- and 3-methylthiophenes and 2,5-dichlorothiophenes and 2,5-dibromothiophenes (10, 12) demonstrates, however, that the negative end of the dipole is toward sulfur. This, coupled with the evidence that 2-thiophenecarboxylic acid is essentially flat (13) and that its dipole moment is considerably less than that of benzoic acid, establishes the conformation of 2-thiophene carboxylic acid as being I or II or a combination of the two but not III:



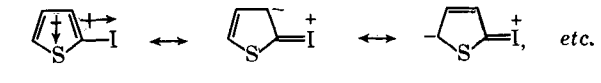
I II III

Only in I or II is the dipole in the thiophene ring in a position to reduce the resultant moment of the carboxyl group. There are conflicting reports on the conformation of 2,2′-bithiophene (12, 14). Thiophene itself has a dipole moment of 0.52 *D*. The dipole moment of 2,2′-bithiophene (0.96 *D* in benzene, 1.15 *D* in dioxane) unequivocally indicates that the two thiophene rings are in a *cis*-conformation rather than in a *trans*-conformation, because the latter conformer should have a moment much lower than 0.52 *D*:

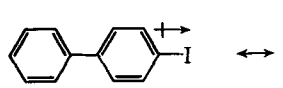
cis *trans*

IV V

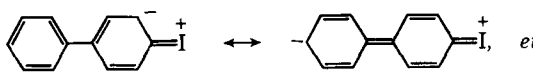
Generally speaking, dipole moments measured in dioxane are higher than in benzene (positive $\mu_D - \mu_B$), because the local dipoles of dioxane tend to augment the dipole moment of the solute molecules. However, for 2-iodothiophene and 4-iodobiphenyl, negative $\mu_D - \mu_B$ values were obtained. This may be due to the lower electronegativity of iodine as compared with that of bromine or chlorine and a greater contribution of the resonance structures in dioxane, opposing the dipole of the C—I bond:



VI*a* VI*b* VI*c*



VII*a*



VII*b* VII*c*

The resonance structure like VII*c* is impossible for 5,5′-dihalo-2,2′-

[1] Eastman Organic Chemicals.

[2] By Dr. J. C. Craig and Dr. A. R. Naik of the University of California, School of Pharmacy.

Table II—NMR Data of 2-Halothiophenes and 5,5′-Dihalo-2,2′-bithiophenes (Measured in $CDCl_3$)

	Chemical Shift (δ) p.p.m. Relative to TMS				Coupling Constant, c.p.s.		
X	H_4	H_3	H_5	No. of Lines	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$
Cl	6.88	6.96	7.07	8	2.5	1.3	5.0
Br	6.84	7.09	7.21	12	4.0	1.5	5.5
I	6.81	7.28	7.42	11	4.0	1.0	5.8

X	$H_3=H_3'$	$H_4=H_4'$		$J_{3,4} = J_{3',4'}$
Br	6.76	6.88	4	4.0
I	6.73	7.10	4	3.7

bithiophene; therefore, positive $\mu_D - \mu_B$ values would be expected. The experimental data fulfill this expectation, since a $\mu_D - \mu_B$ of 1.02 *D* is obtained for 5,5′-diiodo-2,2′-bithiophene.

For 5-iodo-2,2′-bithiophene, 0.51 *D* is obtained for $\mu_D - \mu_B$; this may be due to the noncoplanarity of the bithiophene system and the decreased contribution from dipolar forms like VIIc. It has been shown by electron-diffraction study that in biphenyl two benzene rings form an angle of 45° (15).

For the 2-thiophenecarboxylic acid derivatives, the dipole moments measured in dioxane are higher than those of the corresponding benzene ring compounds. This may be attributed to the greater resonance-transmitting character of the thiophene ring, since dioxane tends to stabilize the dipolar forms. In benzene, no such general trend is observed because benzene does not have local dipoles. For the purpose of structure–activity correlation studies, the dipole moments obtained from dioxane may be better than the moments obtained from benzene, since water in the biological system is a highly polar solvent.

For the NMR data in Table II, the assignment of the coupling constant of 2-halothiophenes is simplified by the study of 5,5′-dihalo-2,2′-bithiophenes, since in the latter case only one coupling constant exists ($J_{3,4}$) which is about 4.0 c.p.s. in both cases where the halogen is Br or I. For 2-chlorothiophene, $J_{3,4}$ is somewhat lower (2.5 c.p.s.), probably due to the higher electronegativity of the chlorine atom and lower electron density in the C_3—C_4 bond. The order of the coupling constants varies as $J_{4,5} > J_{3,4} > J_{3,5}$. This is explainable since there is more double-bond character in the C_4—C_5 bond than in the C_3—C_4 bond. $J_{3,5}$ is the smallest because there are four bonds between H_3 and H_5, while only three bonds are between H_3 and H_4.

For the 2-halothiophenes, the chemical shift of the proton at the 4-position appears to be determined by the inductive effect of the halogen, *i.e.*, the higher the electronegativity of the halogen, the lower the field for the resonance of the proton. This is as expected, since the lower the electron density, the less will be the shielding effect due to the diamagnetism of the circulating electrons (16). On the other hand, for the chemical shifts of the protons at the 3- and 5-positions, an opposite order was obtained. Namely, H_3 and H_5 of 2-iodothiophene (least electronegativity of I) appear at a lower field than those of 2-bromothiophene and 2-chlorothiophene. This is probably due to the contribution from the paramagnetic effect of the C—X bond, since this effect would be the greatest for iodine (17). Free halide ion, having a spherically symmetrical charge distribution, will be magnetically isotropic. The C—I bond has less ionic character than the C—Cl bond, and the magnetic anisotropy of the former would be greater than the latter.

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