

Chemistry of Thienopyridines. XX.
The Relation of Dipole Moment to Molecular Structure (1)

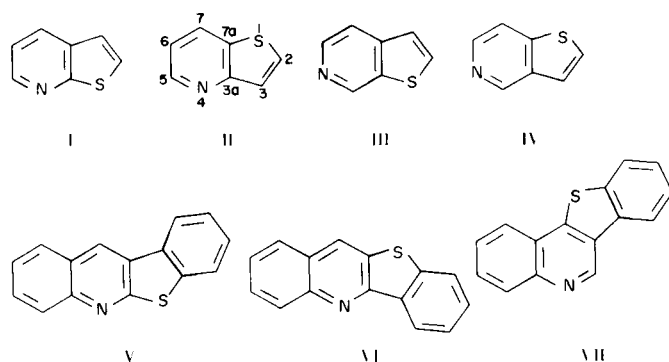
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Received February 10, 1975

Dipole moments were measured for three bicyclic thienopyridines and three tetracyclic dibenzothienopyridines in benzene solution at 25°. Results agreed closely with predicted values based on vector addition of dipole moments for reference constituent compounds.

In continuation of our investigations on the chemistry of thienopyridines, particularly in regard to interring effects, we determined the dipole moments, μ , of six compounds, *viz.* the bicyclic substances I-III and the tetracyclic ones V-VII, measured in benzene solution at 25°. Experi-



mental results are presented in Table I, where they are compared with data predicted from vector addition of dipole moments for molecular constituents.

Examination of Table I shows that, with the possible exception of III, predictions by our method fall within ± 0.13 D units of the measured values. In the case of III, our measured value is 0.24 D greater than that reported by Gronowitz and Sandberg (3). It is not clear why this difference occurs (4).

Reference compounds used in making our predictions of μ are thiophene (T, 0.53 D), benzo[*b*]thiophene (BT, 0.62 D), and dibenzo[*b,d*]thiophene (DBT, 0.83 D) (6) for sulfur heterocycles, plus pyridine (P, 2.21 D), quinoline (Q, 2.20 D), isoquinoline (IQ, 2.54 D), acridine (A, 2.09 D), and phenanthridine (PN, 2.39 D) (7) for nitrogen heterocycles (8). Although a number of erroneous interpretations occur in the chemical literature, it is now firmly established (9-11) that the heteroatom resides at the negative end of the dipole moment vector in thiophene. From

considerations of symmetry in the molecule this vector will coincide with the C_{2v} axis. Analogous relationships apply for the dipole moment vectors in the molecules P (12), A (13), and DBT. The direction of the dipole moment vectors in the unsymmetrical molecules, BT, Q, IQ, and PN are uncertain. We have assumed that these directions can be calculated by vector summation (law of cosines) of two component portions (14). One component is ascribed to the heterocyclic ring *per se* and involves a vector (μ_1) which bisects the C-X-C angle (where X is thiophene S or pyridine N) and has its negative end on the heteroatom. Its magnitude is equal to that of T or P, respectively. The other vector component (μ_2) is ascribed to interaction between the heteroatom and the fused benzene ring. Its direction is taken to coincide with

TABLE I

Dipole Moments for Some Thienopyridines

Compound No.	Dipole Moment, μ (Debyes)		Reference Compounds Used in Predictions (c)
	Found (a)	Predicted (b)	
I	2.81	2.76	Q + BT
II	1.80	1.70	Q + BT
III	2.85	2.58	IQ + BT
IV	2.16 (d)	2.05	IQ + BT
V	2.90	2.84	A + DBT
VI	1.30	1.43	A + DBT
VII	1.89	1.83	PN + DBT

(a) Measured in dilute benzene solution at 25°. (b) Predicted by vector addition on model compounds (see text). (c) A = acridine; BT = benzo[*b*]thiophene; DBT = dibenzo[*b,d*]thiophene; IQ = isoquinoline; PN = phenanthridine; Q = quinoline. (d) Reported in ref. 3.

TABLE II
Expected Effects of Specific S-N Electronic Interactions on μ of Thienopyridines I-IV (a)

Compound No.	pK_a	Relative Extent of S \rightarrow N Electronic Interaction		Effect on μ -Component		Net Effect on μ
		-I	+R	for μ_S	for μ_N	
I (b)	2.75	very large	overwhelmed	decreases	increases	little or decreases
II (b)	4.35	medium	small	decreases	increases	decreases (c)
III (d)	5.58	medium	medium	little or increases	little or decreases	little
IV (d)	5.67 (e)	small	medium to large	increases	decreases	increases (c)

(a) Data on pK_a and postulated electronic interactions are given in ref. 5. (b) Compare pK_a value with that of quinoline (4.90). (c) Net effect apparently is very small. (d) Compare pK_a value with that of isoquinoline (5.40). (e) See ref. 3.

TABLE III
Raw Experimental Data for Solutions Used in Determination of Dipole Moments

Substrate No.	Solution Composition (in g.)		Refractive Index n_D^{25}	Density d^{25} (g./ml.)	Dielectric Constant ϵ
	Substrate	Benzene			
I	0	(neat)	1.4979	0.8731	2.274 (a)
	0.1016	8.6782	1.4992	0.8761	2.346
	0.1735	8.5711	1.5001	0.8790	2.403
	0.2919	8.5286	1.5017	0.8822	2.492
	0.5975	8.3063	1.5055	0.8925	2.730
II	0.0528	8.6241	1.4983	0.8747	2.292
	0.1005	8.6544	1.4990	0.8760	2.307
	0.1263	8.5970	1.4993	0.8775	2.315
	0.1897	8.5299	1.5002	0.8793	2.338
III	0.0759	8.6515	1.4990	0.8759	2.333
	0.1725	8.6212	1.5001	0.8787	2.408
	0.3017	8.5280	1.5019	0.8830	2.509
	0.5916	8.3235	1.5056	0.8916	2.741
V	0.0439	8.6704	1.4990	0.8746	2.299
	0.0908	8.6368	1.5000	0.8760	2.320
	0.1746	8.5894	1.5019	0.8788	2.364
	0.3686	8.4311	1.5063	0.8855	2.470
VI	0.0365	8.7045	1.4990	0.8751	2.280
	0.0876	8.6559	1.5001	0.8762	2.291
	0.2042	8.5559	1.5029	0.8808	2.307
VII	0.0490	8.6726	1.4989	0.8746	2.289
	0.0835	8.6082	1.4995	0.8758	2.298
	0.1529	8.5912	1.5010	0.8782	2.315

(a) Standard value from ref. 24.

the straight line which joins the centers of the benzene ring and the heteroatom and which, again, has its negative end on the heteroatom. The magnitude of μ_2 (0.11 D in BT, 0 in Q, and 0.35 D in IQ) is calculated as the vector difference between μ and μ_1 . From the law of sines one then calculates the angle which μ makes with μ_1 (7° in BT, 0° in Q, and 3° in IQ). The molecule PN is treated as benzo[c]quinoline ($\mu_2 = 0.41$ D, μ - μ_1 angle = 3°). An

important part of this procedure involves the preparation of a careful scale drawing of the planar molecule based on reasonable bond lengths and angles derived from data available for T, P, and naphthalene (16,17).

Armed with the preceding data and drawings (18), one now calculates a vector sum of the μ values for the two superimposed reference compounds which are assumed to constitute the thienopyridine molecule, e.g. Q plus BT \oplus I,

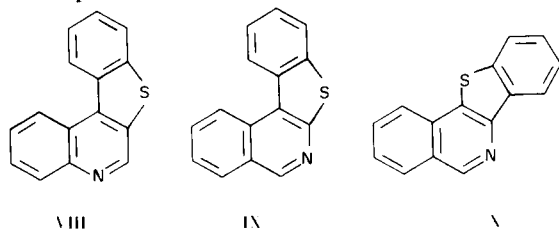
PN plus DBT \rightleftharpoons VII (see Table I). For a bicyclic compound I-IV the reference compounds are a benzopyridine and benzo[*b*]thiophene. For a tetracyclic compound V-VII the reference compounds are a dibenzopyridine and dibenzo[*b,d*]thiophene.

The close agreement of calculated and measured values of μ in I-VII indicates that additivity of dipole moment vectors prevails in these thienopyridines, as given in equation 1, where S and N refer to the corresponding hetero-

$$\mu = \mu_S + \mu_N$$

cyclic reference compounds. Equation 1 should hold only if any specific electronic interaction between the N and S atoms is small or compensatory (or both). The dipole moment of pyridine has been factored into three structural components, *viz.* the lone pair on the nitrogen atom (76%), a π -electron moment (15%), and a $C_{(4)}$ -H bond moment (9%) (19). Others have considered that P, Q, IQ, and A have equal σ contributions (1.74 D), but different π ones (0.41, 0.46, 0.42, and 0.55 D, respectively) (20). Their treatment ignores the effect on μ_σ of differences in basicities (maximum $\Delta pK_a = 0.73$) in the series (15). From experimental data Zahradnik *et al.* (21) resolved the dipole moments of T, BT, and DBT into opposing μ_σ ("almost constant") and μ_π vectors, where the magnitude of the σ contribution overwhelmed that of the π one (calculated to be 1.40, 1.65, and 1.13 D, respectively) in every case. In Table II we have attempted to assess the relative magnitudes of π and σ dipole moments in thienopyridines I-IV in terms of postulated resonance and inductive effects of the S atom on the lone pair (*i.e.* on the pK_a value) of the N atom. Based on close conformance of the compounds to equation 1 three relationships become apparent. For I and III (opposing μ_S and μ_N) specific electronic interactions between S and N are compensatory factors in the overall μ . For II and IV (reinforcing μ_S and μ_N) such interactions must be small (*i.e.* contribute little to the overall μ). The dipole moments of I-IV appear to be relatively insensitive to the large differences in basicities (maximum $\Delta pK_a = 2.92$) amongst them.

It might be noted that the dipole moments for I and II corroborate the original structural assignments made to these isomers (22). Amongst the tetracyclic compounds the order of $V > VII > VI$ in μ is consistent with the order of $I > IV > III$ in the bicyclic systems. Apparently tetracyclic compounds VIII-X are still unknown. Extension to



these compounds of our method of prediction gives μ values of 2.48, 3.15, and 1.76 D, respectively, based on phenanthridine and dibenzothiophene as reference compounds.

EXPERIMENTAL

Starting Materials.

Quinoline (Distillation Products, synthetic) was dried with potassium hydroxide and distilled, b.p. 108-109° (12 mm.), n_D^{25} 1.6248, d^{25} 1.095 g./ml. Thieno[2,3-*b*]pyridine (I), isomerically pure (22), was distilled, b.p. 49-50° (0.15 mm.), n_D^{25} 1.6422, d^{25} 1.2377 g./ml. Thieno[3,2-*c*]pyridine (II), isomerically pure (22), was purified further by VPC at 170° by means of a 9.5 cm. x 2.5-m. column packed with 10% DC 550 silicone oil on 60-80 mesh Chromosorb W. Thieno[2,3-*b*]pyridine (III) (23) was recrystallized from hexane, m.p. 57-59°. [1]Benzothieno[2,3-*b*]quinoline (V) (24) was sublimed at 90° (0.2 mm.), m.p. 140.5-142°. [1]Benzothieno[3,2-*b*]quinoline (VI) (24) was purified previously, m.p. 172-172.5°. [1]Benzothieno[3,2-*c*]quinoline (VII) (24) was purified as noted previously, m.p. 171.5-173°. Reagent grade benzene was fractionally distilled through a column of 11 theoretical plates, b.p. 78.8-78.9°, and stored over sodium wire, n_D^{25} 1.4979, d^{25} 0.8731 g./ml. Reagent grade chlorobenzene was fractionally distilled, b.p. 131-131.1°, n_D^{25} 1.5217.

Apparatus and Procedure.

Measurements of dielectric constant, ϵ , were made by means of a Sargent Model V high-frequency chemical oscillometer, plus attached Sargent oscillometric cell compensator for increasing sensitivity of the oscillometer readings and for making ϵ a linear function of them. The capacitance cell was contained in an insulated, glass-jacketed beaker, thermostated to $25 \pm 0.05^\circ$ by means of circulating water. The instrument was calibrated versus benzene ($\epsilon = 2.274$) and chlorobenzene ($\epsilon = 5.708$) (24) and used for measurements on three or four benzene solutions of each substrate, quinoline (used as a standard; μ found 2.20 D), I-III (concentration range 3.5×10^{-3} to 4×10^{-2} M), and V-VII (concentration range 1.3×10^{-3} to 1.5×10^{-2} M). Densities, d^{25} , and refractive indices, n_D^{25} , were obtained on these same solutions (see Table III). From the linear plots of d and ϵ versus the mole fraction of substrate were calculated values for the dipole moments, μ , according to the procedure of Hedestrand (25) (see Table I). Atomic polarization was taken as zero.

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(18) As an example, bond lengths in II were chosen as follows: 1,2--1.71; 2,3--1.37; 3,3a--1.42; 3a,4--1.35; 4,5--1.32; 5,6--1.41; 6,7--1.36; 7,7a--1.42; 1,7a--1.71; 3a,7a--1.39 (in Å). Angles used were: 1,2,3--110.5°; 2,3,3a--112.5°; 3,3a,7a--112.5°; 1,7a,3a--110°; 2,1,7a--94°; 3a,4,5--120°; 4,5,6--122.5°; 5,6,7--119.5°; 6,7,7a--118°; 3a,7a,7--119°; 4,3a,7a--121°.

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