

treatment of silica 63, however, resulted in an insignificant change in the particle-size distribution.

In Table VI and Fig. 4, the data gathered on selected samples are plotted in first-order fashion. The values for K_1 and K_2 were determined from the slopes of the lines, and the dissolution half-lives were calculated from the K_2 values. Where two first-order processes were evident, K_2 represented the slower process that occurred 60 min after dissolution had commenced (Fig. 4, prednisone-silica 63, solvent deposited). The data in Table VI clearly show that a significant change in dissolution half-life can be affected by solvent deposition on, or ball milling with, the amorphous silicon dioxides.

Fusion of Disubstituted Benzenes

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Abstract □ The entropy of fusion of 84 disubstituted benzenes was essentially constant and independent of the participation of the compounds in intramolecular or intermolecular hydrogen bonding. It was also independent of the shapes, sizes, and dipole moments of the rigid molecules studied. While the entropy of fusion was independent of these parameters, the melting point and the heat of fusion showed a direct dependence on molecular properties.

Keyphrases □ Entropy of fusion—disubstituted benzenes, independent of hydrogen bonding, shape, size, dipole moment of rigid molecules, structure-activity relationships □ Melting point—analysis, disubstituted benzenes, structure-activity relationships □ Benzenes, disubstituted—entropy of fusion, melting point, heat of fusion, structure-activity relationships

The ability to predict the melting point, entropy of fusion, and heat of fusion from chemical structure would make possible the design of compounds having a specified physical state or even a specified melting range. The aqueous solubility of many organic compounds can be predicted from their melting points, entropies of fusion, and octanol-water partition coefficients (1). Since partition coefficients can be predicted by several group contribution methods (2, 3), the estimation of fusion properties makes possible the estimation of aqueous solubility. This possibility has direct implications for drug delivery.

BACKGROUND

In 1908, Walden (4) proposed that entropy of fusion is constant for many classes of compounds. Most elements have entropies of fusion of 2-3 entropy units (eu = cal/deg/mole); salts and small organic molecules usually have entropies of fusion of 5-7 eu; most organic molecules have entropies around 13 eu.

The entropy of fusion rule for organic compounds was later refined to account for molecular geometry (5). If heat of fusion is plotted versus melting point, molecules fall into groups according to molecular shape. The data for the chain-like, disk-like, and spherical molecules fall into regions (6) characterized by:

$$\frac{\Delta H_f}{T_m - a} = K \quad (\text{Eq. 1})$$

where ΔH_f is the heat of fusion, T_m is the melting point, and the constants K and a are characteristic of the spatial form of the molecules. Since at the melting point:

$$\Delta S_f = \frac{\Delta H_f}{T_m} \quad (\text{Eq. 2})$$

REFERENCES

- (1) D. C. Monkhouse and J. L. Lach, *J. Pharm. Sci.*, **61**, 1430 (1972).
- (2) C. Ampolsuk, J. V. Mauro, A. A. Nyhuis, N. Shah, and C. I. Jarowski, *ibid.*, **63**, 117 (1974).
- (3) N. Shah, R. Pytelewski, H. Eisen, and C. I. Jarowski, *ibid.*, **63**, 339 (1974).
- (4) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 765.
- (5) H. Johansen and N. Møller, *J. Pharm. Sci.*, **67**, 134 (1978).

the entropy of fusion is dependent on the melting point for each class of compounds:

$$\Delta S_f = K - \frac{Ka}{T_m} \quad (\text{Eq. 3})$$

The entropy of fusion of flexible chain-like molecules increases as $R \ln 3$ for the addition of each CH_2 group to a chain because there are three potential minima for rotation about a carbon-carbon bond (7). This theory explains the apparent dependencies of ΔS_f on area and volume (8, 9).

The entropy of fusion of rigid molecules does not vary directly with surface area (10, 11) or with molecular volume. The entropy of fusion of rigid hydrocarbons varies according to their moments of inertia and symmetry. Strong dipoles and hydrogen bonding have also been assumed to lower the entropy of fusion by hindering rotation in the liquid.

The purposes of this report are to determine the effect of molecular shape, hydrogen bonding, and dipole moment on ΔS_f for rigid non-spherical organic molecules and to consider the effects of these parameters on heat of fusion and melting point.

EXPERIMENTAL

Data Set—The compounds studied were all disubstituted benzene molecules. They included all 84 combinations of the substituents CH_3 , Cl, Br, NO_2 , OH, NH_2 , and COOH in the *ortho*, *meta*, and *para* positions. The entropy of fusion was either determined experimentally or found in the literature for all compounds solid at room temperature as well as for many that are liquid. These compounds were chosen because of their similar size, shape and symmetry, but the substituents cover a wide range of dipole strengths and hydrogen bonding sites. Entropy of fusion differences due to symmetry and shape should have been minimal, while those due to dipole interactions and hydrogen bonding should have been readily apparent.

Determination of Entropy of Fusion—All entropies of fusion were calculated from the heats of fusion and melting points. These quantities were either obtained from the literature (12) or determined experimentally on a differential thermal analyzer¹ with a high-pressure differential scanning calorimeter cell. The literature values were obtained at atmospheric pressure. The experimental values were obtained at 500 psi to inhibit sublimation of the more volatile compounds. This pressure had little or no effect on the entropy of fusion of nonvolatile compounds and was assumed to have no effect on the entropy of fusion of the volatile crystals.

Reliable values for the entropy of fusion of three solids could not be determined experimentally. *p*-Aminophenol decomposed before melting, even under 1000 psi of nitrogen. Phthalic acid dehydrated to phthalic anhydride upon melting. Terephthalic acid sublimed, even under 1000 psi of nitrogen, as shown by a coating of compound around the inside of the calorimeter cell. This coating was insoluble in dilute sodium hydroxide and had the texture of a polymer, suggesting that some chemical

¹ Dupont model 900.

Table I—Input Data for Disubstituted Benzenes

Name	ΔS_f	MP	σ	α	DM	QM	HNO	IHB
<i>o</i> -CH ₃ -CH ₃	13.20	-25.00	2.00	14.40	0.62	0.27	0.00	0.00
<i>m</i> -CH ₃ -CH ₃	12.40	-47.40	2.00	14.40	0.40	0.27	0.00	0.00
<i>p</i> -CH ₃ -CH ₃	14.30	13.50	4.00	14.40	0.00	0.27	0.00	0.00
<i>o</i> -CH ₃ -Cl	—	-35.10	1.00	14.50	1.38	2.24	0.00	0.00
<i>m</i> -CH ₃ -Cl	—	-47.80	1.00	14.50	1.79	2.24	0.00	0.00
<i>p</i> -CH ₃ -Cl	12.90	7.50	2.00	14.50	1.96	2.24	0.00	0.00
<i>o</i> -CH ₃ -BR	—	-28.00	1.00	15.50	1.45	2.33	0.00	0.00
<i>m</i> -CH ₃ -BR	—	-40.00	1.00	15.50	1.77	2.33	0.00	0.00
<i>p</i> -CH ₃ -BR	12.00	28.50	2.00	15.50	1.99	2.33	0.00	0.00
<i>o</i> -CH ₃ -NO ₂	—	-9.60	1.00	14.80	3.72	9.75	0.00	0.00
<i>m</i> -CH ₃ -NO ₂	11.40	16.00	1.00	14.80	4.20	9.75	0.00	0.00
<i>p</i> -CH ₃ -NO ₂	12.60	54.50	2.00	14.80	4.47	9.75	0.00	0.00
<i>o</i> -CH ₃ -OH	12.40	30.90	1.00	13.20	1.45	2.24	2.00	0.00
<i>m</i> -CH ₃ -OH	9.00	11.50	1.00	13.20	1.61	2.24	2.00	0.00
<i>p</i> -CH ₃ -OH	9.60	34.80	2.00	13.20	1.58	2.24	2.00	0.00
<i>o</i> -CH ₃ -NH ₂	—	-23.70	1.00	13.90	1.59	2.33	2.00	0.00
<i>m</i> -CH ₃ -NH ₂	—	-30.40	1.00	13.90	1.45	2.33	2.00	0.00
<i>p</i> -CH ₃ -NH ₂	13.50	43.70	2.00	13.90	1.36	2.33	2.00	0.00
<i>o</i> -CH ₃ -COOH	12.80	107.00	1.00	15.00	1.70	9.75	2.00	0.00
<i>m</i> -CH ₃ -COOH	9.90	112.00	1.00	15.00	2.05	9.75	2.00	0.00
<i>p</i> -CH ₃ -COOH	12.40	182.00	2.00	15.00	2.05	9.75	2.00	0.00
<i>o</i> -COOH-COOH	—	231.00	2.00	15.60	2.45	19.22	4.00	2.00
<i>m</i> -COOH-COOH	18.90	348.00	2.00	15.60	2.27	19.22	4.00	0.00
<i>p</i> -COOH-COOH	—	440.00	4.00	15.60	0.00	19.22	4.00	0.00
<i>o</i> -BR-BR	11.00	7.10	2.00	16.60	2.05	5.99	0.00	0.00
<i>m</i> -BR-BR	12.10	-7.00	2.00	16.60	1.47	5.99	0.00	0.00
<i>p</i> -BR-BR	13.50	87.30	4.00	16.60	0.00	5.99	0.00	0.00
<i>o</i> -BR-NO ₂	16.30	43.00	1.00	15.90	4.19	20.72	0.00	0.00
<i>m</i> -BR-NO ₂	13.70	56.00	1.00	15.90	3.44	20.72	0.00	0.00
<i>p</i> -BR-NO ₂	10.00	127.00	2.00	15.90	2.66	20.72	0.00	0.00
<i>o</i> -BR-OH	9.70	5.60	1.00	14.30	1.37	5.10	2.00	0.00
<i>m</i> -BR-OH	—	33.00	1.00	14.30	2.15	5.10	2.00	0.00
<i>p</i> -BR-OH	10.50	66.40	2.00	14.30	2.27	5.10	2.00	0.00
<i>o</i> -BR-NH ₂	13.00	32.00	1.00	15.00	1.71	5.18	2.00	0.00
<i>m</i> -BR-NH ₂	—	18.50	1.00	15.00	2.66	5.18	2.00	0.00
<i>p</i> -BR-NH ₂	14.40	66.40	2.00	15.00	2.95	5.18	2.00	0.00
<i>o</i> -BR-COOH	13.20	150.00	1.00	16.10	2.73	12.60	2.00	0.00
<i>m</i> -BR-COOH	11.90	155.00	1.00	16.10	2.17	12.60	2.00	0.00
<i>p</i> -BR-COOH	15.50	254.00	2.00	16.10	2.10	12.60	2.00	0.00
<i>o</i> -OH-OH	14.40	105.00	2.00	12.00	2.62	4.20	4.00	0.00
<i>m</i> -OH-OH	13.30	111.00	2.00	12.00	2.09	4.20	4.00	0.00
<i>p</i> -OH-OH	14.60	174.00	4.00	12.00	1.40	4.20	4.00	0.00
<i>o</i> -OH-NH ₂	12.80	174.00	1.00	12.70	1.85	4.29	6.00	0.00
<i>m</i> -OH-NH ₂	11.20	123.00	1.00	12.70	1.90	4.29	6.00	0.00
<i>p</i> -OH-NH ₂	—	187.00	2.00	12.70	1.45	4.29	6.00	0.00
<i>o</i> -OH-COOH	10.80	159.00	1.00	13.80	2.65	11.71	4.00	1.00
<i>m</i> -OH-COOH	14.70	202.00	1.00	13.80	2.39	11.71	4.00	0.00
<i>p</i> -OH-COOH	12.20	215.00	2.00	13.80	2.76	11.71	4.00	0.00
<i>o</i> -Cl-Cl	12.10	-17.00	2.00	14.60	2.20	5.78	0.00	0.00
<i>m</i> -Cl-Cl	12.30	-24.70	2.00	14.60	1.35	5.78	0.00	0.00
<i>p</i> -Cl-Cl	13.40	53.10	4.00	14.60	0.00	5.78	0.00	0.00
<i>o</i> -Cl-BR	—	-12.30	1.00	15.60	2.20	5.88	0.00	0.00
<i>m</i> -Cl-BR	12.20	-21.50	1.00	15.60	1.52	5.88	0.00	0.00
<i>p</i> -Cl-BR	13.30	68.00	2.00	15.60	0.00	5.88	0.00	0.00
<i>o</i> -Cl-NO ₂	13.70	34.00	1.00	14.90	4.30	20.61	0.00	0.00
<i>m</i> -Cl-NO ₂	16.10	46.00	1.00	14.90	3.30	20.61	0.00	0.00
<i>p</i> -Cl-NO ₂	11.70	83.60	2.00	14.90	2.59	20.61	0.00	0.00
<i>o</i> -Cl-OH	9.10	9.00	1.00	13.30	1.31	4.99	2.00	0.00
<i>m</i> -Cl-OH	9.20	33.00	1.00	13.30	2.15	4.99	2.00	0.00
<i>p</i> -Cl-OH	11.10	43.50	2.00	13.30	2.25	4.99	2.00	0.00
<i>o</i> -Cl-NH ₂	—	-14.00	1.00	14.00	1.79	5.18	2.00	0.00
<i>m</i> -Cl-NH ₂	—	-10.30	1.00	14.00	2.70	5.18	2.00	0.00
<i>p</i> -Cl-NH ₂	13.80	72.50	2.00	14.00	2.99	5.18	2.00	0.00
<i>o</i> -Cl-COOH	14.90	142.00	1.00	15.10	2.50	12.60	2.00	0.00
<i>m</i> -Cl-COOH	13.30	158.00	1.00	15.10	2.22	12.60	2.00	0.00
<i>p</i> -Cl-COOH	15.00	243.00	2.00	15.10	2.02	12.60	2.00	0.00
<i>o</i> -NH ₂ -NH ₂	12.00	102.00	2.00	13.40	1.45	4.38	4.00	0.00
<i>m</i> -NH ₂ -NH ₂	11.50	101.00	2.00	13.40	1.79	4.38	4.00	0.00
<i>p</i> -NH ₂ -NH ₂	10.40	140.00	4.00	13.40	1.52	4.38	4.00	0.00
<i>o</i> -NH ₂ -COOH	11.70	147.00	1.00	14.50	1.52	11.80	6.00	1.00
<i>m</i> -NH ₂ -COOH	11.60	174.00	1.00	14.50	2.73	11.80	6.00	0.00
<i>p</i> -NH ₂ -COOH	10.90	189.00	2.00	14.50	3.39	11.80	6.00	0.00
<i>o</i> -NO ₂ -NO ₂	14.00	118.50	2.00	15.20	6.04	35.45	0.00	0.00
<i>m</i> -NO ₂ -NO ₂	12.50	90.20	2.00	15.20	3.83	35.45	0.00	0.00
<i>p</i> -NO ₂ -NO ₂	15.00	174.00	4.00	15.20	0.58	35.45	0.00	0.00
<i>o</i> -NO ₂ -OH	12.50	45.50	1.00	13.60	3.15	19.83	2.00	1.00
<i>m</i> -NO ₂ -OH	13.80	97.00	1.00	13.60	3.91	19.83	2.00	0.00
<i>p</i> -NO ₂ -OH	13.00	115.00	2.00	13.60	5.05	19.83	2.00	0.00
<i>o</i> -NO ₂ -NH ₂	11.20	71.50	1.00	14.30	4.28	19.91	4.00	1.00
<i>m</i> -NO ₂ -NH ₂	14.70	114.00	1.00	14.30	4.85	19.91	4.00	0.00
<i>p</i> -NO ₂ -NH ₂	12.00	149.00	2.00	14.30	6.32	19.91	4.00	0.00
<i>o</i> -NO ₂ -COOH	15.90	147.00	1.00	15.40	3.82	27.33	2.00	2.00
<i>m</i> -NO ₂ -COOH	11.30	141.00	1.00	15.40	3.50	27.33	2.00	0.00
<i>p</i> -NO ₂ -COOH	17.20	242.00	2.00	15.40	3.50	27.33	2.00	0.00

Table II—Results of Regression Analyses

Dependent Variable	r	Independent Variable Estimated Coefficient (T Value)							
		σ	α	QM	HNO	IHB	MP	DM	Intercept
ΔS_f : 1.83	0.179	0.49 (1.64)	0.31 (1.17)	0.08 (2.03)	0.09 (0.58)	-0.09 (-0.12)		-0.01 (-0.04)	6.31 (1.51)
MP: 43.2	0.796	29.7 (4.60)	28.7 (4.80)	5.40 (6.44)	41.8 (12.90)	-28.5 (-2.02)		-10.2 (-1.87)	-492 (-5.30)
MP: 44.6	0.778	36.9 (6.44)	30.2 (5.06)	4.07 (6.58)	40.4 (12.54)				-535 (-6.01)
ΔH_f : 1169	0.476	540 (3.13)	491 (2.94)	75 (4.36)	526 (5.50)				-5231 (-266)
ΔH_f : 672	0.829	-27.6 (-0.25)	-79.7 (-0.74)	-2.01 (-0.17)	-268 (-3.02)		21.4		4474 (2.65)
ΔH_f : 735	0.783						11.4 17.7 (15.5)		3065 (21.9)

change (possibly to a linear anhydride) occurred as well. These data were excluded from the analysis.

Variables—One purpose of this study was to determine whether the thermodynamic properties of melting point, MP, heat of fusion, ΔH_f , and entropy of fusion, ΔS_f , are dependent on other, easily predicted properties. Molecular properties rather than bulk properties were chosen as parameters for two reasons. First, they can be estimated from the molecular structure so they can be used for predictions about little-studied compounds and about compounds that have not yet been synthesized. Second, the effects of molecular properties are more easily interpreted and are more valuable in explaining and understanding any discovered relationship.

Because these three thermodynamic properties are directly related [$\Delta H_f = (\Delta S_f) \times T_m$, where T_m is the Kelvin melting point], only two of them need be determined to obtain all three. Melting point is among the most difficult properties to predict. Fortunately, it is easily determined and frequently reported, so it is usually known. The entropy of fusion is largely predictable from previous work. The effects of certain electronic factors have not yet been determined and were the focus of this study.

The maximum possible number of hydrogen bonds (HNO) and the dipole moment (DM) were selected because they are known to affect the degree of disorder in the liquid state. They also affect the entropy of fusion. The simulated quadrupole moment (QM) accounted for electronic effects that are strong in the closely packed crystal but weak at the greater intermolecular distances in the liquid. The parameters (HNO, DM, and QM) can be predicted accurately from molecular structure alone (3), although experimental literature values were used in most cases.

The orientational symmetry number, σ , accounted for the statistical likelihood of finding a molecule properly oriented for incorporation into the crystal. Sigma is defined as the orientational degeneracy of a molecule, i.e., the number of orientations of the molecule that will appear identical when viewed from a given point. The *ortho*-, *meta*-, and *para*-dichlorobenzenes have sigma values of 2, 2, and 4, respectively; *ortho*-, *meta*-, and *para*-bromochlorobenzenes have values of 1, 1, and 2, respectively. In this report, polyatomic groups such as CH₃, NH₂, NO₂, OH, and COOH are treated as monoatomic substituents which are coplanar with the benzene ring.

The polarizability, α , reflected the ability of the compound to interact with dipoles or induced dipoles. Polarizabilities were calculated from the following group incremental values: C₆H₄, 10.0; CH₃, 2.2; Cl, 2.3; Br, 3.3; NO₂, 2.6; NH₂, 1.7; OH, 1.0; and COOH, 2.8.

The dipole moments (DM) for all compounds were found in Ref. 13 except for *m*-bromophenol, terephthalic acid, and *p*-hydroxyaniline. The bromo compound was assigned the same value as the corresponding chloro compound because their group contributions were similar. *p*-Hydroxyaniline was estimated as being in the same ratio to *p*-dihydroxybenzene and *p*-diaminobenzene as the corresponding *ortho* and *meta* values. Terephthalic acid was assumed to be zero by its planarity and symmetry.

The simulated quadrupole moment is an artificial variable. It is the sum of the squares of the group dipole contributions from the two substituents:

$$QM = \mu_1^2 + \mu_2^2 \quad (\text{Eq. 4})$$

The squares were used because quadrupole moment is defined by $q = \sum er^2$, where e is the charge and r is the distance between the charges, whereas dipole moment is simply proportional to the distance:

$$\mu = \sum er \quad (\text{Eq. 5})$$

The maximum number of possible hydrogen bonds touching each molecule was the smaller of:

$$HNO = 2 \times H_a \quad (\text{Eq. 6a})$$

or:

$$HNO = 2 \times H_d \quad (\text{Eq. 6b})$$

where H_a is the number of hydrogen bond acceptor sites (electron pairs on oxygen or nitrogen) and H_d is the number of hydrogen bond donor sites (hydrogen attached to oxygen or nitrogen). The smaller of the two values was used instead of the number of protons because repeating networks of association in the liquid must have an acceptor for each donor.

The IHB variable indicated the ability of a molecule to form intramolecular hydrogen bonds. Internal hydrogen bonding competes with external (intermolecular) hydrogen bonding and thus would be expected to decrease melting point. The IHB is unity if the compound is capable of forming a hydrogen bond in a six- or seven-membered ring and zero if it is not. Thus, for resorcinol and related compounds, IHB = 0.0.

The data were analyzed by multiple linear regression using the Statistical Analysis System. The r^2 value was used as a measure of correlation for each set tested. Values above 0.9 were considered quantitatively useful; values above 0.7 were considered a qualitative correlation, indicative of a trend but not good enough for accurate predictions; values below 0.7 were considered random. The T values were used to determine the significance of each independent variable's contribution to the whole equation in multiple regressions. Values above 3 were considered to be borderline correlations, and values above 4 were considered to be significant contributions. The results of these tests are given in Tables I and II.

RESULTS AND DISCUSSION

The data consisted of ΔS_f , MP, σ , α , DM, QM, HNO, and IHB values for all 84 compounds (Table I). The ΔH_f and ΔS_f have been determined for only 69 compounds. If any of the variables were missing for a compound in a given analysis, that compound was not included in that run. The number of common values determined the size of the data set for each regression.

The results of the more interesting regression analyses for ΔS_f , ΔH_f , and MP are given in Table II.

Inspection of Table II shows that ΔS_f does not depend on any of the parameters against which it was measured ($r^2 < 0.40$). It is independent of the number of hydrogen bonds, of dipole moment, and of other measures of attractive electronic factors. It is approximately constant, with a value of 12.7 ± 2 eu (mean \pm SD) for all 69 data points. Constancy is also shown by the low estimated coefficients, which indicate an approximately horizontal slope. The low T value for σ (Table II) indicates that the effect of molecular geometry is also insignificant. Symmetry, moment of inertia, and other structurally related properties do not affect the entropy of fusion for these compounds. However, because this set of compounds was chosen to minimize these geometrical effects, this result cannot be generalized.

The fact that the entropy of fusion is independent of the electronic attractive factors (Table III) contradicts previous reports (10). For the 24 compounds in the upper left quadrant (Table III), neither substituent has a hydrogen bond-forming hydrogen. The average value of ΔS_f for this group is 13.0 ± 1.48 eu. The upper right quadrant is occupied by the 30 compounds with one hydrogen bond-forming substituent. The mean ΔS_f for these compounds is 12.7 ± 2.20 eu. (Two compounds with questionable values were excluded.) The average for all three groups is between 12.5 and 13 eu, with no systematic decrease apparent.

Bondi (10) stated that any factors that interfere with free rotation in the liquid would decrease the entropy. Hydrogen bonds and strong di-

Table III—Fusion Entropies (eu) of Disubstituted Benzene Compounds

Substituents	CH ₃	Cl	Br	NO ₂	OH	NH ₂	CO ₂ H
CH ₃ : <i>o</i>	13.2	<i>L</i> ^a	<i>L</i>	<i>L</i>	12.4	<i>L</i>	12.8
<i>m</i>	12.4	<i>L</i>	<i>L</i>	11.4	9.0	<i>L</i>	9.9
<i>p</i>	14.2	12.9	12.0	12.6	9.6	13.5	12.4
Cl: <i>o</i>		12.1	<i>L</i>	13.7	9.1	<i>L</i>	14.9
<i>m</i>		12.3	12.2	16.1	9.2	<i>L</i>	13.3
<i>p</i>		13.4	13.3	11.7	11.1	13.8	15.0
Br: <i>o</i>			11.0	16.3	9.7	[13.0] ^b	[13.15]
<i>m</i>			12.1	13.7	<i>L</i>	<i>L</i>	[11.9]
<i>p</i>			13.5	[10.0]	10.5	[14.4]	[15.5]
NO ₂ : <i>o</i>				14.0	12.5	11.2	15.9
<i>m</i>				12.5	13.8	14.7	11.3
<i>p</i>				15.0	13.0	12.0	17.2
OH: <i>o</i>					14.4	[12.8]	[10.8]
<i>m</i>					13.3	[11.2]	[14.7]
<i>p</i>					14.6	— ^c	[12.2]
NH ₂ : <i>o</i>						[12.0]	11.7
<i>m</i>						[11.5]	11.6
<i>p</i>						[10.4]	10.9
CO ₂ H: <i>o</i>							[23.3] ^d
<i>m</i>							[18.9] ^e
<i>p</i>							[31.3] ^e

^a *L* = liquid at room temperature. ^b Values in brackets were determined experimentally by differential scanning calorimetry. All others are literature values. ^c Decomposed before melting. ^d Evidence of reaction during melting. *Not used.* ^e Evidence of reaction and sublimation during melting. *Not used.*

Table IV—Entropy of Fusion Differences between Substituted Phenols and Their Hydrocarbon Homomorphs

Hydroxy Derivative	Hydrocarbon Homomorph	ΔΔ <i>S</i> _f
<i>o</i> -Hydroxytoluene	<i>o</i> -Toluene	0.8
<i>m</i> -Hydroxytoluene	<i>m</i> -Toluene	3.4
<i>p</i> -Hydroxytoluene	<i>p</i> -Toluene	4.6
<i>o</i> -Chlorophenol	<i>o</i> -Chlorotoluene	—
<i>m</i> -Chlorophenol	<i>m</i> -Chlorotoluene	—
<i>p</i> -Chlorophenol	<i>p</i> -Chlorotoluene	1.8
<i>o</i> -Bromophenol	<i>o</i> -Bromotoluene	—
<i>m</i> -Bromophenol	<i>m</i> -Bromotoluene	—
<i>p</i> -Bromophenol	<i>p</i> -Bromotoluene	-2.4
<i>o</i> -Nitrophenol	<i>o</i> -Nitrotoluene	—
<i>m</i> -Nitrophenol	<i>m</i> -Nitrotoluene	2.4
<i>p</i> -Nitrophenol	<i>p</i> -Nitrotoluene	0.4
<i>o</i> -Aminophenol	<i>o</i> -Aminotoluene	—
<i>m</i> -Aminophenol	<i>m</i> -Aminotoluene	—
<i>p</i> -Aminophenol	<i>p</i> -Aminotoluene	—
<i>o</i> -Dihydroxybenzene	<i>o</i> -Hydroxytoluene	-2.0
<i>m</i> -Dihydroxybenzene	<i>m</i> -Hydroxytoluene	-3.3
<i>p</i> -Dihydroxybenzene	<i>p</i> -Hydroxytoluene	-5.0
<i>o</i> -Hydroxybenzoic acid	<i>o</i> -Toluic acid	2.0
<i>m</i> -Hydroxybenzoic acid	<i>m</i> -Toluic acid	-4.8
<i>p</i> -Hydroxybenzoic acid	<i>p</i> -Toluic acid	-0.2
R-C ₆ H ₄ OH	R-C ₆ H ₄ CH ₃	-0.18 ^a

^a Average.

poles restrict free rotation and decrease the disorder in the liquid state. The lack of effect of these phenomena on the entropy of fusion can be explained on the basis of the effect of hydrogen bonding in the crystal.

Entropy is related to disorder by a logarithmic function:

$$\Delta S_{or} = R \ln \frac{\Omega_r}{\Omega_{tor}} \quad (\text{Eq. 7})$$

The orientational contribution to the entropy is determined by the ratio of the number of complexions available in the liquid to the number of complexions available in the crystal. If the magnitude of the torsional oscillations were restricted in the crystal by the same percentage as the rotations are restricted in the liquid, there would be no change in entropy. The effect of hydrogen bonding on bulk crystalline properties such as packing density and melting point shows that factors that lead to association in the liquid also hold the molecules more tightly in the solid. The smaller A-B intermolecular distances and the appearance of A-H...B vibrational modes in the IR regions provide evidence that hydrogen bonds might restrict these torsional oscillations in the crystal (14).

The lack of a consistent effect of hydrogen bonding can be demonstrated by comparing the entropy of fusion of hydroxyl compounds with that of their methyl homomorphs (Table IV).

The heat of fusion equals the product of the entropy and the melting point. If the entropy is a constant, Δ*H*_f should depend only on MP. Therefore, the value of the correlation coefficient of the regression Δ*H*_f versus MP indicates how well 12.7 approximates the entropy of the set of compounds tested. Table II shows that Δ*H*_f does indeed depend only on MP. The *r*² value of 0.78 shows that a strong correlation exists but accurate values must be determined experimentally.

The regression analysis of melting point is also given in Table II. Four parameters were necessary to obtain a definite trend. These results were difficult to interpret because of the low *r*² value for the number of parameters and the large contribution of the sigma parameter, which probably includes a large variety of unspecified factors. The most interesting results is the much larger contribution of QM than DM as a result of the proximity of the molecules in the crystal. In the tightly packed, highly ordered crystal lattice, the molecules arrange themselves so that the negative parts of one molecule are closest to the positive portions of neighboring molecules. At these distances, a negative group is strongly attracted to the positive charge adjacent to it, but it is largely unaffected by the repulsive forces at the other end of the molecule since quadrupole fields fall off so rapidly with distance (much more rapidly than dipoles). Although no definite conclusions can be drawn from the melting-point correlations, they provide some encouragement for the eventual ability to understand and predict melting point.

REFERENCES

- (1) S. Yalkowsky, in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," E. B. Roche, Ed., APhA, Washington, D.C., 1977, chap. 13, p. 392.
- (2) C. Hansch, A. Leo, and D. Nikaitani, *J. Org. Chem.*, **37**, 3090 (1972).
- (3) G. G. Nys and R. F. Rekker, *Eur. J. Med. Chem.*, **9**, 361 (1974).
- (4) P. Walden, *Z. Electrochem.*, **14**, 713 (1908).
- (5) J. Pirsch, *Ber.*, **70**, 12 (1937).
- (6) J. Pirsch, *Mikrochim. Acta.*, **1-6**, 992 (1956).
- (7) R. H. Aranow, L. Witten, and D. H. Andrews, *J. Phys. Chem.*, **62**, 812 (1958).
- (8) A. Luttinghaus and G. Vierk, *Ber.*, **82**, 376 (1949).
- (9) H. Shinke and F. Sauerwald, *Z. Phys. Chem.*, **216**, 26 (1961).
- (10) A. Bondi, "Physical Properties of Molecular Crystals, Liquids, and Glasses," Wiley, New York, N.Y., 1968.
- (11) A. Bondi, *Chem. Rev.*, **67**, 565 (1967).
- (12) R. C. Weast, "Handbook of Chemistry and Physics," CRC, Cleveland, Ohio, 1975.
- (13) A. L. McClellan, "Tables of Dipole Moments," Freeman, San Francisco, Calif., 1963.
- (14) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," Freeman, San Francisco, Calif., 1960.