The Estimation of Melting Points and Fusion Enthalpies Using Experimental Solubilities, Estimated Total Phase Change Entropies, and Mobile Order and Disorder Theory

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Melting points and fusion enthalpies are predicted for a series of 81 compounds by combining experimental solubilities in a variety of solvents and analyzed according to the theory of mobile order and disorder (MOD) and using the total phase change entropy estimated by a group additivity method. The error associated in predicting melting points is dependent on the magnitude of the temperature predicted. An error of ± 12 K (± 1 σ) was obtained for compounds melting between ambient temperature and 350 K (24 entries). This error increased to ± 23 K when the temperature range was expanded to 400 K (46 entries) and ± 39 K for the temperature range 298−555 K (79 entries). Fusion enthalpies were predicted within ± 2σ of the experimental values (± 6.4 kJ mol^{-1}) for 79 entries. The uncertainty in the fusion enthalpy did not appear dependent on the magnitude of the melting point. Two outliers, adamantane and camphor, have significant phase transitions that occur below room temperature. Estimates of melting temperature and fusion enthalpy for these compounds were characterized by significantly larger errors.

INTRODUCTION

Melting points and enthalpies of fusion are important and useful thermochemical properties. Their estimation has proven to be a difficult problem.[1,2] Many compounds, including some of environmental and pharmaceutical interest, decompose prior to or during melting. Thermochemical data for compounds such as some sugars, amino acids, explosives, simple carbohydrates, and peptides are frequently unavailable because of the lack of sufficient thermal stability. The ability to estimate these properties accurately would be extremely useful.

Our laboratories have had an interest in developing methods for estimating various thermochemical properties. Efforts in St. Louis have been directed toward developing models for the estimation of fusion enthalpies. Models to estimate total phase change entropies have been developed.[3,4] Total phase change entropy in this discussion refers to the total entropy change associated with all phase changes occurring between 0 and 298 K. It is frequently identical to the fusion entropy. The estimation of fusion enthalpy from fusion entropy requires an experimental or reasonable estimate of the melting temperature. A simple empirical method for estimation of melting points of homologous series has been reported recently.[5] This method, while reasonably accurate for estimating melting points (±6.6 K), is only applicable to members of a homologous series.

Efforts in Lausanne have focused on theoretical models to predict solubility.[6−12] This has resulted in the development of Mobile Order and Disorder Theory (MOD). In this publication, we would like to report the results of a study in which we have combined MOD Theory with estimates of total phase change entropy and experimental solubility measurements in nonaqueous solvents to predict fusion enthalpies and melting points. The compounds were chosen on the basis of available fusion enthalpy, melting temperature, and experimental solubility in two or more nonaqueous solvents. These data permitted direct comparisons between experimental and estimated values. The compounds in the database are characterized by diversity in chemical structure.

DISCUSSION

A number of theoretical and empirical approaches have been proposed to estimate solubility.[6−18] Many of these approaches describe the solubility of organic nonelectrolytes by the following equation

$$\ln X = -[(\Delta_{fus}H/R)(1/T-1/T_{fus}) + \Sigma(\Delta_{trans}H/R)(1/T-1/T_{trans})] - \ln \gamma \quad (1)$$

where X is the observed solubility in mole fraction, $\Delta_{fus}H$ is the enthalpy of fusion, T_{fus} is the melting point of the compound of interest, and R and T refer to the gas constant and temperature of measurement, respectively. When the compound undergoes solid-state transformations between T and T_{fus}, $\Delta_{trans}H$ and T_{trans} are the enthalpy and temperature of transition, respectively. Experimental data are frequently used to evaluate the first term in eq 1, when available. The second term, the logarithm of the activity coefficient, is often estimated.

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Table 1. Standard Group Interaction Stability Constants and Related Parameters at 298 K[a]

constant	value	comment
r_S	0	for nonassociated solvents (all hydrocarbons, esters, ketones nitriles,...)
r_S	1	for strongly associated solvents forming single hydrogen bonds (alcohols)
r_S	2	for water and diols (molecules involved in double hydrogen bonded chains
b	0	for nonaqueous solvents
K_{OH}	40	solute donor: −OH; solvent acceptor: $-C\equiv N$; $-NO_2$
K_{OH}	200	solute donor: −OH; solvent acceptor: aromatic ring; CH_2Cl_2
K_{OH}	230	solute donor: secondary amine; solvent acceptor: −OH
K_{OH}	300	solute donor: −OH; solvent acceptor: $CHCl_3$
K_{OH}	1000	solute donor: secondary amide; solvent acceptor: −OH
K_{OH}	1500	solute donor: aromatic or conjugated amine; solvent acceptor: −OH
K_{OH}	2000	solute donor: −OH; solvent acceptor: ketone
K_{OH}	2500	solute donor: −OH; solvent acceptor: ester; ether
K_{OH}	5000	solute donor: −OH; solvent acceptor: −OH
K_O	110	solute acceptor: ester. ether; HN−N=; solvent donor: −OH
K_O	170	solute acceptor: ketone; solvent donor: −OH
K_O	300	solute acceptor: tertiary amine; solvent donor: −OH
K_O	600	solute acceptor: tertiary amide; solvent donor: −OH
K_{BB}	0	solute acceptor: secondary amine; solvent donor: secondary amine
K_{BB}	1000	solute acceptor: secondary amide; solvent donor: secondary amide
K_{BB}	1500	solute acceptor: aromatic or conjugated amine; solvent donor: aromatic or conjugated amine
K_{BB}	5000	solute acceptor: −OH; all steroids; solvent donor: −OH; all steroids

[a] Units for K_O and K_{OH} are $cm^3\ mol^{-1}$.

Mobile Order and Disorder Theory (MOD) is the form of eq 1 we have chosen to model fusion enthalpies and melting points. This theory has been developed by Ruelle, Kesselring, Huyskens, and others.[6−12] The relationship between a substances' solubility and eq 1 as described by MOD is given by eq 2. The solubility Φ_B on a volume fraction scale ($\Phi_B = XV_B/(XV_B-(1-X)V_S)$ of a solute B in a solvent S is evaluated by a series of terms. Each of these terms is defined in eqs 3−8.

$$\ln \Phi_B = A + B + D + F + O + OH \quad (2)$$

$$A = -(\Delta_{fus}H/R)(1/T-1/T_{fus}) - \Sigma(\Delta_{trans}H/R)(1/T-1/T_{trans}) \quad (3)$$

$$B = 0.5\,\Phi_S(V_B/V_S - 1) + 0.5\ln(\Phi_B + \Phi_S V_B/V_S) \quad (4)$$

$$D = -\Phi_S 2\,V_B(\delta_B - \delta_S)^2/[RT(1.0 + \max(K_{OH}, K_O)\Phi_S/V_S)] \quad (5)$$

$$F = -r_S\Phi_S V_B/V_S + \Sigma\nu_{OHi}\,\Phi_S(r_S + b_i) \quad (6)$$

$$O = \Sigma\nu_{Oi}\ln[(1 + K_{Oi}(\Phi_S/V_S - \nu_{Oi}\Phi_B/V_B)] \quad (7)$$

$$OH = \Sigma\nu_{OHi}[\ln(1 + K_{OHi}\Phi_S/V_S + K_{BBi}\Phi_B/V_B) - \ln(1 + K_{BBi}V_B)] \quad (8)$$

The terms represent different factors that can influence the solubility of each respective compound, including such factors as hydrogen bonding, nonspecific cohesion forces, entropic factors, and others. In eqs 2−8, Φ_S is the volume fraction of the solvent, S, and Φ_B is the volume fraction of the solute, B. The terms V_B and V_S are the molar volumes of the solute and solvent, respectively; these terms can be estimated by group additivity. The terms δ_B and δ_S are modified cohesion parameters; δ_S values are tabulated for the most common solvents. The terms K_O, K_{OH}, and K_{BB} refer to stability constants that describe the strength of association between solute−solvent and solute−solute molecules, respectively, resulting from hydrogen bonding; r_S and b are structuration factors associated with amphiphilic solvents. These constants are defined, and their values are tabulated in Table 1.

Substitution of the appropriate terms in eqs 3−5 affords A, B, and D. The designation max(K_{OH}, K_O) in eq 5 refers to the use of the larger of the two association constants, if both are applicable. In eq 7, the term ν_{Oi} refers to the number of K_{Oi} type interactions in polyfunctional molecules. Similarly in eq 8, ν_{OHi} refers to the number of K_{OHi} type interactions between solute and solvent. In eqs 7 and 8, each term is summed over all the different interactions present in the molecule as defined by the K_O and K_{OH} constants in Table 1. In cases where functional groups lie in close proximity to each other, the use of a value less than their sum may be necessary in order to reproduce the experimental solubility.[12]

RESULTS

If the solubility of a solute in a common solvent is available, then Φ_B can be evaluated experimentally, and the B, F, O, and OH terms can be calculated directly. Only two parameters in eqs 3−8 cannot be assigned numerical values. These terms include the δ_B and the A term, both of which are associated with the solute. If experimental solubilities are obtained in more than one solvent for each solute being investigated, a set of independent equations result, and A and δ_B can be solved for simultaneously. Once the A term has been evaluated, it is possible to approximate eq 3 with eq 9 and rearrange it to solve for the total phase change enthalpy in terms of gas constant R, the A term, and the total phase change entropy. In cases where there are no additional phase changes associated in going from the solid at 0 K to the isotropic liquid at the melting point, eqs 9 and 10 become equalities.

$$A \approx -(\Delta_{tpce}H/R)(1/T_{sol} - 1/T_{fus}) \text{ where } \Delta_{tpce}H = \Delta_{fus}H + \Sigma_i\Delta_{trans}H_{(i)} \text{ and } T_{trans} > T_{sol} \quad (9)$$

$$\Delta_{tpce}H \approx -(298.15)(RA + \Delta_{tpce}S) \quad (10)$$

Table 2. Evaluation of δ_B and A Terms for Methyl Hexadecanoate and Estradiol

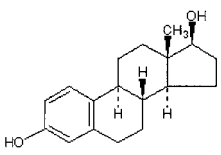
solvent[2]	δ_{SO}	V_{SO}	Φ_{BO} expt	B	D	A	F	O	OH	lnΦ_{BO} calcd	lnΦ_{BO} expt
A. for Methyl Hexadecanoate[a]											
chloroform	18.77	80.7	0.83	0.436	−0.016	−0.75	0	0	0	−0.33	−0.186
carbon tetrachloride	17.04	97.1	0.792	0.415	−0.001	−0.75	0	0	0	−0.336	−0.234
benzene	18.95	89.4	0.775	0.497	−0.033	−0.75	0	0	0	−0.286	−0.255
toluene	18.1	106.9	0.743	0.441	−0.016	−0.75	0	0	0	−0.325	−0.297
1,2-dichloroethane	20.99	78.8	0.797	0.53	−0.096	−0.75	0	0	0	−0.317	−0.227
cyclohexane	14.82	108.8	0.689	0.513	−0.043	−0.75	0	0	0	−0.281	−0.373
butyl acetate	19.66	132.5	0.596	0.485	−0.182	−0.75	0	0	0	−0.447	−0.518
acetone	21.91	74	0.691	0.832	−0.328	−0.75	0	0	0	−0.246	−0.369
eethyl acetate	20.79	98.5	0.687	0.59	−0.207	−0.75	0	0	0	−0.367	−0.375
hexane	14.56	131.6	0.604	0.481	−0.091	−0.75	0	0	0	−0.36	−0.504
octane	14.85	163.5	0.553	0.366	−0.087	−0.75	0	0	0	−0.471	−0.592
1-butanol	17.16	92	0.308	1.3	−0.007	−0.75	−2.324	0.541	0	−1.24	−1.178
1-propanol	17.29	75.1	0.304	1.66	−0.011	−0.75	−2.862	0.647	0	−1.316	−1.19
methanol	19.25	40.7	0.206	3.533	−0.165	−0.75	−6.03	1.123	0	−2.289	−1.581
B. for Estradiol[b]											
cyclohexane	14.82	108.8	1.2E−5	1.094	−1.405	−5.25	0	0	−6.055	−11.617	−11.331
benzene	18.95	89.4	0.00044	1.445	−0.006	−5.25	0	0	−3.702	−7.512	−7.729
toluene	18.1	106.9	0.00031	1.123	−0.006	−5.25	0	0	−3.943	−8.076	−8.079
chloroform	18.77	80.7	0.002	1.647	−0.001	−5.25	0	0	−2.939	−6.543	−6.166
dichloromethane	20.53	64.5	0.002	2.155	−0.101	−5.25	0	0	−3.219	−6.415	−6.32
tetrahydrofuran	19.3	81.4	0.21	1.332	−0.002	−5.25	0	0	0.705	−3.214	−1.561
dioxane	20.89	85.8	0.1	1.393	−0.017	−5.25	0	0	0.692	−3.182	−2.303
diethyl ether	18.78	104.8	0.006	1.151	−0.0003	−5.25	0	0	0.368	−3.731	−5.083
acetone	21.91	74	0.062	1.738	−0.039	−5.25	0	0	0.578	−2.973	−2.781
ethyl oleate	17.69	356.9	0.013	−0.308	−0.009	−5.25	0	0	−1.855	−7.422	−4.343
methanol	19.25	40.7	0.023	3.472	−0.0004	−5.25	−4.153	0	3.544	−2.388	−3.772
ethanol	17.81	58.7	0.032	2.334	−0.001	−5.25	−2.259	0	2.808	−2.368	−3.442
1-decanol	16.35	191.6	0.021	0.3	−0.017	−5.25	0.658	0	0.533	−3.777	−3.863
1,2-ethanediol	19.9	56	0.016	2.494	−0.002	−5.25	−5.004	0	2.925	−4.838	−4.135

[a] $V_B = 309$ cm^3 mol^{-1}; $\delta_B = 16.7$ (J cm^{-3})$^{0.5}$. [b] $V_B = 254$ cm^3 mol^{-1}; $\delta_B = 18.2$ (J cm^{-3})$^{0.5}$; $\nu_{OH} = 2$.

If additional phase change enthalpies are present, then only those transitions occurring above the temperature of the solubility measurements, T_{sol}, are relevant to eq 9. The total phase change entropy (ΔS_{tpce}) in eq 10 can be estimated by a group additivity method with an uncertainty of approximately ± 13 J mol^{-1} K^{-1} (±1 σ).[3,4] Substitution of an estimated value for $\Delta_{tpce}S$ along with the experimentally determined value for A in eq 10 permits a solution of both the total phase change enthalpy ($\Delta_{tpce}H$) and the melting point, T_{fus} (calculated as $\Delta_{fus}H/\Delta_{fus}S$). Considerable error may be introduced in T_{fus} and $\Delta_{tpce}H$ in cases where additional transitions accompany fusion and $T_{trans} < T_{sol}$.

Two examples of how nonaqueous solubilities, eqs 3−8, and estimated values of $\Delta_{tpce}S$ can be used to determine T_{fus} and $\Delta_{tpce}H$ are illustrated in Table 2A,B for methyl hexadecanoate and estradiol.

$CH_3(CH_2)_{14}CO_2CH_3$ methyl hexadecanoate



estradiol

The experimental solubilities (as volume fractions), the molar volumes of the solute and solvents, and the appropriate constants from Table 1 are substituted into eqs 3−8, and A and δ_{BO} are allowed to vary in order to minimize the function $\Sigma[(\ln \Phi_{Bj}$ expt $- \ln \Phi_{Bj}$ calcd$)/(\ln \Phi_{Bj}$ expt $+ \ln \Phi_{Bj}$ calcd$)]^2$; Φ_{Bj} represents the solubility of each individual entry in the sum. The calculated values for these two parameters for both methyl hexadecanoate and estradiol are reported in columns 2 and 3 of Table 3, respectively. The results obtained for methyl hexadecanoate illustrate typical behavior observed for a number of compounds melting near room temperature; both the fusion enthalpy and T_{fus} are well reproduced. The fusion temperature for estradiol is considerably higher. The error associated with T_{fus} is correspondingly larger. However, the fusion enthalpy is still reasonably well reproduced.

Table 3. Parameters and Results Obtained for Methyl Hexadecanoate and Estradiol

	δ_B	A	$\Delta_{tpce}S$ (J/mol K)	T_{fus} (K)	$\Delta_{tpce}H$ (kJ/mol)
methyl hexadecanoate					
experimental values		−0.43	182.9	304	55.6
calculated values	16.7	−0.75	174	304	52.7
estradiol					
experimental values		−5.4	91.2	452	40.6
calculated values	18.52	−5.25	67.3	491	33.1

Using this protocol, we have obtained estimates of melting point and fusion enthalpy for a total of 81 compounds with a variety of structures, some as complex as steroids and others as simple as alkanes. The results are reported in Table 4. The first two columns in the table identify compounds according to molecular formula whose solubilities have been measured in at least two different nonaqueous solvents. The experimental melting point is given in the third column. The melting point calculated in associated, nonassociated, and mixed solvent systems are listed in columns 4−6. An associated solvent in the present context refers only to alcohols; all other solvents are considered nonassociated. Mixed solvent systems include combined measurements conducted both in associated and nonassociated solvents.

Table 4. Total Phase Change Enthalpies and Melting Points Estimated from Solubility Measurements[a]

molecular formula	compound	T_{fus} expt	T_{fus} calcd[b]	T_{fus} calcd[c]	T_{fus} calcd[d]	$\Delta_{tpce}S$ estd[e]	$\Delta_{tpce}H$ calcd[d]	$\Delta_{tpce}H$ expt
$C_6H_4O_2$	*p*-benzoquinone	388	412			29.4	12.1	18.5
$C_8H_8O_3$	methyl 4-hydroxybenzoate	400		403		60.2	24.3	22.6
C_8H_9NO	acetanilide	386		402		48.6	19.5	22.0
$C_8H_9NO_2$	4-hydroxyacetanilide	442		502		54	27.1	27.0
$C_9H_{10}O_3$	Nipagin A	389		387		67.3	26.0	25.5
$C_9H_{11}NO_2$	benzocaine	363		401		68.5	27.5	23.6
$C_{10}H_8$	naphthalene	353	348	371	365	44.4	16.2	19,1
$C_{10}H_{16}O$	camphor	452		309		38.0	11.7	21.5
$C_{10}H_{12}$	acenaphthene	367		442		41.0	18.1	21.5
$C_{10}H_{12}O_3$	propyl 4-hydroxybenzoate	369		366		74.5	27.3	28.0
$C_{10}H_{13}NO_2$	risocaine	347		337		75.6	25.5	20.5
$C_{10}H_{13}NO_2$	phenacetin	407		422		63.1	26.6	31.3
$C_{10}H_{15}NO$	ephedrine	312		344		55.3	19.0	20.4
$C_{10}H_{16}$	adamantane	541		486		44.9	20.7	14.3
$C_{11}H_{12}N_2O$	antipyrine	386		479		49.1	23.5	24.5
$C_{11}H_{14}O_3$	butyl 4-hydroxybenzoate	343		337		81.6	27.5	26.8
$C_{11}H_{15}NO_2$	*n*-butyl 4-aminobenzoate	331		344		82.7	28.4	20.5
$C_{12}H_8S_2$	thianthrene	428		481		60.5	29.1	25.4
$C_{12}H_{26}O$	1-dodecanol	300	302	302	302	122	36.8	40.2
$C_{12}H_{10}$	biphenyl	343	338			59.2	20.0	18.7
$C_{13}H_8OS$	thioxanthen-9-one	488		563		56.0	31.1	35.5
$C_{13}H_{17}N_3O$	aminophenazone	382		516		52.9	27.3	26.9
$C_{14}H_{10}$	anthracene	490	566	568	568	44.2	25.1	28.8
$C_{14}H_{10}$	phenanthrene	369	385	393	388	44.2	17.1	18.6
$C_{14}H_{10}O_2$	benzil	368	347			68.4	23.7	23.6
$C_{14}H_{12}$	*trans* stilbene	398		397		69.7	27.7	27.4
$C_{14}H_{22}N_2O$	lidocaine	340		339		66.5	22.5	15.3
$C_{14}H_{30}O$	1-tetradecanol	311	315	304	309	141	44.1	49.4
$C_{16}H_{10}$	pyrene	424	432	471	442	43.8	19.4	17.1
$C_{16}H_{34}O$	1-hexadecanol	322	337	324	334	159	53.2	58.4
$C_{17}H_{34}O_2$	methyl hexadecanoate	304	304	301	304	174	52.7	55.6
$C_{18}H_{20}O_2$	diethylstilbestrol	442			402	97.8	39.3	28.8
$C_{18}H_{24}O_2$	estradiol	452	467	520	491	67.3	33.1	40.6
$C_{18}H_{24}O_3$	estriol	555			638	67.9	43.3	42.7
$C_{18}H_{38}$	*n*-octadecane	301		302		185	55.7	61.4
$C_{18}H_{38}O$	1-octadecanol	334	350	336	336	178	59.8	70.1
$C_{19}H_{28}O_2$	prasterone	423	380			61.7	23.4	24.4
$C_{19}H_{28}O_2$	testosterone	427		436		60.5	26.4	29.5
$C_{19}H_{30}O_2$	androstanolone	454	383			60.9	22.5	30.0
$C_{19}H_{38}O$	10-nonadecanone	330	332	332	332	189	62.7	67.3
$C_{19}H_{38}O_2$	methyl octadecanoate	312	323	309	323	192	62.0	64.4
$C_{20}H_{26}O_2$	norethindrone	479			563	54.7	30.8	39.6
$C_{20}H_{26}O_2$	norethindrone acetate	480			424	62.3	26.4	27.3
$C_{20}H_{28}O_3$	testosterone formate	398	348		349	66.3	23.1	26.4
$C_{20}H_{30}O_2$	17-methyltestosterone	438		445		57.9	25.7	25.7
$C_{20}H_{42}$	*n*-eicosane	310		310		203	63.0	69.9
$C_{20}H_{42}O$	1-eicosanol	337	332	340	340	196	66.6	78.4
$C_{21}H_{27}FO_6$	triamcinolone	543		573		86.6	49.6	42.6
$C_{21}H_{28}O_5$	cortisone	495			554	74.1	41.1	36.9
$C_{21}H_{28}O_5$	prednisolone	513		554	537	76.7	41.2	38.9
$C_{21}H_{30}O_2$	progesterone	403			393	64.4	25.3	24.4
$C_{21}H_{30}O_3$	deoxycorticosterone	414			448	69.4	31.1	28.0
$C_{21}H_{30}O_3$	testosterone acetate	413	365		366	67.8	24.7	22.5
$C_{21}H_{30}O_5$	hydrocortisone	485			534	86.4	46.1	33.9
$C_{21}H_{42}O$	11-heneicosanone	337	335	338	336	208	69.8	76.2
$C_{22}H_{29}FO_5$	betamethasone	503			499	82.0	41.0	37.7
$C_{22}H_{29}FO_5$	dexamethasone	539			529	82.0	43.4	42.0
$C_{22}H_{30}O_3$	stanolone formate	415	381		382	66.9	25.5	26.6
$C_{22}H_{32}O_3$	methyltestosterone acetate	448	393		393	65.4	25.7	25.6
$C_{22}H_{32}O_3$	testosterone propionate	393	357	369	357	74.8	26.7	22.1
$C_{23}H_{30}O_6$	cortisone acetate	509			467	78.8	36.8	38.4
$C_{23}H_{34}O_3$	testosterone butyrate	382			348	81.9	28.5	25.3
$C_{23}H_{34}O_3$	methyltestosterone propionate	418	384			72.5	27.9	34.1
$C_{23}H_{32}O_3$	stanolone acetate	430	375			68.3	25.6	27.8
$C_{23}H_{32}O_4$	deoxycorticosterone acetate	430			443	79.5	35.2	29.7
$C_{23}H_{32}O_6$	hydrocortisone-21-acetate	497			546	86.1	47.0	48.4
$C_{23}H_{46}O$	12-tricosanone	342	343	341	341	226	77.2	78.0
$C_{23}H_{48}$	tricosane*	321	319	318	318	231	73.5	75.7
$C_{24}H_{34}O_3$	stanolone propionate	394.2	386			75.4	29.1	24.5
$C_{24}H_{36}O_3$	testosterone valerate	380			355	89.0	31.6	31.0
$C_{25}H_{31}FO_8$	triamcinolone diacetate	508			478	92.8	44.5	38.3
$C_{25}H_{36}O_3$	stanolone butyrate	364	364			82.6	30.0	22.7
$C_{25}H_{36}O_6$	hydrocortisone-17-butyrate	395			371	114	45.3	20.8

Table 4 (Continued)

molecular formula	compound	T_{fus} expt	T_{fus} calcd[b]	T_{fus} calcd[c]	T_{fus} calcd[d]	$\Delta_{tpce}S$ estd[e]	$\Delta_{tpce}H$ calcd[d]	$\Delta_{tpce}H$ expt
$C_{26}H_{36}O_3$	estradiol-17-cypionate	424.2			401	97.6	39.1	29.4
$C_{26}H_{54}$	hexacosane*	329		322		259	83.4	91.7
$C_{27}H_{37}FO_6$	betamethasone-17-valerate	456			494	107	52.7	32.4
$C_{27}H_{46}O$	cholesterol*	421	399	394	394	74	29.0	28.4
$C_{28}H_{58}$	octacosane*	334	336	337	337	278	93.6	100.1
$C_{29}H_{48}O_2$	cholesterol acetate	388			363	97.3	35.3	22.4
$C_{32}H_{66}O$	hexadecyl ether	324.7	327		327	319	104.3	115.3
$C_{34}H_{50}O_2$	cholesterol benzoate*	419			392	109	42.8	33.4

[a] All experimental data taken from references cited in the Supporting Information tables. [b] Nonassociated solvents. [c] Associated solvents. [d] Computed using all experimental solubility data. [e] See Supporting Information tables for details.

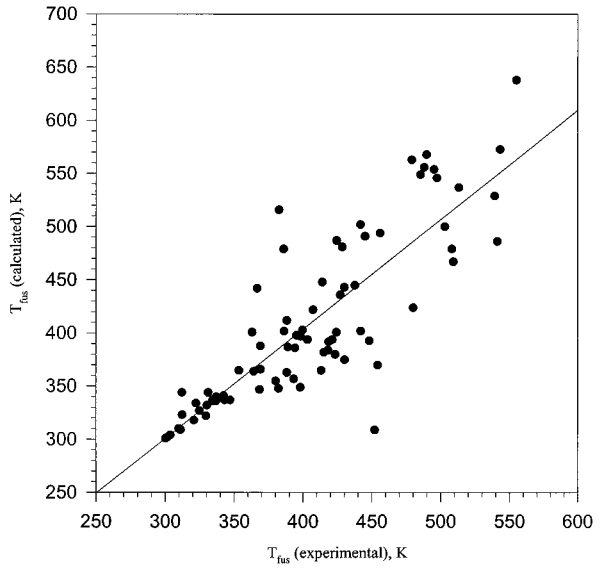


Figure 1. A comparison of fusion temperatures calculated from solubility measurements and estimated total phase change entropies with experimental values.

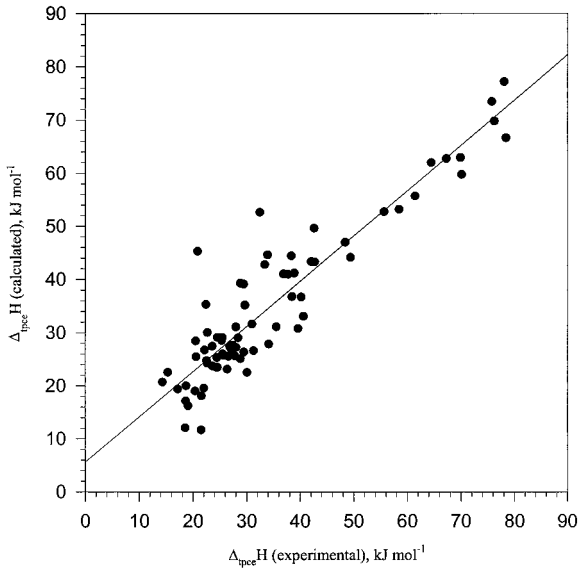


Figure 2. A comparison of calculated total phase change enthalpies with experimental values for all 81 compounds in the database.

Measurements in associated solvents have been segregated from those in nonassociated solvents because the number of terms needed in the estimation of solubility differ. It would be useful to know if the accuracy of the estimation of T_{fus} depended on using a particular solvent system. The data in columns 4−6 suggests that the accuracy of estimation of T_{fus} is not highly dependent on the nature of solvent systems used in the measurements. In a few cases sufficient data were not available to allow for segregation according to solvent classification.

Column 7 includes the total phase change entropy estimated by group additivity.[4] Details on the estimations of $\Delta_{tpce}S$ for each compound are available in the Supporting Information. The last two columns in Table 4 compare calculated and experimental total phase change enthalpies. The values of $\Delta_{tpce}H$ in column 8 were calculated using A values derived from solubility measurements obtained in both associated and nonassociated solvents.

The calculated and experimental melting temperatures are compared in Figure 1 for all 81 compounds investigated. An examination of this figure suggests that the errors are not totally random; the magnitude of the error appears to be dependent on the magnitude of the melting point. A total of 24 compounds are estimated to melt between room temperature and 350 K. The standard deviation between calculated and experimental values is just under ±12 K. The number of compounds predicted to melt between room temperature and 400 K is 46. The standard deviation associated with these compounds increases to just under ±23 K. For 79 compounds, a standard deviation of ±39 K is obtained between the calculated and experimental value. Two compounds, camphor and adamantane, are the only compounds in the database known to have significant phase transitions occurring below room temperature. Their errors of 143 and 55 K, respectively, were not included in these statistics. The average fractional error of all 81 entries estimated is just under 0.07. It should also be noted that 17 of these estimations are based on solubilities determined in only two solvents.

Unlike the uncertainty in the fusion temperature, the error in total phase change enthalpy ($\Delta_{tpce}H$) does appear to be random. This is evident by examining Figure 2 and the last two columns in Table 4. Total phase change enthalpies in Table 4 (column 8) were calculated from the A values according to eqs 9 and 10 by using estimated values of $\Delta_{tpce}S$ and T_{fus}. A number of the compounds in the database are known to have additional phase transitions occurring above room temperature. The magnitude of these transitions is included in the experimental total phase change enthalpy listed in the last column of Table 4. These compounds are identified in the table by an asterisk that follows their name. The standard deviation in $\Delta_{tpce}H$ between experimental and estimated values is ± 6.4 kJ mol^{-1}. This is approximately twice the standard deviation generally associated with typical

Table 5. Predicted Fusion Enthalpies and Melting Points from Solubility Measurements

compound		T_{fus} (expt) K	T_{fus} (calcd) K	$\Delta_{tpce}S$ (estd) J mol^{-1} K^{-1}	$\Delta_{tpce}H$ (estd) kJ mol^{-1}
$C_{18}H_{18}O_2$	dienestrol	500.2	416	94.2	39.2
$C_{18}H_{22}O_2$	estrone	533.2	538	62.9	33.8
$C_{18}H_{26}O_2$	nandrolone	385.2	424	64.0	27.1
$C_{19}H_{28}O_2$	prasterone formate	413.2	389	67.8	26.4
$C_{19}H_{30}O_3$	oxandrolone	498.2	424	62.5	26.5
$C_{20}H_{28}O$	lynestrenol	432.2	540	41.6	22.5
$C_{20}H_{28}O_2$	methandienone	436.2	463	51.8	24
$C_{20}H_{32}O$	ethylestrenol	350.2	397	54.2	21.5
$C_{20}H_{24}O$	ethynyl estradiol	456.2	457	59.5	29.3
$C_{20}H_{30}O$	prasterone acetate	440.2	377	69.3	26.1
$C_{20}H_{32}O_2$	mestanolone	465.2	503	58.6	29.5
$C_{20}H_{32}O_2$	dromostanolone propionate	399.2	361	78.5	28.3
$C_{21}H_{26}O_5$	prednisone	507.2	560	69.4	38.9
$C_{21}H_{28}O_2$	dydrogesterone	442.2	454	61.5	27.9
$C_{21}H_{28}O_2$	norgestrel	482.2	535	61.8	33.1
$C_{21}H_{32}N_2O$	stanozolol	508.2	521	67.3	35.1
$C_{21}H_{32}O_2$	pregnenolone	466.2	493	70.6	34.8
$C_{21}H_{32}O_2$	prasterone propionate	470.2	388	76.4	29.6
$C_{21}H_32O_3$	oxymetholone	452.2	472	65.6	31
$C_{22}H_{29}FO_4$	fluorometholone	568.2	561	67.1	37.6
$C_{22}H_{30}O_5$	methylprednisolone	513.2	568	79.6	45.2
$C_{22}H_{34}O_2$	prasterone butyrate	436.2	383	83.5	32
$C_{23}H_{34}O_3$	pregnenolone acetate	423.4	406	78.2	31.7
$C_{23}H_{36}O_2$	prasterone valerate	393.2	372	90.6	33.7
$C_{24}H_{30}F_2O_6$	fluocinolone acetonide	539.2	516	81.6	42.1
$C_{24}H_{32}O_4$	ethynodiol diacetate	399.2	380	75.8	28.8
$C_{24}H_{32}O_6$	methylprednisolone-21-acetate	498.2	533	84.3	44.9
$C_{24}H_{33}FO_6$	flurandrenolide	523.2	541	88.7	48.0
$C_{24}H_{34}O_6$	hydrocortisone-21-propionate	484.2	527	93.2	49.1
$C_{24}H_{38}O_3$	stanolone valerate	375.7	352	90.6	31.9
$C_{25}H_{36}O_6$	hydrocortisone-21-butyrate	463.2	395	100.3	39.6
$C_{26}H_{32}F_2O_7$	fluocinonide	583.2	497	84.6	42
$C_{26}H_{38}O_6$	hydrocortisone-21-valerate	457.2	379	107.4	40.7
$C_{26}H_{40}O_4$	desoxycorticosterone pivalate	476.2	419	91.8	38.5
$C_{27}H_{38}O_3$	testosterone-17β-cypionate	374.2	343	90.4	31
$C_{27}H_{40}O_3$	17α-hydroxyprogesterone caproate	393.2	322	98.5	31.7
$C_{27}H_{40}O_6$	hydrocortisone 21-hexanoate	388.2	331	114.5	37.9
$C_{28}H_{37}ClO_7$	beclomethasone-17,21-dipropionate	393.2	472	101.1	47.7
$C_{28}H_{42}O_6$	hydrocortisone 21-heptanoate	384.2	315	121.6	38.3
$C_{28}H_{44}O_3$	nandrolone decanoate	308.2	315	129.9	40.9
$C_{29}H_{50}O$	β-sitosterol	413.3	370	74.9	27.7
$C_{30}H_{41}FO_7$	triamcinolone hexacetonide	569.2	502	89.3	44.8

experimental fusion enthalpies reported in the literature. The error in $\Delta_{tpce}H$ obtained by using estimated $\Delta_{tpce}S$ (Table 4, column 7) and experimental melting temperatures (Table 4, column 3) results in a comparable standard deviation, $\pm$6.8 kJ mol^{-1}.

Using the protocol just described, fusion enthalpies are predicted for a series of hydroxysteroids whose solubilities in different solvents have been measured but whose fusion enthalpies are presently unavailable. The results are included in Table 5. Melting points for these steroids are available, and the experimental values can be compared to those calculated. Most of the melting temperatures of the hydroxysteroids are above 400 K. The standard deviation between calculation and experiment is $\pm$ 50 K, very similar to the error associated with the compounds in Table 4 possessing similar melting points. We would expect a standard error of approximately $\pm$6 kJ mol^{-1} to be associated with these fusion enthalpy predictions. Since the fusion enthalpies of many of these steroids are likely to be measured experimentally, these estimations offer a good test of the predictive capability of this protocol for estimating fusion enthalpies.

Supporting Information Available: Tables containing the experimental and calculated solubilites, values for the various terms in eq 2, estimated entropies, all constants, and references. This material is available free of charge via the Internet at http://pubs.acs.org.

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