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Enthalpy/Entropy Compensation as a Competition between Dynamics and Bonding: The Relevance to Melting of Crystals and Biological Aggregates

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The remarkable variations which are observed in the enthalpies of melting of compounds are ill-understood. For example, we have previously noted that the enthalpy of melting of bromine (mp 266 K) is only 19% less than that of barium fluoride (mp 1593 K).[1] In this communication, we use data on the entropies, enthalpies, and volume changes of melting of hydrocarbons to support the hypothesis that it is the change in dynamics between two states (measured by the entropy change) that is primarily correlated with the reduction in bonding between the two states (measured by the enthalpy change). We also propose that these changes are important in determining the behavior of biological aggregates.

The most characteristic difference between a pure liquid and its corresponding solid state is that in the liquid state neighboring molecules can change places rapidly, whereas in the solid they do not do so.[2] The most probable structures of the solid and liquid at the melting point are otherwise usefully regarded as similar (in the relative orientations of neighboring molecules). Given these simplifications, it is also clear that internal rotors will "rock" more freely in the liquid than in the solid state.[3] Consequently, some hydrocarbons have a much greater opportunity to increase their dynamic motion than others upon melting. For example, X-ray structures of compounds containing *n*-alkyl chains establish that the *n*-alkyl chain is typically restricted in a herringbone arrangement in the crystal. However, this restriction of motion is much less in the liquid state, as evidenced by the marked increase in the entropy of melting with increasing chain length.[3]

The effects of internal rotors upon entropies of melting are illustrated by the data in Table 1. Data for the isomers of C_5H_{12}, and for cyclopentane, are given in Table 1a and data for the isomers of C_6H_{14}, and for cyclohexane, in Table 1b. We note the following points:

(i) The variation in melting point (K) within either of the two data sets is only about a factor of 2. The relatively small value of this factor illustrates that the melting temperature is primarily (but of course not exclusively) influenced by the surface areas of the molecules and the kinds of bonds (these are similar within either data set).

(ii) The variations in enthalpies and entropies of melting for a given set of isomers are enormously greater (up to a factor of 22). If ΔH_m is the enthalpy of melting (change in noncovalent interactions upon melting), ΔS_m is the entropy of melting (effectively a measure of the increase in motion upon melting), and T_m the melting point, then $\Delta H_m = T_m \Delta S_m$. Therefore, the relatively small variance in T_m for a given set of isomers requires that a large ΔH_m is always associated with a large ΔS_m.

Table 1. Enthalpies of Melting (ΔH_m) and Entropies of Melting (ΔS_m) for a Number of Alkanes (straight-chain, branched, and cyclic)[13,14]

	compd	T_{melt}/K	ΔH_m/kJ mol^{-1}	ΔS_m/J mol^{-1} K^{-1}
(a)	*n*-pentane	143	8.4	59
	2-methylbutane	113	5.1	45
	2,2-dimethylpropane	256	3.3	13
	cyclopentane	179	0.6	3
(b)	*n*-hexane	178	13.1	74
	2-methylpentane	119	6.3	53
	2,2-dimethylbutane	174	0.6	3.3
	2,3-dimethylbutane	144	0.8	5.5
	cyclohexane	267	2.6	9.7

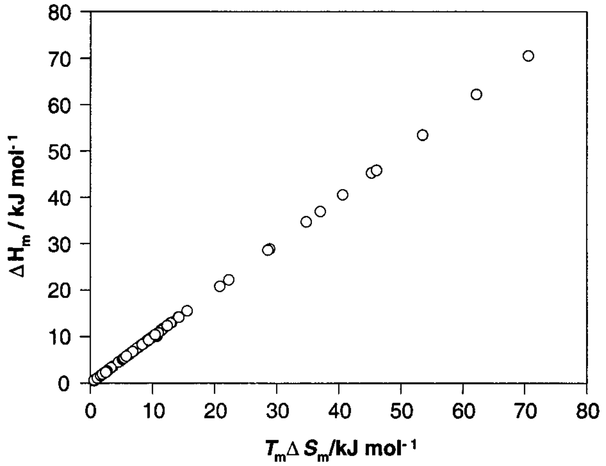

Figure 1. Plot of ΔH_m vs $T_m \Delta S_m$ for a number of alkanes (straight-chain, branched, and cyclic).[13,14]

These points suggest that (within this data set) a single physical effect relates the enthalpy of melting with the entropy of melting. We propose that it is the physical change of a relatively large increase in motion on melting which correlates with a relatively large decrease in bonding. The increased motions of an alkyl chain on passing from solid to liquid inevitably increase the average distances between neighboring molecules (see below), and therefore lead to a reduction in bonding between neighboring molecules.

It is productive to consider this conclusion in terms of the reverse process, that of crystallization. Thus, adjacent cyclopentane and cyclohexane molecules are interacting in a relatively cooperative way in the liquid state, and little improvement of the noncovalent interactions between them occurs on crystallization (small ΔH_m). In contrast, the internal motions of *n*-pentane, or *n*-hexane, in the liquid state preclude the operation of highly efficient noncovalent interactions between adjacent molecules. When these internal rotations are restricted upon crystallization, adjacent *n*-pentane, or *n*-hexane, molecules bond to each other more cooperatively i.e., the noncovalent interactions between them are greatly improved (large ΔH_m).

The generality of the above conclusions is supported by the much wider data set of alkanes used in Figure 1. Large increases in entropies of melting are correlated with large increases in enthalpies of melting. Since $\Delta H_m = T_m \Delta S_m$, it is axiomatic that the plot in Figure 1 is a straight line with a slope of 1. The interesting point is the physical origin of the very large spread in ΔH_m and $T_m \Delta S$. Large improvements in bonding upon crystallization are correlated with large restrictions in motion.

The above conclusions are further supported by considering volume changes of alkanes on melting. Figure 2 shows that for

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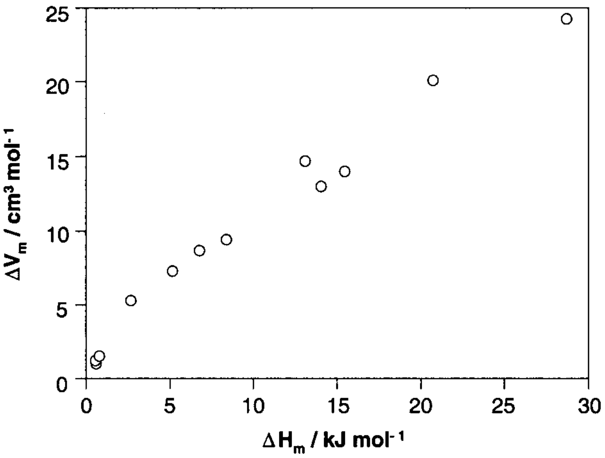

Figure 2. Plot of ΔH_m vs volume changes on melting (ΔV_m) for a number of alkanes (straight-chain, branched, and cyclic).[4]

a set of cyclic, branched, and linear alkanes, there is an excellent correlation between the volume increase on melting (ΔV_m) and ΔH_m. (The data used to construct Figure 2 were determined by A. Würflinger,[4] although the correlation between ΔV_m and ΔH_m had not been reported by the author.) Given the causal relationship between ΔH_m and ΔS_m, this result is easily rationalized. As the extent to which molecules increase their motions on melting increases (ΔS_m increases), their relative intermolecular distances will increase (ΔV_m increases), and the bonding between them will decrease (ΔH_m increases). Thus, enthalpy/entropy compensation[5-11] is seen to be relevant to melting and, as is physically plausible, ΔH_m, ΔS_m, and ΔV_m are all correlated.

The generalizations drawn from the melting of hydrocarbons have relevance to the noncovalent complexes that are involved in biological function. Consider the melting of DNA duplexes as an example. A duplex of self-complementary DNA dodecamers has been shown to form in aqueous solution from its constituent single strands with an exothermicity of −430 kJ mol^{-1}.[12] Upon the introduction of only two mismatches into the sequence the magnitude of the exothermicity of duplex formation drops by ca. 220 kJ mol^{-1}.[12] This extremely large fall in the exothermicity of duplex formation is associated with a correspondingly dramatic fall in the adverse entropy for duplex formation (from −1164 to −577 J mol^{-1} K^{-1}). The dramatic changes in ΔH and ΔS suggest that the motion that is gained in the mismatched complex is expressed over the entire dodecamer (the localized changes in base−base interactions and loss of a few hydrogen bonds would be much too small to account for such changes). This illustrates how enthalpy/entropy compensations are relevant in Nature's systems. The adverse effect that a reduction in bonding has on the stability of an assembly is offset by an increase in its dynamics and these offsetting effects may be remarkably large. Looked at in another way, the self-complementary duplex forms with a much larger positive cooperativity than does the mismatched duplex.

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