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CONSEQUENCES FOR MOLECULAR RECOGNITION AND LIGAND-RECEPTOR COMPLEMENTARITY OF ENTROPY CHANGES IN PHASE TRANSITIONS

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Abstract: Many agonists bind to receptors with large enthalpies of interaction, and it is proposed that this equates with a high degree of complementarity. The price paid is a large unfavourable entropy of binding, for which comparisons are drawn with analogous enthalpy/entropy compensations observed in the fusion of hydrocarbon crystals.

The boiling points of linear hydrocarbons increase smoothly in proportion to the increase in surface area, while branching of chains always results in a lowering of boiling point in proportion to the reduction in surface area. Melting points, however, vary irregularly with the degree of branching such that those molecules with a high degree of (near spherical) symmetry are often associated with higher melting points. The origin of this apparent anomaly between the *decrease* in hydrocarbon surface area and *increase* in melting temperature has frequently been explained, even in the most modern text books on organic chemistry[1,2] by misleading statements, for example, regarding ".....the general effect of molecular symmetry on intracrystalline forces. The more symmetrical a compound, the better it fits into a crystal lattice, and hence the higher the melting point."[1] Examination of the enthalpies of fusion within the C5 series of saturated hydrocarbons[3,4] reveals quite the opposite dependence of the melting temperature on the strength of van der Waals interactions in the crystal (measured by the enthalpy of fusion), to those quoted above.

C5-Hydrocarbons	T_m *(K)*	ΔH_f *(kJ mol⁻¹)*	ΔS_f *(J K⁻¹ mol⁻¹)*	$T\Delta S_f$ *(kJ mol⁻¹, 300K)*
n-pentane	143	8.4	59	17.6
2-methylbutane	113	5.1	45	13.5
2, 2-dimethylpropane	256	3.3	13	3.9
cyclopentane	179	0.6	3	1.0

Those molecules with high symmetry (for example, cyclopentane and 2, 2-dimethyl-propane) have small enthalpies of fusion (ΔH_f) but, most importantly, very small entropies of fusion (ΔS_f). Since the two are related at the melting temperature (T_m) by the expression: $\Delta H_f/\Delta S_f =$

T_m, it is evident that such large apparent stabilities (large T_m values) can arise when crystals, that are held together by weak intermolecular interactions, have very small entropies of fusion. This is the explanation offered by more authorititive sources[5]. However, the consequences for molecular recognition phenomena and ligand-receptor complementarity of enthalpy/entropy compensations in phase transitions do not appear to have been considered. The origin of such small entropy changes when crystals melt lies in the amount of residual motion present in the solid. Many spherically symmetrical molecules undergo solid-solid phase transitions such that entropies of vibrations in the crystal, just below the melting point, are similar to the entropies of translation and rotation found in the melt[6]. Conversely, molecules with large amplitude motions in the crystal form only weak van der Waals contacts with their nearest neighbours, enthalpies and entropies of fusion working in a compensatory manner. This is further illustrated by the data plotted in Figure 1 that show enthalpy versus entropy for the fusion of a large number of organic compounds (selected with few or zero internal rotors) of similar molecular weight that melt at a common temperature of 30°±10°C. The relationship $\Delta H_f = T_m \Delta S_f$ ensures that a linear correlation is obtained, but the data illustrate the wide range of enthalpy/entropy values that give rise to a common T_m. The more polar organic molecules are generally associated with larger enthalpies of fusion, indicative of stronger electrostatic interactions in the crystal, but pay the price by having much larger adverse entropies of crystallisation (c.f. complexation).

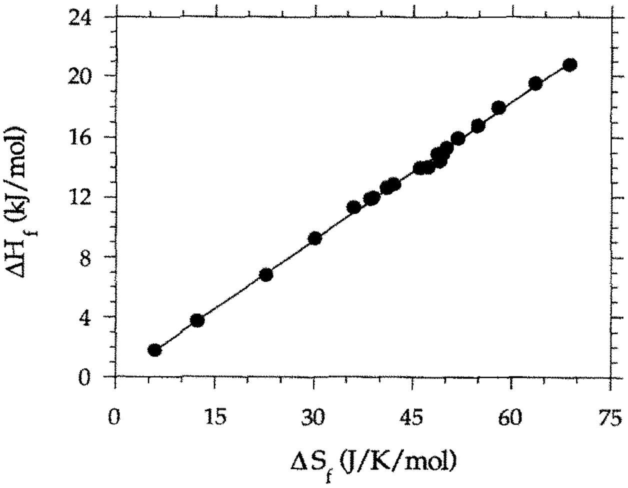

Figure 1: *Enthalpy versus entropy of fusion for organic molecules (RMM ≈ 100-300 g mol^{-1}) with melting temperatures of 30°±10°C.*

The compensatory nature of the enthalpy and entropy changes suggest a relationship between the enthalpy of interaction in the crystal and the "quality of fit" within the lattice. In the context of molecular recognition phenomema in biology, this "quality of fit" can be viewed as a measure of ligand-receptor complementarity[6]. Where the interaction has evolved under the influence of natural selection, we equate a large enthalpy of interaction with the capacity to elicit a biological response, but the price to be paid is a large negative entropy change because motions are severely restricted in the complex.

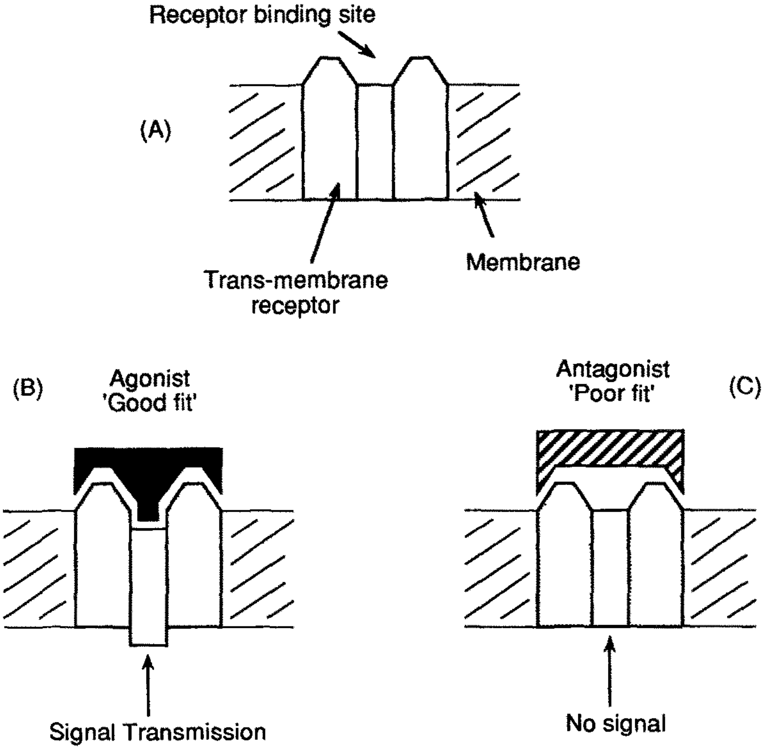

Figure 2: *Schematic representation of complementarity/response effects of agonist and antagonist binding to a common receptor site. (A) unmodified membrane-bound receptor, (B) agonist-bound receptor, (C) antagonist-bound receptor.*

Indeed, the binding of many agonists to receptor sites is found to be associated with an enthalpy-driven mechanism.[8,9] Although antagonists (man-made inhibitors) bind with comparable free energies (and hence binding constants) to the same receptor site,[8,9] they are, in the cases cited[8,9], bound only "loosely" by having much less negative enthalpies of interaction. The corollary is that greater residual motion in the complex compensates for the poorer complementarity by yielding much smaller unfavourable negative entropy changes on binding. While the antagonist is capable of blocking the receptor site, it is not capable of triggering a biological response, as illustrated schematically in Figure 2.

This model of the difference in the thermodynamics of agonist and antagonist binding seems quite compatible with the ubiquitous phenomenon of enthalpy/entropy compensation found in chemistry and biology.

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