Komplexe und die für ihre Verwertung beschriebenen Verfahren ergeben bereits jetzt eine reiche Quelle für die Quantifizierung intermolekularer Kräfte.

Stichworte: Korrespondenzen · Molekulare Erkennung · Wasserstoffbrücken · π-π-Wechselwirkungen

Eingegangen am 17. Dezember 1996 [C20016]

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Stellungnahme von Christopher A. Hunter*

Reference[1] describes a new method that we have developed for quantifying noncovalent interaction energies in a synthetic supramolecular system. The viability of the approach was demonstrated by measuring a weak aromatic interaction, and while the value obtained is not in itself particularly significant, the success of the methodology opens the way for the kind of systematic structure–activity studies that have not been possible before. With the exception of studies on simple functional group interactions like hydrogen bonding, the data on small molecule interactions are of limited utility, because the orientation of the interacting groups (often not known) changes from one complex to the next. Supramolecular systems can overcome this problem, but the thermodynamic analysis is complicated by the many different interactions which are present. The advantage of the zipper system is that *both* interacting groups can be modified easily without disturbing the central recognition motif. This allows us to use the double mutant cycles that have proved so powerful for studying functional group interactions in proteins. This approach not only factors out contributions from the other interactions that are present but also removes many potential sources of error such as restriction of rotation of the cyclohexyl–anilide bonds in **1**, **2**, and **3**. The utility of quantitative studies of weak intermolecular interactions is limited by the choice of the experimental system used, and we do not claim that the zippers are ideal in any absolute sense. There are limitations: we assume that the alkyl groups do not interact; the binding constants are small; entropy–enthalpy compensation is not accounted for in the analysis. However, the zippers do offer significant advantages over other systems in the literature.

The experimental binding constant for complex **D** (shown here as **6**) appears not to agree with the literature values for the magnitude of a hydrogen bond, but this is exactly what one should expect. The observed free energy of complexation is the sum of an enthalpic contribution, in this case from hydrogen bonds and aromatic interactions, and an entropic contribution due to loss of translational and rotational degrees of freedom on formation of the complex. We have not yet measured the magnitude of the entropy changes in this system, but it is clear that the free energy of complexation is not equal to the total enthalpy of hydrogen bonding. It will be substantially lower due to the large entropy change. There is no discrepancy here.

This paper reports our first attempt to measure a noncovalent interaction using this approach. We have not yet made many measurements, but in the systems we are currently studying, we are finding consistent results and useful structure–activity relationships. This work will be reported in due course and will answer the criticism about the number and range of interactions examined.

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