Experimental tests for non-covalent interactions in large molecules

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Abstract

In classical descriptions of molecular interactions, steric bulk repels. Yet careful experiments on simple model systems have revealed that two large, nonpolar substituents placed in close proximity can attract one another, stabilising the very arrangements that steric arguments would disfavour. This counterintuitive behaviour is a signature of London dispersion: the weak, attractive interaction arising from correlated fluctuations of electron density, which acts between all pairs of atoms in contact. Although each pairwise contribution is small — well below 1 kcal mol^{-1} — the interaction is strictly additive and scales steeply with molecular size. In molecules of 50–200 atoms, the cumulative dispersion energy can reach tens of kilocalories per mole, sufficient to determine conformational preferences, influence reaction barriers, and control stereoselectivity. London dispersion has accordingly become a recognised design element in modern organic and organometallic chemistry, yet its direct, quantitative measurement in large, chemically realistic molecules remains challenging. In solution, interactions with the solvent compensate 40–80% of the gas-phase dispersion energy, obscuring the intrinsic interaction. Isolating and measuring London dispersion therefore calls for the gas phase.

To this end, we have developed a series of gas-phase molecular torsion balances in which London dispersion is placed in direct, tunable competition with a well-defined reference interaction. The systems investigated are substituted pyridinium ions and proton-bound onium ions, electrosprayed into the gas phase and interrogated by a combination of complementary structural probes: cryogenic ion vibrational predissociation (CIVP) spectroscopy, infrared multiphoton dissociation (IRMPD) spectroscopy at a free-electron laser, and trapped ion mobility spectrometry (TIMS).[1,2,3] In each series, the size of the pendant alkyl substituents is varied systematically from hydrogen to methyl to tert-butyl, progressively increasing the dispersion contribution while keeping the molecular framework constant. The N–H stretching mode, whose frequency is exquisitely sensitive to the local non-covalent environment, serves as a diagnostic conformational reporter, complemented by collision cross sections as an independent structural observable.

The talk will present results obtained across three series of test systems of increasing complexity, illustrating how the interplay between London dispersion, electrostatics, and conformational flexibility can be disentangled experimentally, and what these measurements reveal about the reliability of widely used computational models for non-covalent interactions.

References

1. A. Tsybizova, L. Fritsche, V. Gorbachev, L. Miloglyadova, and P. Chen, “Cryogenic ion vibrational predissociation (CIVP) spectroscopy of a gas-phase molecular torsion balance to probe London dispersion forces in large molecules,” J. Chem. Phys. 151(23), 234304 (2019).

2. V. Gorbachev, A. Tsybizova, L. Miloglyadova, and P. Chen, “Increasing Complexity in a Conformer Space Step-by-Step: Weighing London Dispersion against Cation−π Interactions,” J. Am. Chem. Soc. 144(20), 9007–9022 (2022).

3. V. Gorbachev, A. Savoy, A. Tsybizova, R. Pollice, L. van Tetering, J. Martens, J. Oomens, G. Berden, and P. Chen, “Probing London Dispersion in Proton-Bound Onium Ions: Are Alkyl−Alkyl Steric Interactions Reliably Modeled?” J. Am. Chem. Soc. 147(11), 4308–4323 (2025).