

Conformations of Small Molecules

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While the role and importance of conformations and conformational analysis for understanding the functioning of biomolecules has been recognized long ago, the relevance of presence of multiple conformers (or even isomers) for molecules routinely encountered in organic and inorganic synthesis and analysis is often overlooked. Very small molecules consisting of a dozen of atoms may possess an obvious global minimum on the potential energy surface, easily found by following chemical intuition. On the contrary, somewhat larger molecules, which have become accessible to DFT methods during the last decade, can possess multiple local minima, and determining the lowest energy one by intuition alone can yield misleading results. Furthermore, depending on the barriers on interconversion pathways, solvent, reaction temperature, etc, the different geometries may represent either isomers, or conformers, the latter being in a chemical equilibrium and giving rise to a Boltzmann distribution of the various forms.

In this contribution, several examples are presented, where only a careful conformational analysis has made it possible to understand the particular chemical or physical phenomenon. The examples include:

- pK_a calculations of organic bases (bipiperidine and bismorpholine) [1]
- Tautomeric equilibria in substituted purinamines [2]
- Assignment of J -coupling constants in NMR spectra of bicyclooctanes [3]
- Interpretation of Vibrational Circular Dichroism spectra of chlorooxindoles [4]
- Complex formation between Ti^{4+} and cyclic diketones (unpublished)

In all these examples, a simplistic use of a single geometry, even if representative of the lowest point on the potential energy surface, would have led to an inaccurate or even incorrect interpretation of the experimental facts being studied. Consideration of the relative abundancies of the various conformers and isomers, however, led to a significantly improved explanation of the phenomenon at hand.

[1] Uudsemaa, M., Kanger, T., Lopp, M., Tamm, T. *Chem. Phys. Lett.*, 485:83-86, 2010

[2] Gundersen, L-L., Görbitz, C., Neier, L., Roggen, H., Tamm, T, *Theor. Chem. Acc*, 129:349-358, 2011

[3] Aav, R., Pehk, T., Tamp, S., Tamm, T., Kudrjašova, M., Parve, O., Lopp, M., *Magn. Reson. Chem.*, 49:76-82, 2011

[4] Noole, A., Ošeka, M., Pehk, T., Öeren, M., Järving, I., Elsegood, M., Malkov, A., Lopp, M., Kanger, T., *Adv. Synth. Catal.*, 355:829–835, 2013

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