

Insight into the Spontaneity of Hydrogen Bond Formation between Formic Acid and Phthalimide Derivatives

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INTRODUCTION

Phthalimide derivatives have been demonstrated to reduce serum cholesterol and serum triglycerides¹ and, as a result, had several of their possible derivatives synthesized with their hypolipidemic activities determined. This set of derivatives also comprise a convenient test set for the study of the multiple factors involved in the energetics of hydrogen bond formation.

Accordingly, we carried out quantum chemical calculations on the hydrogen-bonded complexes formed between a sample of phthalimide derivatives with formic acid (Fig. 1) with the intent of identifying the most important electronic and structural factors related to how their strength and spontaneity vary across the series.

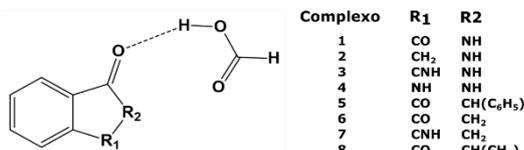


Figure 1. Hydrogen bonded complexes.

METHODS

All eight complexes considered are indicated in Fig. 1. All isolated molecules and possible interaction arrangements have been considered and had their geometries fully optimized at the DFT B3LYP/6-31++G(d,p) level, followed by frequency calculations to determine their Gibbs free energies of hydrogen bond formation using Gaussian 2009. Atomic ZDO charges of both neutral and positively charged isolated phthalimide derivatives to be used in the quantitative structure property relationship part of this work have been computed using RM1.

RESULTS AND DISCUSSION

Our intent with this study was to identify which electronic and structural factors could be playing a role in the differentiation between the hydrogen bond formation Gibbs free energy across the phthalimide derivative series considered.

The most important property explaining the different Gibbs free energy of formation across the series was found to be an electronic property: the difference in the charge at the carbonyl oxygen between the neutral and cationic forms of the phthalimide derivatives, computed by RM1. This is related to the easiness of electron donation by the hydrogen bond acceptor.

The next relevant property was the number of hydrogen atoms that can function as hydrogen bond donors. Finally, the last explaining property was the number of oxygen atoms that can function as hydrogen bond acceptors.

A kernel partial least squares regression, KPLS, of these three variables on the Gibbs free energy of hydrogen bond formation is shown in Fig. 2.

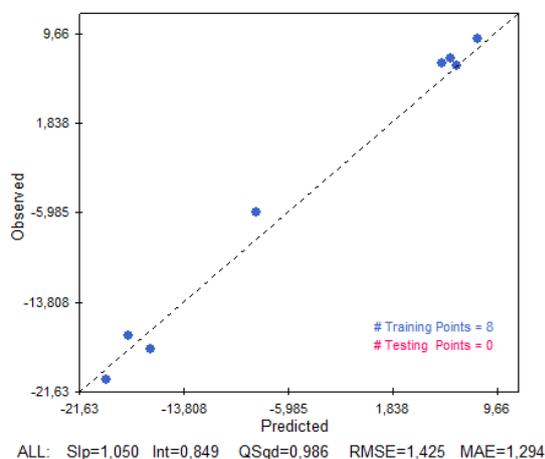


Figure 2. KPLS predicted and theoretical (Obs.) Gibbs free energies of hydrogen bond formation.

CONCLUSIONS

The easiness of electron donation by the hydrogen bond acceptor emerged as the most important property differentiating the spontaneity of hydrogen bond formation in these complexes.

ACKNOWLEDGMENTS

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¹Chapman, J. M., et al., J. Pharm. Sci. **73**, 10 (1984).