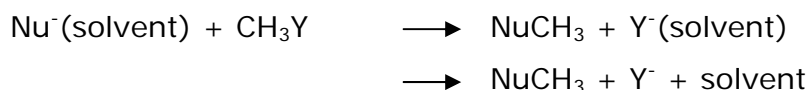


Dr. Gustavo Davico, along with collaborators at the Univ. of Colorado, and the Middle East Technical University (Ankara, Turkey), have recently reported some very exciting results on the well-known S_N2 reactions in the Journal of Physical Chemistry. (*J. Phys. Chem. A*, 108 (45), 9887-9891, 2004). This publication describes the *solvent kinetic isotope effect* on S_N2 reactions. The mechanism of this reaction is probably the most studied in organic chemistry, both in solution and the gas-phase. There is an extensive body of information on this reaction from sources as diverse as most entry-level organic chemistry textbooks to more recent gas-phase results pioneered by Chuck DePuy (Colorado) and John Brauman (Stanford). The energetics of this reaction are not only important from an organic chemistry perspective but also in biological chemistry and biochemistry since the S_N2 reaction is ubiquitous in many biological processes, where it is also called methyl transfer reaction. Previous work, pioneered by Dick Schowen (Kansas), had shown the use of deuteration in the substrate to evaluate transition state properties, such as transition state compression and enzymatic catalysis. Obviously, solvent effects and "solvation" by biological structures (like amino acid side chains in enzymes) often play a crucial role.

The accepted model for solvent kinetic isotope effects (the ratio between the reaction rate in the undeuterated and that in deuterated solvent), proposed by Swain and Bader in 1960, is based on the solvent-structure breaking in the first solvation shell since, in this class of reactions, the transition state has a less localized charge and therefore solvation is weaker than in reactants. Since there is less solvent-structure breaking in the transition state than at reactants, the model predicts an *inverse* kinetic isotope effect. (Kinetic isotope effects are called *normal* when the rate involving the undeuterated compound is faster than the rate for the deuterated compound, $k_H/k_D > 1$; and *inverse* when $k_H/k_D < 1$).

The results reported by Davico and his co-workers highlight the crucial role of the solvent in the reaction energetics. By using cluster anions, or microsolvated ions in the gas-phase, and observing these ions using unique

instrumentation, they were able to solvate the nucleophile one solvent at the time. For a monosolvated ion the reaction observed is:



They measured the reaction rate for the deuterated and undeuterated microsolvated nucleophiles and obtained strongly inverse solvent kinetic isotope effects, comparable to bulk solvation values; however, with only one solvent molecule there is no solvent structure! Clearly the standard model cannot explain these results since at least two solvent molecules are required to establish a solvent structure and obviously more to fill the first hydration shell. Earlier computational results from Truhlar (Minnesota) on microhydrated ions (with water as the solvent) using transition state theory suggested that the effect of water solvent should be re-evaluated and proposed that the inverse solvent kinetic isotope effect originates because a particular bond in the solvent that becomes stronger in the transition states. The bond, shown in blue in the figure below that illustrates the transition state in the reaction $\text{F}^-(\text{CH}_3\text{OH}) + \text{CH}_3\text{Cl}$, becomes stronger in the transition state as the charge is being transferred to the leaving group (chlorine) and the hydrogen bond between the solvent and the nucleophile becomes weaker. If this new model is correct then the solvent kinetic isotope effect (in particular the one obtained by deuterating the hydrogen atom involved in the hydrogen bond) should be dependent on the solvent acidity, which is what they observed experimentally and also report in the article published in the *Journal of Physical Chemistry*.

However, new theoretical results using transition state theory do not agree quantitatively with all the experiments reported and Davico and his colleagues are carrying out high level computations to further refine the new model.

Although there are several recent reports pointing out that there are more similarities than differences between gas phase and condensed phase reactions, it might be argued that microsolvation is not a good model for bulk

solvation. Extending these results by adding more than one solvent molecule should be very interesting and important in trying to close the gap between these two environments.

An intriguing result they also report in this article is the observation of both solvated and unsolvated leaving-group anions as reaction products, which can be interpreted as the solvent molecule being “boiled” out due to the reaction exothermicity, and is of crucial importance in understanding the reaction dynamics.

These results are not only important to comprehend the role of the solvent in organic reactions, but also in further understanding hydrogen bonding and more generally the effect of interactions of nucleophiles with hydrogen bond donors in methyl transfer reactions.

