REACTIVITY EXTRAPOLATION FROM SMALL TO LARGE MOLECULAR SYSTEMS VIA ISODESMIC REACTIONS FOR TRANSITION STATES (RESLIR)

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Introduction

Numerous applications of chemistry benefit from computational methods of exploring reactivity. Quantum chemistry based techniques of evaluating reaction energy barriers, however, encounter problems when large molecular systems are considered. A number of high-level quantum chemical methods are capable of providing accuracy in evaluating reaction barriers on the order of 1 – 3 kcal mol^{-1}, which is sufficient for many (although not all) practical applications. Unfortunately, these methods are rarely used for the computational treatment of practical systems as they are generally applicable only to relatively small molecules. The computational resources required to use these methods scale as N^7 (where N is the number of atoms in the molecular system considered), making their use impossible in most cases of practical interest. The N^7 scaling also means that, even with the fast pace of progress in the development of computer hardware, one cannot expect a major improvement of these size limitations within the observable future.

Here, a method of evaluating barriers of chemical reactions involving large molecules is presented. The method is based on the extrapolation of reactivity from small molecular systems (for which high-level quantum chemical calculations can be performed) to large ones via low level (and thus low computational cost) calculations. The notation RESLIR (abbreviation of "Reactivity Extrapolation from Small to Large molecular systems via the formalism of Isodesmic Reactions for transition states") is proposed for ease of reference. The RESLIR method is a further development of the technique of isodesmic reactions for transition states (IRTS),[1,2] which has been demonstrated to yield very high accuracy in predicting reactivity in two classes of atom abstraction reactions.

Method Description

Background (IRTS[1,2]) Isodesmic reactions,[3] i.e., (usually) fictitious reactions which conserve the types of chemical bonds and their numbers, are often used in computational thermochemistry (e.g., refs 4-9). Enthalpies of these reactions are usually obtained in quantum chemical calculations and it is expected that computational errors that are specific to a particular bond type will, to a large extent, cancel on both sides of the chemical equation. The IRTS method[1,2] applies the same formalism to transition states. For example, for any two reactions of the same class expressed via chemical equations

$$\text{Reactants}(1) \rightarrow (\text{TS}(1)^{\ddagger}) \rightarrow \text{Products}(1) \quad (1)$$

$$\text{Reactants}(2) \rightarrow (\text{TS}(2)^{\ddagger}) \rightarrow \text{Products}(2) \quad (2)$$

one can write a formal isodesmic reaction

$$\text{Reactants}(1) + \text{TS}(2)^{\ddagger} = \text{Reactants}(2) + \text{TS}(1)^{\ddagger} + \Delta\text{H}(\text{ISO}) \quad (3)$$

provided that the class of reactions is defined by the similarity of the chemical transformations taking place and the structures of the transition states ($\text{TS}(i)^{\ddagger}$ where i in the reaction number).

In the IRTS technique, first, the energy barrier E(Ref) for one of the reactions within the reaction class (a "reference" reaction) is evaluated on the basis of reliable experimental data on the temperature dependence of the reaction rate constant, k(T). Then, for all other reactions within the class, formal isodesmic reaction schemes of the type

$$\text{Reactants}(i) + \text{TS(Ref)}^{\ddagger} = \text{Reactants(Ref)} + \text{TS}(i)^{\ddagger} + \Delta\text{H}(\text{ISO}(i)) \quad (4)$$

are written and their 0 K enthalpies, $\Delta\text{H}(\text{ISO}(i))$, are obtained in quantum chemical calculations. Here, Reactants(Ref) and $\text{TS(Ref)}^{\ddagger}$ are the reactants and the transition state for the "reference" reaction and i is the reaction number. Finally, energy barriers for all cognate reactions are calculated using the values of E(Ref) and $\Delta\text{H}(\text{ISO}(i))$:

$$\text{E}(i) = \text{E(Ref)} + \Delta\text{H}(\text{ISO}(i)) \quad (\text{I})$$

The values of $\Delta\text{H}(\text{ISO}(i))$ are expected to be accurate due to cancellation of errors on both sides of the chemical equation (4); this accuracy is expected to propagate into the values of E(i). Note that for any two reactions within the class (reactions 1 and 2), the 0 K enthalpy of the isodesmic reaction (3) equals the difference in the energy barriers of these reactions. Thus, the primary postulation of the IRTS technique is equivalent to the assumption that, although a particular quantum chemical method may not yield accurate absolute values of energy barriers, differences between the energy barriers of individual reactions can be calculated with a high degree of accuracy for a series of reactions of the same type.

The RESLIR method The RESLIR method is based on the use of the IRTS technique to extrapolate reactivity from small to large molecular systems within the same class of reactions. Unlike the previous applications[1,2] of the IRTS technique, it does not rely on the existence of extensive experimental information on the kinetics of at least one reaction within the class. Instead, high-level predictive calculations are performed for the reference reaction, which is chosen in such a way as to include only small molecules.

The algorithm of the RESLIR method is as follows.

1. A class of reactions is defined by the similarity of the chemical transformations occurring and the structures of the transition states. This class includes reactions involving both small and large molecules.
2. Within this class, a "reference" reaction involving only molecules of small sizes is chosen.
3. Two quantum chemical methods of different levels are selected: a low-level (LL) method and a high-level (HL) method.
4. High-level quantum chemical calculations are performed for the "reference" reaction to evaluate its energy barrier.
5. For other reactions of interest within the same class, including reactions involving large molecules, isodesmic reaction schemes of the type given by equation 4 are designed. 0 K enthalpies of these reactions, $\Delta\text{H}(\text{ISO}(i))$, are computed at the low level of theory.
6. Finally, energy barriers of the reactions of interest are calculated using the relationship of equation I.

The notation RESLIR(HL|LL) is proposed to indicate the HL and the LL methods used within the RESLIR algorithm.

Evaluation of Method Performance

Diels-Alder Reactions The RESLIR method was applied to calculation of energy barriers for a series of eleven Diels-Alder reactions involving molecules of various sizes, ranging from C_6H_{10} to $C_{12}H_{16}O_3$ for reaction products and transition states. The simplest of these reactions, that of cycloaddition of ethylene to butadiene, was

used as the "reference" reaction. A large body of experimental information on the temperature dependences of the rate constants of these reactions in the gas phase exists on the literature (e.g., see ref 10 and references cited therein.). Moreover, it is known that the kinetics of Diels-Alder reactions in non-polar solvents is not influenced by solvent effects; the same values of the rate constants have been obtained for some of these reactions in the gas and in the liquid phases. Thus, it is possible to use both the liquid phase[11] and the gas phase[10] kinetic information to compare theory and experiment.

In this work, the "experimental" values of the reaction energy barriers were derived from the experimental data on the reaction rate constant dependences using transition state theory models based on the molecular structures and frequencies obtained in calculations using the same (low-level) quantum chemical method. The calculated energy barriers were obtained using the RESLIR technique with the QCISD(T)/aug-cc-pvtz(extrapolated)//QCISD/cc-pvdz method as the high-level quantum chemical method. Here the QCISD(T)/aug-cc-pvtz(extrapolated) energies were obtained in a basis set extrapolation scheme via the following formula:

$$\text{QCISD(T)/aug-cc-pvtz(extrapolated)} = \text{QCISD(T)/aug-cc-pvdz} + (\text{MP2/aug-cc-pvtz} - \text{MP2/aug-cc-pvdz}) \qquad \text{(II)}$$

For the low-level quantum chemical methods, the HF/6-311G(d)-level geometry optimization and energy calculation was used and, in addition, two different single-point-energy methods were used with the HF/6-311G(d)-level structures: BH&HLYP/cc-pvtz and MP2/6-311G(d,p).

For all three HL|LL combinations used, the application of the RESLIR algorithm resulted in significant improvement of the agreement between calculation and experiment compared with the results obtained at the LL methods alone. Figure 1 demonstrates the results obtained with LL= HF/6-311G(d). Here, the calculated values of the energy barriers are plotted as a function of those derived from the experimental data. The open symbols represent the barriers obtained at the LL level of quantum chemistry without the use of the RESLIR method. At this level, the barrier values are completely unrealistic. The filled symbols display the barriers obtained with the RESLIR method. As can be seen from the plot, application of the RESLIR method results in dramatic improvement of the agreement.

The average absolute deviations between calculations and experiment are 2.6, 2.5, and 3.1 kcal mol^{-1} for LL = HF/6-311G(d), LL = BH&HLYP/cc-pvtz//HF/6-311G(d), and LL = MP2/6-311G(d,p)//HF/6-311G(d), respectively. The maximum deviations are 7.2, 6.8, and 6.1 kcal mol^{-1}, respectively.

It should be noted that ideal agreement between the calculated barriers and those derived from the experimental rate data is not expected because of the finite accuracy of the determination of the "experimental" barrier values. The latter were derived from transition state theory fits to the experimental k(T) dependences. Since calculated preexponential factors, generally, do not provide perfect agreement with experiment, uncertainties in the preexponential factors propagate into the uncertainties in the derived values of the energy barrier. The "error limits" of the filled data points on the plot indicate the range of the expected uncertainties in the "experimental" energy barriers caused by the imperfect description of the preexponential factors. These "error limits" should be taken as pertaining not to individual data points but rather to the whole group of reactions, approximately indicating the range of uncertainty associated with the determination of the "experimental" reaction barrier values.

Other reactions Evaluation of the performance of the RESLIR method in other reactions, such as addition of radicals to double bonds, are currently underway.

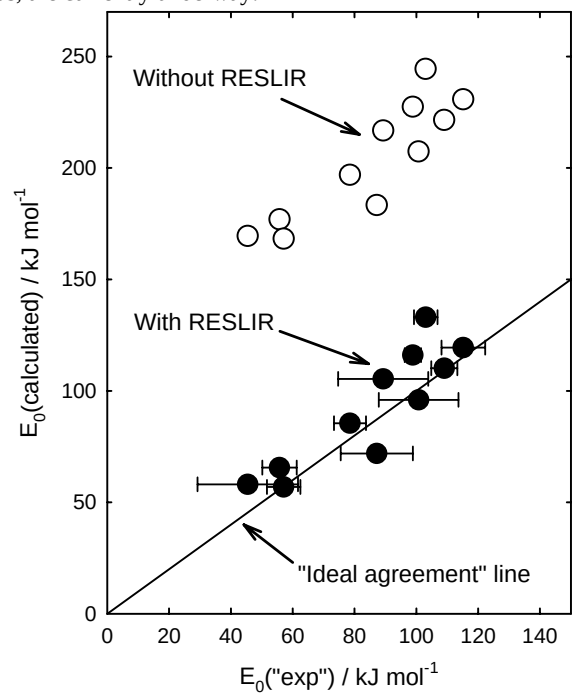

Figure 1. Calculated vs "experimental" values of the reaction energy barriers obtained for a series of Dials-Alder reactions with and without the RESLIR method. Open symbols, barriers obtained at the HF/6-311G(d) level. Filled symbols, barriers calculated using the RESLIR(QCISD(T)/aug-cc-pvtz(ex)//QCISD/cc-pvdz|HF/6-311G(d)) extrapolation method. Error bars for the "experimental" barrier values should be understood as indicating the range of uncertainty resulting from imperfect computational description of the preexponential factors for the group of reactions as a whole, as described in the text.

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