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Reactivity Extrapolation from Small to Large Molecular Systems via Isodesmic Reactions for Transition States

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A method for calculating potential energy barriers of chemical reactions involving large molecules is presented and validated through evaluation of its performance for two classes of reactions. 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 (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). Unlike the previous applications of the IRTS technique, it does not rely on the existence of extensive experimental information on the kinetics of at least one (reference) 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. Predictive performance of the method is evaluated for two classes of reactions: eleven Diels−Alder reactions and twenty reactions of the addition of CH_3 and CF_3 radicals to C═C double bonds.

I. Introduction

Numerous applications of chemistry benefit from computational methods of exploring reactivity. A large fraction of related studies concentrates on evaluation of reaction energy barriers. Quantum chemistry based techniques of calculating 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 ~4−10 kJ mol^{-1} (e.g., CCSD(T), QCISD(T), G2, G3, CBS-Q, see refs 1−8), which is sufficient for many (although certainly not all) practical applications. Unfortunately, these methods are rarely used for 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.

In the current work, 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 larger ones via low-level (and thus low computational cost) calculations. The notation RESLIR (Reactivity Extrapolation from Small to Large molecular systems via 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), which has been demonstrated to yield very high accuracy in predicting reactivity in three classes of atom abstraction reactions.[9,10]

The performance of the RESLIR method is evaluated in the current study via application to two sets of reactions belonging to different classes: eleven Diels−Alder reactions and twenty reactions of radical addition to C═C double bonds. Many of these reactions have been studied theoretically before (e.g., refs 11−17 and references therein). These studies, generally, are not discussed here as the current work is concerned, primarily, not with individual reactions but with the development of a computational technique and the assessment of its accuracy and predictive ability.

The article is organized as follows. The first section is an introduction. The description of the RESLIR method is given in section II. Evaluation of the method performance is described in section III. A discussion is presented in section IV.

II. Method Description

II.1. Background: The Technique of Isodesmic Reactions for Transition States (IRTS). Isodesmic reactions,[18] i.e., (usually) fictitious reactions that conserve the types of chemical bonds and their numbers, are often used in computational thermochemistry (e.g., refs 19−24). Enthalpies of these reactions are usually obtained in quantum chemical calculations and it is expected that computational errors (arising from lack of electron correlation and deficiencies in the basis sets) that are specific to a particular bond type will, to a large extent, cancel on both sides of the chemical equation. The method of Isodesmic Reactions for Transition States (IRTS)[9,10] applies the same formalism to transition states. For example, for any two reactions of the same class expressed via chemical equations

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

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

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one can write a formal isodesmic reaction

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

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). An example of a suitably designed isodesmic reaction involving transition states for reactions $\text{Cl} + \text{R}_1\text{H} \rightarrow (\text{Cl}\cdots\text{H}\cdots\text{R}_1^{\ddagger}) \rightarrow \text{HCl} + \text{R}_1$ and $\text{Cl} + \text{R}_2\text{H} \rightarrow (\text{Cl}\cdots\text{H}\cdots\text{R}_2^{\ddagger}) \rightarrow \text{HCl} + \text{R}_2$ is given by the following equation:

$$\text{R}_1\text{H} + \text{Cl}\cdots\text{H}\cdots\text{R}_2^{\ddagger} = \text{R}_2\text{H} + \text{Cl}\cdots\text{H}\cdots\text{R}_1^{\ddagger} (+ \Delta H(4)) \quad (4)$$

In the IRTS technique, first, the energy barrier $E(\text{Ref})$ 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

$$\text{Reactants}(i) + \text{TS(Ref)}^{\ddagger} = \text{Reactants(Ref)} + \text{TS}(i)^{\ddagger} + \Delta H(\text{ISO}(i)) \quad (5)$$

are written and their 0 K enthalpies, $\Delta H(\text{ISO}(i))$, 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 by using the values of $E(\text{Ref})$ and $\Delta H(\text{ISO}(i))$:

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

The values of $\Delta H(\text{ISO}(i))$ are expected to be accurate due to cancellation of errors on both sides of the chemical eq 5; 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 potential 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 class. Here, again, the class of reactions must be defined in such a way as to allow construction of isodesmic reaction schemes conserving the types of chemical bonds and their numbers (eqs 3 and 5).

The IRTS technique has been applied earlier[9,10] to three classes of reactions: abstraction of H by an H atom, abstraction of Cl by an H atom (from chloroalkanes), and abstraction of H by a Cl atom from halogenated methanes. These studies demonstrated that the IRTS approach yields very high accuracy in predicting reactivity. For example, average deviations between calculated and experimental rate constants for the seven H + chloroalkane reactions considered in ref 9 are only 17−24%, depending on the quantum chemical method used within the IRTS technique.

II.2. Description of 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[9,10] 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 potential 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 eq 5 are designed. 0 K enthalpies of these reactions, $\Delta H(\text{ISO}(i))$, are computed at the low level of theory.
6. Finally, potential energy barriers of the reactions of interest are calculated by using the relationship of eq I.

The notation RESLIR(HL|LL) is proposed to indicate the HL and the LL methods used within the RESLIR algorithm. Here, both the LL and the HL methods can include compound methods with different levels of theory and basis sets used for optimization of molecular structures and for single-point energy calculations, e.g., LL = MP2/6-311G(2d,2p)//HF/6-31G(d).

III. Evaluation of the RESLIR Method

III.1. Approaches to Evaluation and Reaction Sets Used. To evaluate the performance of the RESLIR technique, one can suggest two different approaches. In the first, *experiment-based approach*, energy barriers obtained with the RESLIR method can be compared with those derived from experimental data on the kinetics of reactions involving large molecules. In the second, *computations-based approach*, the results of the RESLIR calculations performed at the HL|LL combination of high- and low-level quantum chemical methods can be compared with the results obtained in the HL-level calculations performed for both small and large molecules. Both approaches were used in the current study (see below).

In the experiment-based approach to evaluation, one can distinguish two questions whose answers determine the degree of agreement: (1) How well does a particular high-level (HL) quantum chemical method describe the type of reactions considered and (2) how well can barrier calculations be extrapolated from small to large molecular systems by using low-level (LL) quantum chemical methods? The experiment-based approach cannot answer these individual questions but rather can demonstrate the overall success or failure of the technique. This means that in the case of a success (the experiment is well described by the calculations) both of these questions are answered positively but in the case of a failure disagreement can be caused by either an unsuitable HL method or an inaccurate LL extrapolation.

It should be noted that the substance of the RESLIR technique lies in the extrapolation from small to large systems. Thus, the second question is more relevant to the evaluation of the technique performance. The computations-based approach to evaluation answers the second question directly, i.e., it tests the extrapolating ability of the RESLIR technique. The most accurate of the HL quantum chemical techniques cannot be used

TABLE 1: Experimental Data Set of Diels−Alder Reactions Used for Experiment-Based Method Evaluation

reaction no.	diene	dienophile	E_{EXP}[a]/kJ mol^{-1}	T/K	refs
6	ethylene	1,3-butadiene	100.8 (12.9)	760−921	28
7	1,3-butadiene	1,3-butadiene	89.3 (14.6)	446−923	28,29
8	ethylene	cyclopentadiene	87.2 (11.7)	521−563	30
9	isoprene	acrolein	78.5 (5.2)	492−606	31
10[b]	isoprene	maleic anhydride	55.7 (5.6)	298−308	27
11[b]	2-*tert*-butyl-1,3-butadiene	maleic anhydride	45.4 (16.3)	288−298	27
12	cyclopentadiene	acrolein	57.1 (5.4)	351−483	31
13[c]	1,3-cyclohexadiene	propene	109.0 (4.2)	512−638	32
14[d]	1,3-cyclohexadiene	propene	115.2 (7.1)	512−638	32
15[e]	1,3-cyclohexadiene	1,3-cyclohexadiene	103.0 (3.8)	471−639	33
16[f]	1,3-cyclohexadiene	1,3-cyclohexadiene	98.9 (2.6)	471−639	33

[a] Energy barriers obtained in the transition state theory modeling of the experimental data. Evaluated uncertainty due to imperfect description of the preexponential factor is given in parentheses (see text). [b] Liquid-phase kinetic data. All other experiments were conducted in the gas phase. [c] Product is *endo*-5-methylbicyclo[2.2.2]oct-2-ene. [d] Product is *exo*-5-methylbicyclo[2.2.2]oct-2-ene. [e] Product is *exo*-dicyclohexadiene. [f] Product is *endo*-dicyclohexadiene.

in these computations-based tests because they are applicable only to small molecules. However, a compromise can be found between the performance of quantum chemical method/basis set combinations and their applicability to moderately large systems that would allow conducting a test of extrapolating ability.

In the current work, a series of Diels−Alder reactions was selected to be used in the experiment-based approach to method evaluation. Diels−Alder reactions proceed via molecular (nonradical) mechanisms (e.g., refs 15 and16 and references therein). The absence of radical-driven secondary chemistry enabled accurate experimental investigations of these reactions, most of which were performed between 1935 and 1975, before the advance of modern sensitive experimental methods of gas-phase chemical kinetics that switched the main focus of experimentalists' attention to reactions of free radicals. A large body of experimental information on the temperature dependences of the rate constants of Diels−Alder reactions in the gas phase exists in the literature (e.g., see ref 25 and references therein). Moreover, it is known that the kinetics of Diels−Alder reactions in nonpolar solvents is not influenced by solvent effects to any significant extent; the same values of the rate constants have been obtained for some of these reactions in the gas and in the liquid phases.[25,26] Thus, it is possible to use both the liquid phase (e.g., ref 27) and the gas phase[25] kinetic information to compare theory and experiment. Substituent effects result in significant variations in the potential energy barriers of Diels−Alder reactions. Gas-phase activation energies range from 62 to 126 kJ mol^{-1} ,[25] and some of the barriers obtained from the kinetics in the liquid phase[27] are even lower than 60 kJ mol^{-1}. This range provides sufficient opportunities for investigation of the ability of the RESLIR technique to accurately describe the influence of large substituent groups on reactivity. Details of the calculations and the results of the evaluation of the technique performance using the experiment-based approach are described below, in section III.2.

For the computations-based approach, a series of 20 reactions of addition of CH_3 and CF_3 radicals to C═C double bonds was selected. In this set of reactions, variations in the addition barriers range from 7 to 49 kJ mol^{-1} (obtained in HL calculations). Substituent groups used are $-F$, $-CH_3$, $-CF_3$, and $-C_6H_6$; sizes of the transition states considered range from three to eleven heavy (non-hydrogen) atoms. Details and results of these calculations are presented below, in section III.3.

III.2. Experiment-Based Evaluation: 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 (Table 1, reactions 6−16[27−33]). The simplest of these reactions, that of the cycloaddition of ethylene to butadiene, was used as the "reference" reaction:

$$C_2H_4 + CH_2CHCHCH_2 \rightarrow \textit{cyclo}\text{-}C_6H_{10} \qquad (6)$$

For reactions 6−16, energy barriers were calculated with the RESLIR technique with the QCISD(T)/aug-cc-pVTZ(extrapolated)//QCISD/cc-pVDZ[4,34] as the high-level (HL) quantum chemical method. Here the QCISD(T)/aug-cc-pVTZ(extrapolated) energies were obtained in a basis set extrapolation scheme via the following formula:

$$\begin{aligned}&\text{QCISD(T)/aug-cc-pVTZ(extrapolated)} = \\ &\qquad \text{QCISD(T)/aug-cc-pVDZ} + \\ &\qquad (\text{MP2/aug-cc-pVTZ} - \text{MP2/aug-cc-pVDZ}) \quad (\text{II})\end{aligned}$$

For the low-level (LL) calculations, two methods were used for geometry optimization: HF/6-311G(d) and the semiempirical PM3[35,36] method. In addition, four single-point energy methods were used with the optimized molecular structures: HF/6-311G(d), BH&HLYP/cc-pVTZ, BH&HLYP/6-311G(d), and MP2/6-311G(d,p). A version of the BH&HLYP[37,38] functional implemented in the Gaussian 98 program[39,40] was used (Gaussian 98 was used in all calculations) which, as described in the program manual, is different from that of ref 37.

Individual reactions from the selected set have been studied experimentally in refs 27−33 (see Table 1). Knowledge of energy barriers can be extracted from the experimental rate constant data only through modeling, e.g., by adjusting model parameters to reproduce the experimental data. In the current work, the "experimental" energy barriers were evaluated by fitting of the experimental temperature dependences of the reaction rate constants with transition state theory-based models created on the basis of quantum chemical calculations. Classical transition state theory[41] was used in calculations; tunneling corrections were introduced via the barrier width method.[42−45] The following algorithm was applied. First, transition state theory models were created for all reactions by using vibrational frequencies and molecular structures obtained in HF/6-311G(d) (LL) calculations. In addition, a model for the reference reaction was created on the basis of HL calculations. Second, preexponential factors A(HL) and A(LL) obtained with the HL and the LL models for the reference reaction were compared at the temperature of 600 K corresponding to the middle of the experimental temperature range for the whole reaction set and a preexponential correction factor $F_A = A(\text{HL})/A(\text{LL}) = 1.61$

TABLE 2: RESLIR[a] Energy Barriers[b] for Diels−Alder Reactions and Deviations from Experiment

	reaction no.[d]											deviations[e]	
LL[c]	6	7	8	9	10	11	12	13	14	15	16	av	max
HF/6-311G(d) optimization													
HF/6-311G(d)	96.0	105.4	71.9	85.5	65.6	58.1	56.9	110.1	119.4	133.0	116.1	10.8	30.0
MP2/6-311G(d,p)	96.0	89.9	68.5	75.1	50.3	38.2	45.4	83.8	92.7	86.4	73.2	12.9	25.7
BH&HLYP/6-311G(d)	96.0	103.5	81.0	83.8	65.9	55.9	64.8	110.5	118.6	129.2	114.9	9.6	26.2
BH&HLYP/cc-pVTZ	96.0	104.2	81.4	84.1	67.4	56.5	65.8	112.1	120.4	131.3	116.6	10.6	28.3
PM3 optimization													
HF/6-311G(d)	96.0	108.2	68.9	89.5	65.3	63.9	55.9	102.4	122.9	129.7	106.6	11.9	26.7
MP2/6-311G(d,p)	96.0	92.9	70.0	78.4	56.2	50.6	49.0	76.8	94.5	78.3	61.0	14.1	37.9
BH&HLYP/6-311G(d)	96.0	107.6	80.0	89.2	69.4	65.4	67.7	104.7	121.0	125.3	107.5	11.5	22.3
BH&HLYP/cc-pVTZ	96.0	108.1	81.0	89.1	70.5	65.4	69.4	107.2	122.9	128.1	110.2	12.1	25.1
“experimental” [f]	100.8	89.3	87.2	78.5	55.7	45.4	57.1	109.0	115.2	103.0	98.9	8.1[g]	16.3[g]

[a] With HL = QCISD(T)/aug-cc-pVTZ(extrapolated)//QCISD/cc-pVDZ|LL, see text. [b] Energy units are kJ mol^{-1}. Zero-point vibrational energies obtained by using the indicated methods for geometry optimization are included. [c] Low-level (LL) methods used. [d] Reaction numbering corresponds to that in Table 1. [e] Absolute deviations from the “experimental” barrier values: average (“av”) and maximum (“max”). [f] The “experimental” energy barriers were evaluated by fitting of the experimental temperature dependences of the reaction rate constants with transition state theory-based models (see text). [g] Average and maximum “error limits” for the “experimental” reaction barrier values estimated from the deviations of the calculated preexponential factors from the experimental ones (see text and Table 1).

was derived. Third, rate constants were calculated for all reactions by using the transition state theory models with the F_A correction applied. Finally, “experimental” energy barriers were derived by adjusting the barrier values to provide a best match between the experimental and the calculated rate constants over the experimental temperature intervals. The resultant values of the “experimental” energy barriers thus have the meaning of the barrier values needed to reproduce the experimental data (on average, over the given temperature range), using the HF/6-311G(d)-based preexponential factors with the F_A correction.

In an ideal case, if comprehensive experimental data existed for all reactions, more accurate values of energy barriers could be derived by fitting both the energy barriers and the preexponential factors of the model. However, most of the experimental data available for reactions 6−16 in Table 1 were obtained over very limited temperature ranges; as a result, the reported absolute values of rate constants are more accurate than the Arrhenius parameters derived from the temperature dependences. Nevertheless, deviations between the experimental and the calculated preexponential factors can be used as a group to derive an approximate range of uncertainty associated with the obtained set of the “experimental” energy barriers. Since calculated preexponential factors, generally, do not provide perfect agreement with experiment, errors in the preexponential factors propagate into errors in the derived values of the energy barriers. The corresponding barrier uncertainties can be approximately evaluated by dividing the calculated preexponential factors by the experimental ones and converting the resultant ratios into energies by using the van’t Hoff’s factor at average experimental temperatures. 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.

The “experimental” values of the energy barriers, estimated uncertainties, and the calculated RESLIR(HL|LL) barrier values for individual Diels−Alder reactions are given in Table 2. For all LL methods employed, application of the RESLIR algorithm resulted in significant improvement of the agreement between calculation and experiment compared with the results obtained with the LL methods alone. Figures 1−3 demonstrate the results obtained with LL = HF/6-311G(d), LL = MP2/6-311G(d,p)//HF/6-311G(d), and LL = BH&HLYP/cc-pVTZ//HF/6-311G(d). Here, the calculated values of the energy barriers are plotted as functions of those derived from the experimental data. The open symbols represent the barriers obtained at the LL levels of quantum chemistry without the use of the RESLIR method. At these levels, the barrier values are completely unrealistic. The filled symbols display the barriers obtained with the RESLIR method. As can be seen from the plots, application of the RESLIR method results in dramatic improvement of the agreement bringing the calculated energy barriers significantly closer to the “ideal agreement” lines.

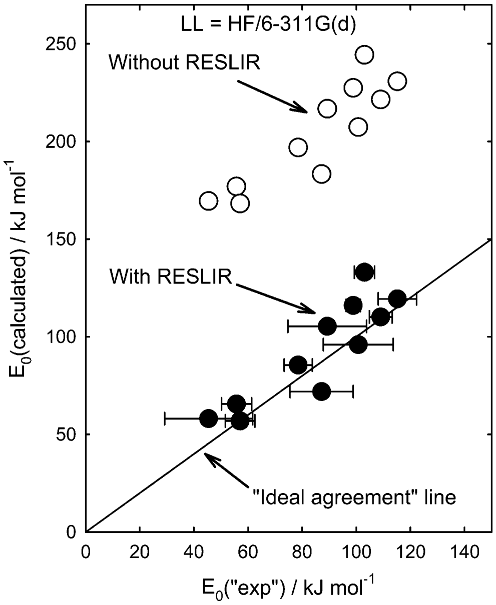


Figure 1. Calculated energy barriers for Diels−Alder reactions vs those derived from the experimental rate constant data (Table 1): open circles, barriers obtained in HF/6-311G(d) calculations without application of the RESLIR technique; filled circles, barriers obtained in RESLIR calculations using LL = HF/6-311G(d) and HL = QCISD(T)/aug-cc-pVTZ(extrapolated)//QCISD/cc-pVDZ.

A completely 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. As can be seen from the plots, the ranges of uncertainty associated with the determination of the “experimental” reaction barrier values (indicated as error bars in Figures 1−3, also see average and maximum values in Table 2) are comparable with the deviations of the RESLIR values from the “ideal agreement” lines indicating that a

TABLE 3: Reaction Set Used for Evaluation of the Extrapolative Ability of the RESLIR Technique

reaction no.	reactant 1	reactant 2	product	$\langle S^2 \rangle^a$
17	CH_3	C_2H_4	n-C_3H_7	0.99
18	CH_3	C_3H_6	*iso*-C_4H_9	1.00
19	CH_3	C_2H_3F	$CH_2-CHF-CH_3$	0.99
20	CH_3	$CH_2{=}CH-CF_3$	$CH_2-CH(CH_3)$-CF_3	1.02
21	CH_3	$CH_2{=}CH-C_6H_6$	$CH_2-CH(CH_3)-C_6H_6$	1.58
22	CH_3	$CH_2{=}CH-C_6H_6$	$CH_2(CH_3)-CH-C_6H_6$	1.61
23	CH_3	$CH_2{=}CF-C_6H_6$	$CH_2-CF(CH_3)-C_6H_6$	1.58
24	CH_3	$(CH_3)_2C{=}C(CH_3)_2$	$(CH_3)_3C-C(CH_3)_2$	1.02
25	CH_3	C_2F_4	$C(CH_3)F_2-CF_2$	1.03
26	CH_3	$CH_2{=}C(CF_3)_2$	$CH_2(CH_3)-C(CF_3)_2$	0.96
27	CH_3	$CH_2{=}C(CF_3)_2$	$CH_2-C(CH_3)(CF_3)_2$	1.03
28	CH_3	$CH_2{=}CH-CF_3$	$CH_2(CH_3)$-$CH-CF_3$	0.98
29	CH_3	$CH_2{=}CF_2$	$CH_2-CF_2-CH_3$	0.99
30	CH_3	$CHF{=}CF_2$	$CH_3-CHF-CF_2$	1.00
31	CH_3	$CHF{=}CF_2$	$CHF-CF_2-CH_3$	1.01
32	CH_3	$CH_2{=}CH-CH{=}CH_2$	$CH_3-CH_2-CH-CH{=}CH_2$	1.26
33	CH_3	$CH_2{=}C(CF_3)-CH{=}CH_2$	$CH_3-CH_2-C(CF_3)-CH{=}CH_2$	1.25
34	CF_3	C_2H_4	$CF_3-CH_2-CH_2$	0.97
35	CF_3	$CH_2{=}CH-CH{=}CH_2$	$CF_3-CH_2-CH-CH{=}CH_2$	1.23
36	CF_3	CH2=CF2	$CH_2-CF_2-CF_3$	0.98

[a] Expectation value of the $\hat{S}^2$ operator obtained for transition states, using UHF/cc-pVDZ wave functions with BH&HLYP/cc-pVDZ optimized molecular structures (see discussion of the effects of spin contamination in the text).

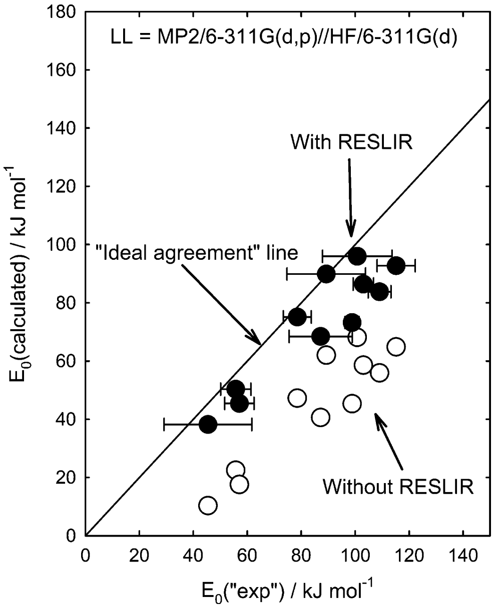


Figure 2. Calculated energy barriers for Diels–Alder reactions vs those derived from the experimental rate constant data (Table 1): open circles, barriers obtained in MP2/6-311G(d,p)//HF/6-311G(d) calculations without application of the RESLIR technique; filled circles, barriers obtained in RESLIR calculations using LL = MP2/6-311G(d,p)//HF/6-311G(d) and HL = QCISD(T)/aug-cc-pVTZ(extrapolated)//QCISD/cc-pVDZ.

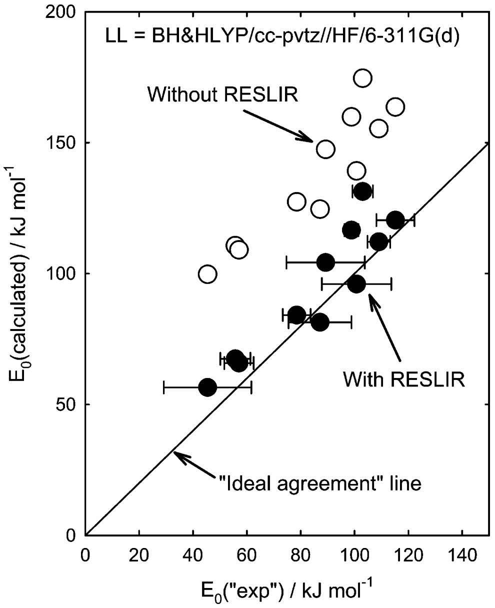


Figure 3. Calculated energy barriers for Diels–Alder reactions vs those derived from the experimental rate constant data (Table 1): open circles, barriers obtained in BH&HLYP/cc-pVTZ//HF/6-311G(d) calculations without application of the RESLIR technique; filled circles, barriers obtained in RESLIR calculations using LL = BH&HLYP/cc-pVTZ//HF/6-311G(d) and HL = QCISD(T)/aug-cc-pVTZ(extrapolated)//QCISD/cc-pVDZ.

significant part of these deviations can be attributed to imperfect computational description of the preexponential factors.

Table 2 also presents average and maximum absolute deviations between the energy barrier values obtained in RESLIR calculations and those derived from the analysis of experimental rate constant data as functions of the LL method used. It can be observed that, on average, use of the computationally efficient PM3 semiempirical method for molecular structure optimization with ab initio or DFT single-point energy calculations produced deviations comparable to those observed in the case of HF/6-311G(d) optimization, without a loss of accuracy in the overall result. Use of a smaller basis set (6-311G(d) vs cc-pVTZ) in BH&HLYP single-point energy calculations does not produce any significant differences. A complete set of results of the quantum chemical calculations performed for all reactions considered, including molecular structures, vibrational frequencies, electronic energies, and barrier widths, is presented in the Supporting Information (Table 3S).

III.3. Computations-Based Evaluation: Radical Addition to C═C Double Bonds. The set of 20 reactions of CH_3 and CF_3 addition to C═C double bonds used in the computations-based evaluation of the extrapolative ability of the RESLIR technique is presented in Table 3. Here, reaction barriers resulting from RESLIR calculations were compared with those obtained in the HL-level calculations performed for all reactions. The high-level (HL) method used is a combination of the CCSD(T)$^{1-3}$ method for single-point energy calculation with

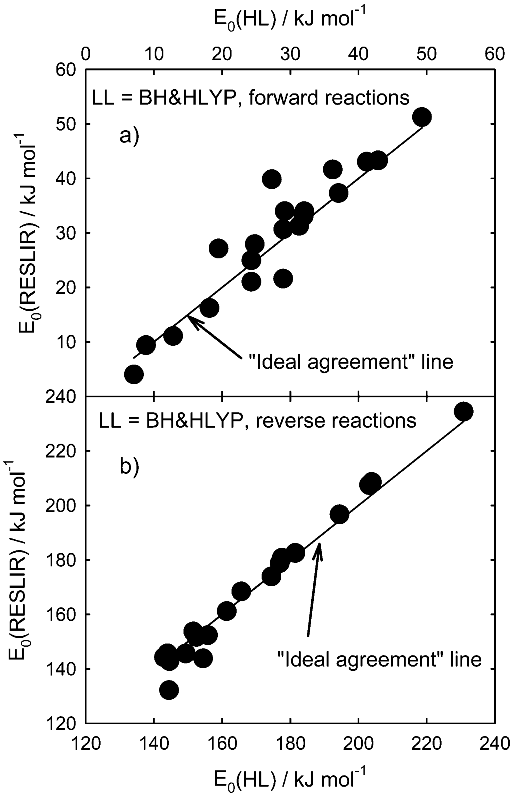


Figure 4. Energy barriers obtained in RESLIR calculation using LL = BH&HLYP and HL = CCSD(T)//BH&HLYP (all with the cc-pVDZ basis set) vs those obtained in HL (high-level) calculations for the reaction set of Table 3. Data are presented for the forward (a) and the reverse reactions (b).

the BH&HLYP[37,38] density functional method (version implemented in GAUSSIAN[39]) for optimization of molecular structures, both used with the cc-pVDZ[34] basis set (HL= CCSD(T)/cc-pVDZ//BH&HLYP/cc-pVDZ).

A variety of LL methods was employed. Three methods (BH&HLYP, HF, and PM3) were used for optimization of molecular structures and, with each of them, single-point energy calculations were performed with HF, MP2,[46] spin-projected PMP2,[47] BH&HLYP,[37−39] and B3LYP[48,49] methods. The same cc-pVDZ basis set was used for all ab initio and density functional calculations. Barriers for both the forward (addition) and the reverse (radical dissociation) reactions were considered. Restricted methods were used for closed-shell structures and unrestricted methods were used for radicals and transition states.

Figure 4 displays the results obtained for LL = BH&HLYP/cc-pVDZ. The barriers obtained in RESLIR calculations demonstrate a good agreement with the HL values: data points are clustered around the “ideal agreement” line with the average absolute deviation of 3.1 kJ mol^{-1} and a maximum absolute deviation of 12.6 kJ mol^{-1} (3.1 and 12.2 kJ mol^{-1} for the reverse reactions). The second LL DFT method used within the RESLIR approach, LL = B3LYP//BH&HLYP, produced a similarly good agreement with the HL barrier values, with average/maximum absolute deviations of 3.3/13.5 and 5.1/16.2 kJ mol^{-1} for the forward and the reverse reactions, respectively. It can be noted that the low-level barriers obtained in the BH&HLYP calculations (without RESLIR) yielded a fortuitously good agreement with the HL barriers, with the systematic corrections of the RESLIR technique, ΔH(ISO) (eq I), of only 2.8 and −6.2 kJ mol^{-1} for the forward and the reverse reactions, respectively; use of B3LYP energies, however, resulted in larger systematic corrections: 11.2 and 10.9 kJ mol^{-1}.

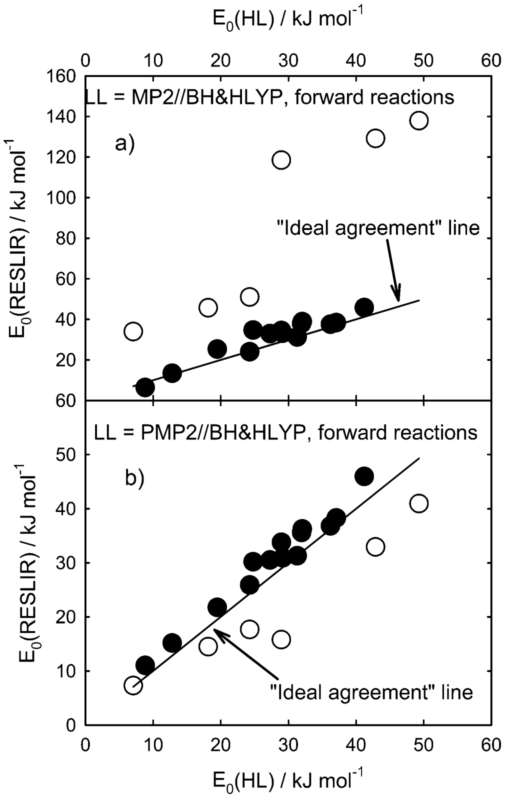


Figure 5. Energy barriers obtained in RESLIR calculations using (a) LL = MP2//BH&HLYP and (b) LL = PMP2//BH&HLYP both with HL = CCSD(T)//BH&HLYP vs those obtained in HL (high-level) calculations for the reaction set of Table 3. Open circles correspond to six reactions (21−23, 32, 33, and 35) significantly affected by spin contamination in the transition states.

The results obtained with HF and MP2 based LL methods present a somewhat different pattern. Figure 5a displays the results obtained with LL = MP2//BH&HLYP. As one can see from the plot, most of the data points are clustered around the “ideal agreement” line; however, six points corresponding to reactions 21−23, 32, 33, and 35 (open circles) lie very far from the line, representing completely unrealistic barrier values. These six reactions are characterized by significant spin contamination[47,50] in the transition states: the expectation values of the $\hat{S}^2$ operator are between 1.23 and 1.61 for all of them, as compared to 0.96−1.03 for the rest of the reactions considered. Annihilation of the largest spin contaminant improves the spin value for all other reactions ($\langle S^2\rangle = 0.76$ after annihilation) but not for these six reactions ($\langle S^2\rangle = 0.87-1.58$ after annihilation). Application of the spin projection method of Schlegel[47] improves the agreement considerably but not completely. Figure 5b displays the RESLIR barrier values obtained for the addition reactions with LL = PMP2//BH&HLYP vs those resulting from the HL calculations. Here, the average/maximum deviations (4.0/13.1 and 3.0/12.3 kJ mol^{-1} for the forward and the reverse reactions, respectively) become comparable with those obtained in the LL = BH&HLYP case (unaffected by spin contamination) but the most outlying points are those corresponding to the transition states with large spin contamination. These results lead to the conclusion that barriers for reactions significantly affected by spin contamination should not be calculated with HF and MP2 based LL methods. DFT based LL methods, however, present a viable alternative for such reactions.

If the six reactions with large spin contamination are removed from the set, the remaining 14 reactions demonstrate a very good agreement between the RESLIR calculations with LL =

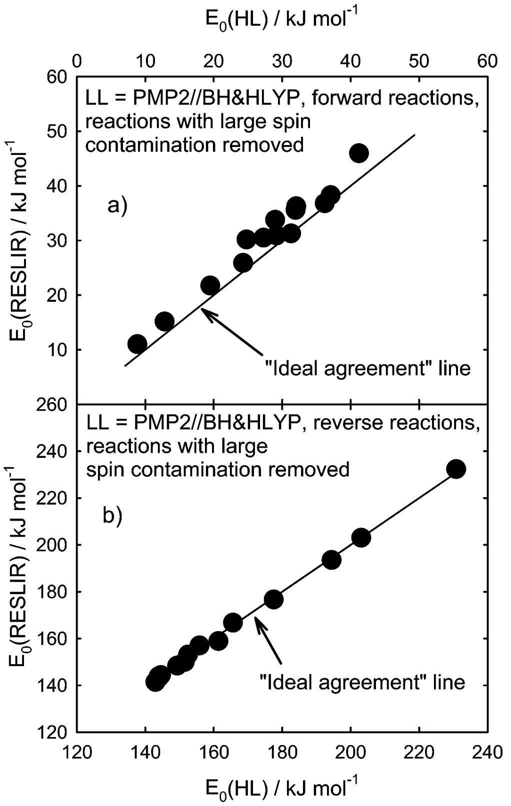


Figure 6. Energy barriers obtained in RESLIR calculations using LL = PMP2//BH&HLYP and HL = CCSD(T)//BH&HLYP (all with the cc-pVDZ basis set) vs those obtained in HL (high-level) calculations for the reaction set of Table 3 with six reactions (21−23, 32, 33, and 35) significantly affected by spin contamination removed. Data are presented for the forward (a) and the reverse reactions (b).

TABLE 4: Average and Maximum Deviations from Ideal Agreement Lines Obtained in the Test of the Extrapolative Ability of the RESLIR Technique with Use of the Reaction Set of Table 3

	deviations (forward/reverse)[b]					
	BH&HLYP opt.[c]		HF opt.[c]		PM3 opt.[c]	
LL[a]	av	max	av	max	av	max
HF[d]	5.2/7.9	16.0/25.2	6.0/6.7	19.0/23.6	7.9/6.7	22.9/17.8
MP2[d]	3.9/3.1	9.9/8.3	8.8/6.1	27.7/28.2	7.9/11.1	19.0/53.8
PMP2[d]	2.7/0.9	5.4/2.4	6.1/2.7	15.4/13.4	5.0/7.8	13.9/27.7
BH&HLYP	3.1/3.1	12.6/12.2	5.4/4.6	19.0/17.2	5.2/6.1	20.9/21.9
B3LYP	3.3/5.1	13.5/16.2	5.6/4.6	19.6/15.9	5.3/8.7	22.6/29.6

[a] The components of low-level (LL) methods used for single-point energy calculation. Methods used for optimization of molecular structures are indicated in the column titles. The cc-pVDZ basis set was used in all ab initio and DFT calculations. [b] Average (av) and maximum (max) absolute deviations are given for forward and reverse reactions in units of kJ mol^{-1}. [c] Methods used for optimization of molecular structures within the LL methods. The cc-pVDZ basis set was used in all ab initio and DFT calculations. [d] Six reactions with large spin contamination in the transition states were removed from the reaction set for HF, MP2, and PMP2 single-point calculations.

MP2 (Figure 5a, closed circles) and LL = PMP2 (Figure 6). The average/maximum deviations for the forward and the reverse reactions are 3.9/9.9 and 3.1/8.3 kJ mol^{-1} for LL = MP2 and 2.7/5.4 and 0.9/2.4 kJ mol^{-1} for LL = PMP2, respectively.

Table 4 presents average and maximum deviations obtained with the various LL methods used. The six reactions (21−23, 32, 33, and 35) with the large spin contamination in the transition states were removed from the set for the LL methods that used HF, MP2, and PMP2 single-point energy calculations but not for DFT based LL methods. As can be seen from the data in the table, the RESLIR method provides, generally, good extrapolation of barrier values. The deviations observed depend on the LL method used, with the most accurate extrapolation given by the LL = PMP2//BH&HLYP combination (average/maximum deviations of 2.7/5.4 and 0.9/2.4 kJ mol^{-1} for the forward and the reverse reactions, respectively). For all LL methods that include electron correlation (i.e., methods beyond HF) that used the same molecular structures as the HL method, average deviations are better than 4 kJ mol^{-1} although maximum deviations of up to 16 kJ mol^{-1} are observed. Use of different methods for structure optimization results in lower accuracy, with, generally, PM3 based structure optimization yielding larger deviations compared to HF optimization. A detailed set of results obtained in quantum chemical calculations for all reactions considered, including electronic energies and reaction barriers, is presented in the Supporting Information (Tables 1S, 2S, and 4S).

IV. Discussion

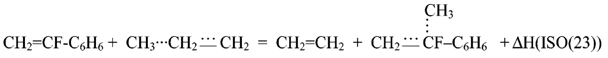
The RESLIR technique described in the current work has certain methodological similarities to the hybrid energy methods such as ONIOM and QM/MM (e.g., refs 13, 14, 51−59). These methods combine different levels of theory in one calculation: a high level of theory is used to describe a small region where chemical transformations take place and low-level calculations are performed for the larger remaining part of the chemical system. The similarity with RESLIR is in the use of high-level quantum chemical methods to describe the chemical transformation (bonds that are being formed or broken) and lower level methods to include the influence of the remaining parts of the molecular system involved. The distinguishing feature of the RESLIR technique is the reliance on the use of isodesmic reactions for transition states. As a result, it takes advantage of the cancellation of bond-specific computational errors, which is expected to considerably improve the accuracy in calculation of reaction energy barriers. At the same time, compared to the ONIOM and QM/MM method, the RESLIR technique has intrinsic limitations of applicability: it can only be used to compute potential energy barriers for reactions where covalent bonds are formed and broken.

Although the formalism of isodesmic reactions[18] is widely used for evaluation of reaction enthalpies and heats of formation of chemical species (e.g., refs 19−24), it has not seen extensive application in assessing the properties of transition states. The isodesmic reaction formalism is sometimes applied for estimation of reaction barriers (in the form of comparison between energy barriers of similar reactions, e.g., ref 60), and the term “isodesmic reaction” has been applied to such calculations in at least one instance.[61] Nevertheless, no systematic studies evaluating the performance of the technique of isodesmic reactions for transition states (IRTS) have been reported in the literature, with the exception of our two recent studies where the IRTS technique was described and validated.[9,10]

The method that is closest to the RESLIR technique is that of the Reaction Class transition state theory (RC-TST) developed by Truong.[60] RC-TST is a technique for rapid estimation of thermal rate constants for large numbers of similar reactions. Rates of a given reaction in a class are estimated relative to those of a “principal reaction” of the same class by using computed differences in the energy barriers. The technique (developed for the purpose of rapid semiautomatic generation of complex kinetic mechanisms) is based on the concept that, within a particular class of reactions involving the same reactive moiety, all elementary reactions have similar potential energy surfaces along the reaction coordinate. The ratio of the rate constant of a given reaction to that of the "principal reaction" is represented as a product of factors due to tunneling, partition functions, and potential energy. The factors (ratios) representing tunneling and partition functions are taken as unity and those due to energy barriers are evaluated in ab initio calculations. It was also mentioned by the author of ref 60 that differences between energy barriers for reactions within the class can be predicted at a relatively low level of theory. The IRTS[9,10] formalism provides an explanation and support for this previously known (largely, from isolated individual studies) but not systematically evaluated and thus seldom used ability of low-level quantum chemical theory to provide accurate differences between energy barriers of similar reactions.

The evaluation of the RESLIR method of extrapolation of reactivity (potential energy barriers) from small to large molecular systems via the method of isodesmic reactions for transition states performed in the current study demonstrates the validity of this approach. The accuracy in determination of energy barriers achieved by using low-level quantum chemical calculations to extrapolate the high-level results for reference reactions to reactions involving larger species is clearly better than that obtained if low-level calculations alone are used. Tests of the extrapolative ability of the method performed for a series of reactions of radical addition to C═C double bonds demonstrate that deviations from ideal agreement depend on the quantum chemical method used. As can be expected, the method fails for transition states with large spin contamination if LL methods based on HF wave function are used; density functional LL methods, however, can still be used for such reactions. One can suggest that, for the benefit of practical use of the RESLIR technique, further quantitative evaluation of its performance for a variety of reaction types and LL methods should be performed to provide ranges of uncertainties associated with particular reaction type/LL method combinations.

When the formalism of isodesmic reactions is used in computational thermochemistry, the results usually display some variation depending on the choice of isodesmic schemes, a choice that is not unique. To evaluate the heat of formation of a particular species, one can design a large number of different isodesmic reactions. Generally, the more similarity can be found in the chemical structures on the two sides of the isodesmic chemical equation, the more effective is the cancellation of errors in energy. For example, homodesmotic reactions (reactions that preserve not only the types and numbers of chemical bonds but also the states of C hybridization and the functional groups) are expected to give better accuracy than isodesmic reactions that are not homodesmotic.[62] The isodesmic reactions used in the current work have significant degrees of similarity between the right- and the left-hand sides. For example, the isodesmic reaction scheme (see chemical eq 5) for the transition state of reaction 23 conserves the C hybridization states and a number of functional groups ($═CH_2$, $-C_6H_6$). At the same time, it does not satisfy the requirement for homodesmotic reactions: e.g., instead of the $\overset{\cdots}{-}CH_2$ group with a partially broken double bond, the right-hand side of the equation has the $\overset{\cdots}{-}CF-C_6H_6$ group.



$$\mathrm{CH_2{=}CF{-}C_6H_6 + CH_3{\cdots}CH_2\overset{\cdots}{—}CH_2 = CH_2{=}CH_2 + CH_2\overset{\cdots}{—}\overset{\overset{\displaystyle CH_3}{\vdots}}{C}F{-}C_6H_6} + \Delta H(\mathrm{ISO}(23)) \qquad (37)$$

One can suggest as a recommendation for practical use of the RESLIR technique that the "reference" reaction should be selected for a particular series of similar reactions on the basis of two criteria: (1) the size of the molecular system involved must be sufficiently small so that high-level calculations can be performed and (2) the corresponding isodesmic reactions (see chemical eqs 5 and 37) have as much similarity as possible between the left- and the right-hand sides in terms of C hybridization states and functional groups. One potentially interesting issue worth further study is whether selecting the "reference" reactions based on similarities between the lengths and angles of the bonds that are being formed or broken in the transition states would provide an improvement of the overall accuracy in energy calculations.

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Supporting Information Available: Detailed results of the quantum chemical calculations: optimized molecular structures, electronic energies, reaction barriers, vibrational frequencies, moments of inertia, and barrier widths associated with individual transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

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