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Adiabatic connection method for $X^- + RX$ nucleophilic substitution reactions (X = F, Cl)

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ABSTRACT: A modified Perdew–Wang one-parameter hybrid density functional (*m*PW1N) was developed for nucleophilic substitution reactions by optimizing the fraction of exact exchange in *v*PW1PW91/6–31+G(d). Activation energies for 20 identity nucleophilic substitution and alkyl halide heterolysis reactions involving fluorine and chlorine were compared to values computed at the MCG3//MC-QCISD level to arrive at an optimal value of 40.6% HF exchange in *m*PW1N. This choice also leads to improved transition-state geometries over the training set. Results from *m*PW1N are compared with those from other common DFT methods, and some sources of error are explored. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: density functional theory; chloride; methyl chloride; S_N2 reaction; S_N2' reaction; electron correlation; Hartree–Fock exchange; activation energy; barrier height; parameterization

INTRODUCTION

Nucleophilic substitutions taking place at aliphatic and allylic positions are typical reactions found in many multistep organic and biological transformations.[1] As such, many researchers have applied high levels of molecular orbital (MO) theory to characterize the stationary points and thermochemistries associated with paradigmatic examples of these reactions, such as chloride/methyl chloride, chloride/allyl chloride, etc.[2–15] Accurate computation of activation and reaction free energies typically requires taking account of electron correlation using very computationally demanding post-Hartree–Fock methods. These methods are made still more demanding in systems having a net negative charge insofar as large basis sets including diffuse functions are essential for computational accuracy.

Further complicating matters, it is well known that solvation effects on reaction coordinates for nucleophilic substitution can be very large, particularly when the system is charged or when reactants and products are characterized by significantly different degrees of charge separation (as in the Menschutkin reaction of neutral amines with alkyl halides, for instance).[16,17] However, while many computational studies of solvation effects on simple nucleophilic substitution reactions have appeared,[18–27] the self-consistent coupling of post-Hartree–Fock electronic structure methods with solvation models remains a challenging proposition, and the computational cost involved effectively limits such applications to fairly small systems.[25]

In this case, density functional theory[28,29] (DFT) might be expected to be an ideal alternative to MO theory because DFT includes electron correlation directly into its self-consistent field (SCF) formalism. This has the double advantage of offering reduced scaling of computational cost as a function of system size in the gas phase while at the same time permitting use of simple self-consistent reaction field (SCRF) formalisms[25] to account for solvation effects. However, modern DFT functionals have uniformly been found to underestimate barrier heights for nucleophilic substitution reactions, and to do so by surprisingly large margins.[9,11,30–32]

In this paper, we report the optimization of a hybrid density functional [i.e. one incorporating some fraction of exact Hartree–Fock (HF) exchange, sometimes called an adiabatic connection method (ACM)] over a training set of X^-/RX nucleophilic substitution reactions and RX heterolysis reactions where X = F and Cl and R = methyl, ethyl, isopropyl and allyl (Fig. 1). The optimized functional, which we name *m*PW1N, predicts activation and reaction energies over this set that are in reasonably good agreement with experiment or, where experiment is not available, with very high levels of post-HF theory. Further improved agreement can be had by using different amounts of HF exchange for different subgroups of the reactions in the training set, although the subgroups are small enough that the exact values of HF exchange used in those instances might be subject to significant

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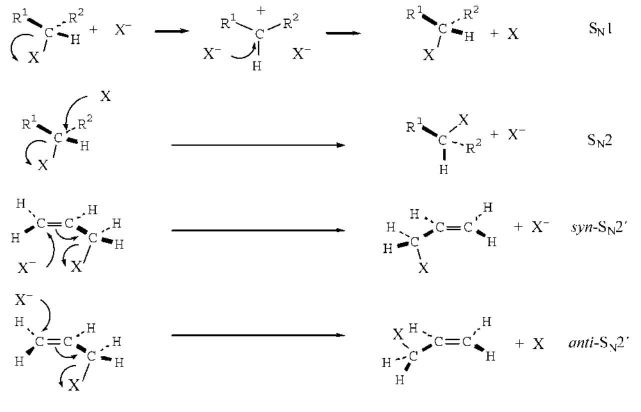


Figure 1. Nucleophilic substitution training set, composed of 20 reactions where R^1 = H, CH_3, R^2 = H, CH_3 and X = F, Cl

variation if reoptimization were to be undertaken over larger data sets.

COMPUTATIONAL METHODS

Density functional methods

Two density functional methods *not* incorporating HF exchange were examined, namely the combination of the gradient-corrected exchange and correlation functionals of Becke[33] and Lee, Yang and Parr,[34] respectively (BLYP), and the combination of the gradient-corrected exchange[35] and correlation[36] functionals of Perdew and co-workers, as modified by Adamo and Barone[31] (*m*PWPW91). In addition, a number of adiabatic connection methods were surveyed. ACM functionals mix some exact HF exchange into the overall DFT energy expression.[37] When the BLYP functional serves as the DFT base, the ACM exchange correlation energy is expressed as

$$E_{\mathrm{xc}}^{\mathrm{ACM}} = (1-a)E_{\mathrm{x}}^{\mathrm{LSDA}} + aE_{\mathrm{x}}^{\mathrm{HF}} + b\Delta E_{\mathrm{x}}^{\mathrm{B}} + (1-c)E_{\mathrm{c}}^{\mathrm{LSDA}} + cE_{\mathrm{c}}^{\mathrm{LYP}} \quad (1)$$

where the superscript LSDA refers to the local spin density approximation,[28,29] subscripts x and c refer to exchange and correlation, respectively, and *a, b* and *c* are empirical constants. In the case of the method called BH&HLYP, $a = 0.5$, $b = 0.5$ and $c = 1.0$,[38,39] Whereas for the method called B3LYP, $a = 0.20$, $b = 0.72$ and $c = 0.81$.[40]

A three parameter ACM called B3PW91 combines the Becke exchange functional[33] with the PW91 correlation functional[36] according to

$$E_{\mathrm{xc}}^{\mathrm{B3PW91}} = (1-a)E_{\mathrm{x}}^{\mathrm{LSDA}} + aE_{\mathrm{x}}^{\mathrm{HF}} + b\Delta E_{\mathrm{x}}^{\mathrm{B}} + E_{\mathrm{c}}^{\mathrm{LSDA}} + c\Delta E_{\mathrm{c}}^{\mathrm{PW91}} \quad (2)$$

where *a, b* and *c* have the same values as those listed above for B3LYP.

Finally, ACM methods based on the *m*PWPW91 functional have also been examined. In this case, only a single parameter is involved according to

$$E_{\mathrm{xc}}^{v\mathrm{PW1PW91}} = (1-a)\left(E_{\mathrm{x}}^{\mathrm{LSDA}} + \Delta E_{\mathrm{x}}^{m\mathrm{PW}}\right) + aE_{\mathrm{x}}^{\mathrm{HF}} + E_{\mathrm{c}}^{\mathrm{LSDA}} + \Delta E_{\mathrm{c}}^{\mathrm{PW91}} \quad (3)$$

For purposes of clarity, we will use the acronym *v*PW1PW91 to imply the use of Eqn. (3) with *any* variable amount of Hartree–Fock exchange, i.e. a specification of the value of *a* must be made for a *v*PW1PW91 functional to be fully defined. Specific functionals that *have* been previously so defined are identified by their own acronym, e.g. *m*PW1PW91,[31] where $a = 0.25$, MPW1K,[41] where $a = 0.428$, and *m*PW1N (as optimized here), where $a = 0.406$.

DFT calculations involved full optimization of all stationary points using the 6–31+G(d) basis set.[42] Stationary points were verified as local minima or transition-state structures based on analytical frequency calculations. These calculations were also used to compute thermal enthalpy contributions using the standard ideal-gas, rigid-rotor, harmonic-oscillator assumption (for monatomic ions, of course, only translational thermal contributions need to be included).[29]

Post-HF calculations

Multi-coefficient correlated *ab initio* calculations were also carried out for the 20 nucleophilic substitution reactions in the training set. Stationary points were optimized at the level of multi-coefficient quadratic configuration interaction with single and double excitations (MC-QCISD).[43] Single-point energy calculations were then carried out at the multi-coefficient Gaussian-3 (MCG3)[44,45] level of theory, which has been demonstrated to predict heats of formation over large sets of molecules to a typical accuracy of 1 kcal mol^{-1} (1 kcal = 4.184 kJ).[46]

Software

MO and DFT calculations were carried out with the Gaussian 98 program suite.[39] Multi-coefficient calculations employed the MULTILEVEL code.[47]

RESULTS AND DISCUSSION

Choice of standard data

Ideally, theoretical models involving parameters should always be fitted to (trustworthy) experimental data. In the case of nucleophilic substitution reactions, however,

Table 1. Computed and experimental enthalpies (kcal mol^{-1}) at 298 K for various reactions comprising the nucleophilic substitution training set

Reaction	Quantity	Predicted[a]	Experiment[b]
$CH_3F \rightarrow CH_3^+ + F^-$	ΔH	255.0	256.8 ± 7.1
$CH_3CH_2F \rightarrow CH_3CH_2^+ + F^-$	ΔH	217.7	217.6 ± 1.4
$(CH_3)_2CHF \rightarrow (CH_3)_2CH^+ + F^-$	ΔH	204.4	203.6 ± 1.7
$CH_2{=}CHCH_2F \rightarrow CH_2CHCH_2^+ + F^-$	ΔH	202.8	203.7 ± 1.7
$F^- + CH_3F \rightarrow FCH_3 + F^-$ (S_N2)	$\Delta H^\ddagger$	0.2	
$F^- + CH_3CH_2F \rightarrow CH_3CH_2F + F^-$ (S_N2)	$\Delta H^\ddagger$	2.3	
$F^- + (CH_3)_2CHF \rightarrow (CH_3)_2CHF + F^-$ (S_N2)	$\Delta H^\ddagger$	4.2	
$F^- + CH_2{=}CHCH_2F \rightarrow CH_2{=}CHCH_2F + F^-$ (S_N2)	$\Delta H^\ddagger$	−0.2	
$F^- + CH_2{=}CHCH_2F \rightarrow FCH_2CH{=}CH_2 + F^-$ (*syn* S_N2')	$\Delta H^\ddagger$	−0.5	
$F^- + CH_2{=}CHCH_2F \rightarrow FCH_2CH{=}CH_2 + F^-$ (*anti* S_N2')	$\Delta H^\ddagger$	−0.1	
$CH_3Cl \rightarrow CH_3^+ + Cl^-$	ΔH	227.7	227.5 ± 0.6
$CH_3CH_2Cl \rightarrow CH_3CH_2^+ + Cl^-$	ΔH	188.9	188.1 ± 0.5
$(CH_3)_2CHCl \rightarrow (CH_3)_2CH^+ + Cl^-$	ΔH	174.2	174.3 ± 1.4
$CH_2{=}CHCH_2Cl \rightarrow CH_2CHCH_2^+ + Cl^-$	ΔH	174.8	174.7 ± 1.1
$Cl^- + CH_3Cl \rightarrow ClCH_3 + Cl^-$ (S_N2)	$\Delta E^\ddagger$	2.4	2.5 ± 1.0
$Cl^- + CH_3CH_2Cl \rightarrow CH_3CH_2Cl + Cl^-$ (S_N2)	$\Delta H^\ddagger$	4.1	
$Cl^- + (CH_3)_2CHCl \rightarrow (CH_3)_2CHCl + Cl^-$ (S_N2)	$\Delta H^\ddagger$	6.1	
$Cl^- + CH_2{=}CHCH_2Cl \rightarrow CH_2{=}CHCH_2Cl + Cl^-$ (S_N2)	$\Delta H^\ddagger$	1.6	
$Cl^- + CH_2{=}CHCH_2Cl \rightarrow ClCH_2CH{=}CH_2 + Cl^-$ (*syn* S_N2')	$\Delta H^\ddagger$	11.0	
$Cl^- + CH_2{=}CHCH_2Cl \rightarrow ClCH_2CH{=}CH_2 + Cl^-$ (*anti* S_N2')	$\Delta H^\ddagger$	8.6	

[a] MCG3//MC-QCISD energies combined with *m*PW1N/6–31+G(d) 298 K thermal enthalpy contributions.

[b] Literature: $\Delta_f H°$ CH_3F;[62] $\Delta_f H°$ $CH_3\cdot$;[61,74–78] *IE* $CH_3\cdot$;[79–92] $\Delta_f H°$ F^-;[54–60] $\Delta_f H°$ C_2H_5F;[93,94] $\Delta_f H°$ $C_2H_5\cdot$;[77] *IE* $C_2H_5\cdot$;[95] $\Delta_f H°$ *i*-C_3H_7F;[94,96] $\Delta_f H°$ *i*-$C_3H_7\cdot$;[77] *IE* *i*-$C_3H_7\cdot$;[80,81,83,90,97,98] $\Delta_f H°$ C_3H_5F;[94,99] $\Delta_f H°$ $C_3H_5\cdot$;[77] *IE* $C_3H_5\cdot$;[100–103] $\Delta_f H°$ CH_3Cl;[61,104–107] $\Delta_f H°$ Cl^-;[94,108] $\Delta_f H°$ C_2H_5Cl;[107] $\Delta_f H°$ *i*-C_3H_7Cl;[51,107,109,110] $\Delta_f H°$ C_3H_5Cl;[111] $\Delta E^\ddagger$ $CH_3Cl + Cl^-$.[50]

high-quality gas-phase data are available for only a very small number of reactions. Given that situation, the next best choice is to parameterize against other theoretical data that derive from a method or methods that exhibit good convergence with respect to approximate solution of the Schrödinger equation (convergence in this case typically referring to one-electron basis-set size and increasingly sophisticated models for including electron correlation effects in molecular orbital theory). We chose as our high-level model MCG3//MC-QCISD, i.e. molecular geometries optimized at the multi-coefficient quadratic configuration interaction level including single and double excitations[43] and energies computed for those geometries at the multi-coefficient Gaussian-3 level.[44,45]

In order to assess the suitability of MCG3//MC-QCISD calculations as standards against which to parameterize a DFT method, we first validated the former against what relevant experimental data *were* available. In the gas phase, the activation energy for only a single nucleophilic substitution reaction in our training set is known, namely that for $Cl^- + CH_3Cl$.[48–50] However, gas-phase heats of formation are available for many of the alkyl halides examined here and also for the alkyl cations and halide anions that are produced by bond heterolysis in these compounds. Since such heterolysis is the equivalent of the dissociative step in an S_N1 nucleophilic substitution mechanism, the accurate calculation of these thermochemistries is another good test of MCG3//MC-QCISD. Table 1 provides MCG3//MC-QCISD 298 K enthalpies for the various processes defining the nucleophilic substitution training set, and compares with experimental data where available.

We note that there is controversy over some of the listed experimental enthalpies of formation; those of the fluorinated hydrocarbons are especially difficult to determine experimentally.[51–53] Thus, the enthalpy of formation used in Table 1 for F^- (-61 ± 1.3 kcal mol^{-1}) is an average of seven experimental values obtained from the NIST WebBook.[54–60] The error for this case (taken as the root mean square of all reported experimental errors) is over 1 kcal mol^{-1}, but it appears to be a reasonable estimate given the available data. The enthalpy of formation of methyl fluoride has also been the subject of some debate. The value of -56 ± 7 kcal mol^{-1} used in Table 1 was obtained from the NIST–JANAF compilation[61] and is based on an experiment by Lossing *et al.*[62] The large experimental uncertainty contributes to our large error bar for the ionization of methyl fluoride. Several groups have investigated other methods with which to derive a better estimate for this heat of formation. Liebman *et al.*[63] recommend a value of -53.87 ± 0.76 kcal mol^{-1} based on an average of five estimations derived from various models. Zachariah *et al.*[64] used bond additivity corrected Møller–Plesset fourth-order perturbation theory (BAC-MP4) to obtain a computed heat of formation of -55.88 ± 1.0 kcal mol^{-1}. Luo and Benson[65] use their electronegativity scale based on the covalent potential (V_x) to correlate V_x with heats of formation and recommend a value of -55.9 ± 1 kcal mol^{-1}. We note that all of these estimates fall within the large experimental error of the number used in Table 1, and all are slightly to moderately smaller in magnitude than the Lossing number, which is entirely consistent with the theoretical prediction for the ionization enthalpy being somewhat smaller than the quoted experimental mean value.

The enthalpies of formation of the remaining alkyl fluorides in Table 1 have similar associated controversies. Indeed, estimation methods similar to those described above have been performed for ethyl,[64–67] isopropyl[65,67] and allyl fluoride,[68–70] and the estimated numbers differ from the experimental by as much as 6 kcal mol^{-1}. However, the MCG3//MC-QCISD heterolysis enthalpies are in very good agreement with those derived from the reported experimental values. Such coincidental agreement seems unlikely, and we regard the computations reported here as providing some validation for the experimental results.

The chlorinated hydrocarbons pose less of a problem with respect to experimental accuracy. The enthalpies of formation of these compounds appear to be well known, and the only case where estimates deviate slightly from experimental values is allyl chloride.[71] In any case, the overall performance of the MCG3//MC-QCISD level is excellent; in every case but one, it makes predictions that fall within the experimental error bars (the one exception has the tightest error bar, and MCG3//MC-QCISD is only 0.3 kcal mol^{-1} outside it), and it has a mean unsigned error over the nine possible comparisons of 0.5 kcal mol^{-1}. As the average error bar on the experimental data is 1.8 kcal mol^{-1}, such agreement should probably be regarded as being as quantitative as may reasonably be expected.

Choice of penalty function

As noted in the Introduction, the primary problem in applying density functional theory to nucleophilic substitution reactions has been the poor quality of predicted relative energies. As such, any parameterization must address this deficiency by significantly weighting energy errors in the optimization penalty function. However, there are other molecular parameters that may also deserve consideration in construction of the penalty function, so that accuracy in these properties is not inadvertently sacrificed to improve relative energetics.

One such property that merits attention is the molecular geometry. Since all modern DFT methods have been shown to be fairly robust in the computation of molecular structure for 'typical' local minima, we restricted our consideration of geometry to transition-state (TS) structures. Table 2 lists heavy atom bond lengths for these structures at the MC-QCISD, BLYP, *m*PWPW91, BH&HLYP, *m*PW1PW91, *m*PW1N, B3LYP and B3PW91 levels of theory.

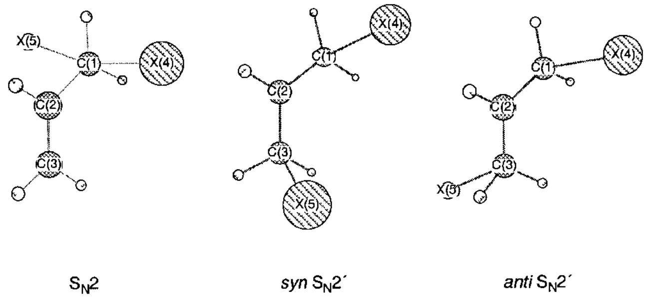
In the case of the S_N2 reactions for methyl, isopropyl and allyl, all TS structures except one had planes of symmetry such that the distances between the substituted carbon and the two halogen atoms were identical, so only one distance is reported in Table 2. The planes of symmetry are those containing all of the carbon atoms. The sole exception involved BH&HLYP applied to the fluoride/allyl fluoride S_N2 reaction. At the BH&HLYP level, the C_s structure analogous to all of the others is predicted to be a second-order saddle point and to be unstable relative to a rotation about the C1—C2 bond such that the final TS structure has all five heavy atoms in a single plane, i.e. the substitution is still a back-side S_N2 attack, but the partial C—F bonds are orthogonal to the vinyl π system instead of parallel to it. The energy difference between the two structures is predicted to be 0.9 kcal mol^{-1}. The same situation was also observed for the case of *v*PW1PW91/$a = 0.999$, a level not listed in Table 2, suggesting that high percentages of HF character contribute to this erroneous prediction of in-plane substitution.

Symmetric TS structures were also predicted by most levels of theory for both *anti* S_N2' reactions and for the *syn* S_N2' reaction of chloride/allyl chloride. For the *syn* S_N2' reaction of fluoride/allyl fluoride, however, all but the BLYP level of theory predicted asymmetric TS structures, with a C_s symmetric structure being an intermediate between mirror image TS structures.

These points having been made, there is considerable variation in heavy-atom bond lengths predicted by different methods. However, interpretation of these data is complicated by how flat the potential energy surface appears to be in several instances. Thus, at the MCG3//MC-QCISD level for the *syn* S_N2' reaction of fluoride/allyl fluoride, the energy separation between the C_1 TS structure (with C—F bond lengths of 1.483 and 1.662 Å) and the C_s intermediate (with symmetrical C—F bond lengths of 1.536 Å) is computed to be 0.02 kcal mol^{-1}. The *anti* S_N2' reaction of fluoride/allyl fluoride also appears to have a very flat reaction coordinate. At the *m*PW1N level, the TS structure is predicted to have C_1 symmetry (with C—F bond lengths of 1.470 and 1.719 Å) and the C_2 structure listed in Table 2 (with symmetrical C—F bond lengths of 1.540 Å) is actually an intermediate. However, the energy difference between the two is predicted to be 0.2 kcal mol^{-1}, so it does not seem legitimate to interpret the large difference between the *m*PW1N and MC-QCISD TS structures as being particularly meaningful.

Given the above analysis, we elected not to include geometric data in our optimization penalty function. Furthermore, to the extent that other molecular properties, e.g. electric multipole moments, would be expected to show strong dependences on geometry, these properties also were not considered. Instead, we decided to use as our penalty function simply the RMS error in activation free energies listed in Table 1. That point having been made,

Table 2. Selected heavy-atom bond lengths (Å) in nucleophilic substitution TS structures



		Level of theory							
Reaction	Bond	MCQCISD	BLYP	*m*PWPW91	BH&HLYP	*m*PW1PW91	*m*PW1N	B3LYP	B3PW91
S_N2 reaction, $X^- + RX \rightarrow XR + X^-$:									
R = Me, X = F	C—F	1.834	1.896	1.865	1.826	1.827	1.809	1.857	1.836
R = Me, X = Cl	C—Cl	2.309	2.409	2.362	2.347	2.330	2.315	2.371	2.340
R = Et, X = F	C—F^{a}	1.855	1.919	1.900	1.855	1.854	1.837	1.883	1.864
	C—F^{b}	1.870	1.947	1.911	1.866	1.866	1.846	1.900	1.878
R = Et, X = Cl	C—Cl^{a}	2.344	2.440	2.397	2.392	2.370	2.358	2.411	2.381
	C—Cl^{b}	2.377	2.527	2.461	2.443	2.417	2.399	2.473	2.431
R = *i*Pr, X = F	C—F	1.897	1.981	1.943	1.904	1.900	1.881	1.936	1.912
R = *i*Pr, X = Cl	C—Cl	2.427	2.586	2.520	2.517	2.481	2.466	2.540	2.497
R = allyl, X = F	C^{1}—F$^{4/5}$	1.845	1.930	1.893	1.843	1.845	1.825	1.882	1.858
	C^{1}—C^{2}	1.471	1.474	1.471	1.488	1.471	1.496	1.472	1.471
	C^{2}—C^{3}	1.336	1.352	1.349	1.327	1.335	1.328	1.339	1.338
R = allyl, X = Cl	C^{1}—Cl$^{4/5}$	2.349	2.519	2.452	2.428	2.403	2.384	2.464	2.420
	C^{1}—C^{2}	1.466	1.458	1.458	1.455	1.458	1.457	1.457	1.458
	C^{2}—C^{3}	1.337	1.355	1.351	1.328	1.337	1.330	1.342	1.400
syn S_N2' reaction, $X^- + RX \rightarrow XR + X^-$:									
R = allyl, X = F	C^{1}—F^{4}	1.483	1.685	1.427	1.459	1.457	1.439	1.526	1.473
	C^{3}—F^{5}	1.662	1.685	2.289	1.766	1.922	1.847	1.742	1.890
	C^{1}—C^{2}	1.449	1.429	1.476	1.454	1.462	1.459	1.448	1.460
	C^{2}—C^{3}	1.404	1.429	1.366	1.384	1.374	1.370	1.402	1.380
	F^{4}—F^{5}	3.726	3.990	4.635	3.851	4.058	3.986	3.895	4.033
R = allyl, X = Cl	C$^{1/3}$—Cl$^{4/5}$	2.211	2.418	2.309	2.303	2.247	2.216	2.343	2.270
	C$^{1/3}$—C^{2}	1.400	1.407	1.407	1.390	1.399	1.395	1.399	1.400
	Cl^{4}—Cl^{5}	4.440	5.058	4.856	4.773	4.693	4.613	4.878	4.759
anti S_N2' reaction, $X^- + RX \rightarrow XR + X^-$:									
R = allyl, X = F	C$^{1/3}$—Cl$^{4/5}$	1.563	1.733	1.668	1.552	1.579	1.540	1.636	1.600
	C$^{1/3}$—C^{2}	1.426	1.421	1.423	1.423	1.423	1.424	1.421	1.423
R = allyl, X = Cl	C$^{1/3}$—Cl$^{4/5}$	2.285	2.472	2.369	2.389	2.317	2.296	2.412	2.338
	C$^{1/3}$—C^{2}	1.391	1.402	1.401	1.383	1.393	1.387	1.393	1.394
MUE			0.097	0.102	0.042	0.041	0.035	0.058	0.048

the geometric error analysis at the bottom of Table 2 (MUE-mean unsigned error) may be taken as indicative that most DFT methods do in any case perform acceptably for geometric prediction, at least within the limits on the analysis imposed by the flat nature of some of the potential energy surface coordinates involved. Moreover, although not specifically optimized against geometries, the *m*PW1N method proved after the fact to be the most accurate of all of the DFT methods surveyed for this property.

Relative energy prediction

We next surveyed the ability of various existing density functionals to reproduce the MCG3 data. Results for BLYP, *m*PWPW91, BH&HLYP, *m*PW1PW91, B3LYP and B3PW91 are provided in Table 3, as is an error analysis for each method (MSE-mean signed error; RMS-root-mean-square error). The comparison here is in terms of changes in electronic energy, not enthalpy, since accurate computation of thermal contributions to enthalpy is a much less demanding process and DFT is well established to be robust for this purpose. Every method surveyed provided a negative mean signed error, implying a systematic underestimation of reaction energies. In the case of BLYP and the popular B3LYP functional, the mean unsigned error was equal in magnitude to the mean signed error, implying that *every* reaction energy was underestimated.

Table 3. Computed activation energies (kcal mol^{-1}) for reactions comprising the nucleophilic substitution training set and errors for DFT methods compared with MCG3//MC-QCISD

	Level of theory							
Reaction and error analysis	MCG3	BLYP	*m*PWPW91	BH&HLYP	*m*PW1PW91	B3LYP	B3PW91	*m*PW1N
A: $CH_3F \rightarrow CH_3^+ + F^-$	258.7	255.4	263.3	258.4	264.4	257.9	262.9	265.2
B: $CH_3CH_2F \rightarrow CH_3CH_2^+ + F^-$	221.2	217.1	222.4	226.3	226.7	221.7	224.7	229.4
C: $(CH_3)_2CHF \rightarrow (CH_3)_2CH^+ + F^-$	208.0	196.4	202.4	208.4	208.5	202.5	206.0	212.1
D: $CH_2{=}CHCH_2F \rightarrow CH_2CHCH_2^+ + F^-$	204.9	194.1	201.9	203.1	206.2	199.0	204.0	208.8
E: $F^- + CH_3F \rightarrow FCH_3 + F^-$ (S_N2)	1.2	−8.2	−7.7	−0.5	−2.9	−4.3	−2.7	−0.6
F: $F^- + CH_3CH_2F \rightarrow CH_3CH_2F + F^-$ (S_N2)	3.4	−4.7	−4.2	3.0	0.8	−0.7	1.1	3.1
G: $F^- + (CH_3)_2CHF \rightarrow (CH_3)_2CHF + F^-$ (S_N2)	5.4	−1.8	−1.2	6.1	4.1	2.3	4.4	6.4
H: $F^- + CH_2{=}CHCH_2F \rightarrow CH_2{=}CHCH_2F + F^-$ (S_N2)	1.1	−8.2	−7.8	0.9	−1.6	−3.2	−1.5	1.3
I: $F^- + CH_2{=}CHCH_2F \rightarrow FCH_2CH{=}CH_2 + F^-$ (*syn* S_N2')	0.4	−9.3	−11.2	−2.3	−7.2	−6.1	−6.7	−5.3
J: $F^- + CH_2{=}CHCH_2F \rightarrow FCH_2CH{=}CH_2 + F^-$ (*anti* S_N2')	0.5	−10.8	−12.9	−3.1	−8.5	−6.9	−7.7	−6.9
K: $CH_3Cl \rightarrow CH_3^+ + Cl^-$	230.5	223.4	231.6	220.5	229.8	223.6	228.9	228.8
L: $CH_3CH_2Cl \rightarrow CH_3CH_2^+ + Cl^-$	191.6	183.0	188.6	186.3	190.1	185.3	188.6	191.1
M: $(CH_3)_2CHCl \rightarrow (CH_3)_2CH^+ + Cl^-$	177.2	160.3	166.9	166.3	170.1	164.1	168.1	171.9
N: $CH_2{=}CHCH_2Cl \rightarrow CH_2CHCH_2^+ + Cl^-$	176.1	160.8	168.8	163.7	170.2	163.3	168.6	171.1
O: $Cl^- + CH_3Cl \rightarrow ClCH_3 + Cl^-$ (S_N2)	2.4	−4.4	−3.6	2.8	0.8	−0.9	0.7	2.9
P: $Cl^- + CH_3CH_2Cl \rightarrow CH_3CH_2Cl + Cl^-$ (S_N2)	5.0	−0.8	0.2	6.2	4.6	2.7	4.6	6.6
Q: $Cl^- + (CH_3)_2CHCl \rightarrow (CH_3)_2CHCl + Cl^-$ (S_N2)	7.0	1.7	3.0	8.6	7.5	5.3	7.5	9.5
R: $Cl^- + CH_2{=}CHCH_2Cl \rightarrow CH_2{=}CHCH_2Cl + Cl^-$ (S_N2)	2.6	−4.7	−3.5	4.6	2.0	−0.2	1.8	4.7
S: $Cl^- + CH_2{=}CHCH_2Cl \rightarrow ClCH_2CH{=}CH_2 + Cl^-$ (*syn* S_N2')	11.9	−0.3	−0.1	13.1	7.0	5.6	6.6	10.9
T: $Cl^- + CH_2{=}CHCH_2Cl \rightarrow ClCH_2CH{=}CH_2 + Cl^-$ (*anti* S_N2')	9.4	−4.3	−3.5	8.6	3.6	1.6	3.0	7.4
MSE		−9.2	−6.3	−1.9	−2.1	−5.3	−2.8	0.0
MUE		9.2	6.9	3.1	3.5	5.3	3.6	3.1
RMS		9.8	7.8	4.8	4.4	6.3	4.5	3.9

Table 4. Computed activation energies (kcal mol^{-1}) for reactions comprising the nucleophilic substitution training set and errors for *v*PW1PW91 compared with MCG3//MC-QCISD as a function of percentage Hartree–Fock exchange[a]

			a^b										
Class	Reaction	MCG3	0.000	0.100	0.200	0.300	0.400	0.500	0.600	0.700	0.800	0.900	0.999
I	A	258.7	263.1	263.6	264.1	264.6	265.1	265.6	266.0	266.4	266.8	267.2	267.2
I	B	221.2	222.1	224.0	225.8	227.6	229.3	231.0	232.7	234.4	236.0	237.5	238.8
I	C	208.0	202.5	205.0	207.5	209.8	212.0	214.0	216.0	217.9	219.6	221.2	222.5
I	D	204.9	201.7	203.6	205.3	207.0	208.7	210.2	211.7	213.1	214.5	215.7	216.6
II	E	1.2	−7.7	−5.6	−3.7	−2.0	−0.6	0.7	1.8	2.7	3.4	4.0	4.6
II	F	3.4	−4.1	−2.0	−0.1	1.6	3.1	4.3	5.3	6.1	6.8	7.3	7.9
II	G	5.4	−1.0	1.2	3.2	4.9	6.3	7.5	8.5	9.3	9.9	10.4	10.9
II	H	1.1	−7.6	−5.0	−2.6	−0.6	1.3	2.9	4.2	5.4	6.4	7.3	8.1
II	I	0.4	−10.9	−9.6	−8.3	−7.2	−6.2	−5.3	−4.5	−3.8	−3.1	−2.5	−1.8
II	J	0.5	−11.6	−10.2	−9.0	−7.9	−6.8	−5.9	−5.1	−4.3	−3.7	−3.1	−2.4
III	K	230.5	231.4	230.8	230.1	229.5	228.8	228.2	227.5	226.9	226.2	225.5	224.6
III	L	191.6	188.5	189.1	189.8	190.4	191.1	191.7	192.2	192.8	193.3	193.8	194.1
III	M	177.2	166.4	167.8	169.2	170.4	171.5	172.6	173.5	174.3	175.1	175.7	176.0
III	N	176.1	168.7	169.3	169.9	170.5	171.0	171.4	171.8	172.2	172.4	172.6	172.5
IV	O	2.4	−3.3	−1.5	0.1	1.6	2.8	4.0	4.9	5.8	6.5	7.0	7.6
IV	P	5.0	0.5	2.3	3.9	5.4	6.6	7.6	8.5	9.2	9.8	10.2	10.7
IV	Q	7.0	3.0	4.9	6.5	8.0	9.2	10.3	11.1	11.8	12.2	12.6	13.0
IV	R	2.6	−2.7	−0.5	1.4	3.2	4.8	6.2	7.4	8.5	9.4	10.2	10.9
IV	S	11.9	0.6	3.3	6.0	8.5	10.8	13.1	15.2	17.1	18.9	20.6	22.3
IV	T	9.4	−3.0	−0.2	2.5	5.0	7.3	9.5	11.5	13.3	14.9	16.5	18.0
Mean unsigned error:													
	Class I		3.5	3.0	2.7	4.1	5.6	7.0	8.4	9.8	11.0	12.2	13.1
	Class II		9.2	7.2	5.4	3.9	2.9	2.9	3.2	3.6	3.9	4.1	4.3
	Class III		5.6	4.7	4.1	3.6	3.2	2.9	2.9	2.9	3.0	3.1	3.3
	Class IV		7.2	5.0	3.0	1.8	1.6	2.1	3.4	4.6	5.6	6.5	7.4
Error over all classes:													
	MSE		−6.1	−4.4	−2.8	−1.4	−0.1	1.1	2.1	3.0	3.8	4.6	5.2
	MUE		6.7	5.2	3.9	3.2	3.1	3.5	4.2	5.0	5.6	6.2	6.8
	RMS		7.6	6.0	4.8	4.1	4.0	4.3	4.9	5.7	6.5	7.2	7.9

[a] Using MC-QCISD geometries.
[b] See Eqn. (3).

The pure DFT method *m*PWPW91 provided better performance than BLYP, and when 25% Hartree–Fock exchange was added (*m*PW1PW91) that performance was considerably improved, resulting in the method with the lowest RMS error. On this basis, we decided to explore in more detail how the amount of HF exchange in Eqn. (3) influenced predicted reaction energies over the training set. Another motivation for choosing the ACM approach represented by Eqn. (3) was the success that Lynch *et al.* had in a similar survey designed to provide an optimal functional for hydrogen-atom transfer reactions, the so-called MPW1K functional, where $a = 42.8\%$ and the use of the 6–31+G(d,p) basis set is implicit.

Table 4 lists predicted activation energies as a function of *a* when that parameter is varied by 0.1 over the interval from 0 to 1. Error analysis in Table 4 is carried out for all of the reactions in the training set, and also, to understand better how sensitive the ACM predictions are to the nature of the nucleophilic substitution, over the ionization reactions of fluoride (class I), the S_N2 and S_N2' reactions of fluoride (class II), the ionization reactions of chloride (class III) and the S_N2 and S_N2' reactions of chloride (class IV). Inspection of the MUE as a function of *a* over these different reaction classes indicates that a single value of *a* is not optimal for all cases. Over class I, the optimal value falls near 0.17, over class II near 0.45, over class III near 0.60 and over class IV near 0.36. There are no clear patterns to this variation. In the fluoride case, ionization reactions prefer a lower value of *a* compared with bimolecular nucleophilic substitution, but the opposite is true for chloride. Such variability is consistent with an analogous study by Poater *et al.* that also found that optimal amounts of HF exchange in the B3LYP functional varied over 11 diverse chemical reactions (and moreover that the value in any given reaction that provided the best energetics was not necessarily the same as the one which gave the best geometries).[72]

When all four classes of reactions are combined, the magnitudes of the mean signed, unsigned and RMS errors are all effectively minimized by an *a* value of 0.406, i.e. 40.6% HF exchange (MSE = 0.0; MUE = 3.1; RMS = 3.9; all values in kcal mol^{-1}). In effect, this value intrinsically works well for the bimolecular nucleophilic substitutions, and roughly splits the difference between the values individually preferred for fluoride and chloride heterolysis reactions. We refer to this choice of *a* in *v*PW1PW91 as *m*PW1N, and its predictions are listed in the last column of Table 3. As a separate comparative point, the *m*PW1N level predicts that the ion–dipole complex of chloride anion and chloromethane has a 298 K enthalpy of $-9.6\,\text{kcal mol}^{-1}$ relative to separated reactants; this value compares very well with the high-pressure mass spectrometric results of Li *et al.*,[73] where a relative enthalpy of $-10.4\,\text{kcal mol}^{-1}$ was measured.

We note that the *m*PW1N *a* value is close to the 42.8% value determined by Lynch *et al.*[41] to be optimal for predicting barriers to hydrogen-atom transfer reactions. The latter choice is referred to as MPW1K. Thus, *m*PW1N and MPW1K are similar to one another and it may be reasonable to infer that the apparent robustness of an *a* value of roughly 41% in the *v*PW1PW91 functional will be more widely applicable. Naturally, this supposition should be tested in future studies.

It should be noted, by comparing to the data in Tables 2 and 3, that the *m*PW1N method represents a very significant improvement over the pure DFT methods BLYP and *m*PWPW91 and also over the hybrid method B3LYP. It also outperforms the remaining hybrid methods BH&HLYP, *m*PW1PW91, and B3PW91, but by a reduced margin. Lastly, for researchers looking for the highest possible accuracy within the formalism of this approach, it may prove valuable to use the data in Table 4 to select an *a* value targeted to a specific reaction or reactions deemed to be most analogous to those in the individual reaction classes I–IV.

A key motivation for us in developing the *m*PW1N model was to validate a gas-phase level of density functional theory that would then prove useful in SCRF calculations to examine the differential effects of solvation on alternative nucleophilic substitution pathways. Results from these studies will be reported in due course.

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