

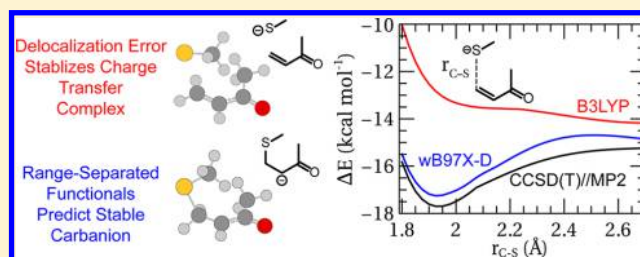
Range-Separated DFT Functionals are Necessary to Model Thio-Michael Additions

Jennifer M. Smith, Yasaman Jami Alahmadi, and Christopher N. Rowley*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland A1B 3X7, Canada

S Supporting Information

ABSTRACT: The textbook mechanism for the addition of a thiol to an olefin is the Michael-type addition, which involves a nucleophilic attack of a thiolate anion on an alkene to form a carbanion intermediate. Previous computational models of these reactions have proposed alternative mechanisms, as no minimum corresponding to the carbanion intermediate was present on the potential energy surface. We show that many popular pure and hybrid DFT functionals, such as PBE and B3LYP, erroneously predict that the carbanion is not an intermediate, favoring a noncovalent charge-transfer complex stabilized spuriously by delocalization error. Range-separated DFT functionals correct this problem and predict stable carbanion structures and energies. In particular, calculations using the ω B97X-D functional are in close agreement with CCSD(T) data for the structures and energies of a series of thio-carbanions. Range-separated functionals will make it possible to model the reaction mechanisms of Michael-type additions that occur in biochemistry, such as the covalent modification of a cysteine side chain by drugs containing an electrophilic double bond.



INTRODUCTION

The addition of a thiol to an olefin is commonly used in the synthesis of thioethers.^{1,2} These reactions also occur between some electrophilic natural products and biological thiols. For example, 15-deoxy- $\Delta^{12,14}$ -prostaglandin J2 regulates the activity of enzymes involved in NF- κ B signaling pathway by reacting with the side chains of cysteine residues.³ This type of reactivity has been exploited by medicinal chemists to develop inhibitors that bind to their target through the covalent modification of a cysteine.^{4–7}

The textbook mechanism for the addition of a thiol to an electrophilic alkene is a Michael-type addition (Scheme 1).⁸ The first step of this mechanism is the deprotonation of the thiol to form a thiolate anion. The thiolate then proceeds through a conjugate addition with the carbon in the β position of the double bond, forming a carbon-centered anion, or carbanion, at the α -carbon. The olefin substituents can stabilize this carbanion by inductive or resonance effects.

Kollman and co-workers reported one of the earliest computational studies of thiol additions, using Hartree–Fock and Møller–Plesset methods to describe the reaction of the hydrogen sulfide anion and methylthiolate with ethylene.⁹ The results of this study were largely consistent with the established mechanism of Michael-type additions, featuring a stable carbanion intermediate. More recently, a series of computational studies using density functional theory (DFT) concluded that the carbanion is not a stable intermediate and proposed alternative mechanisms, including a direct 1,2-addition of the thiol,¹⁰ a concerted water-mediated addition,¹¹ and a base-catalyzed mechanism.^{12–14}

To model the irreversible inhibition of a target through an electrophilic attack on a cysteine side chain will require a quantum chemical method that provides an accurate yet computationally efficient description of the reaction mechanism. In this study, we compare the energies of the reaction profile of the thiolate addition step for a series of wave function and DFT quantum chemical methods. To evaluate the effect of olefin substituents on this mechanism, we performed this analysis for four different functional groups: nitro (NO₂), carboxylic (COOH), methyl ketone (CO(CH₃)), and cyano (CN). Through this analysis, we aim to establish whether thiol addition can proceed through a carbanion mechanism and determine why some DFT methods yield different results than wave function methods.

COMPUTATIONAL METHODS

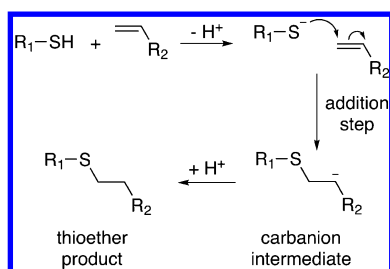
For an accurate, first-principles point of comparison for the DFT methods, we calculated the CCSD(T)¹⁵ energy of the reactants, products, and intermediates in these reactions at the MP2-optimized geometry. This method is denoted as CCSD(T)//MP2.

We evaluated a series of DFT functionals to determine trends based on the type of functional. We evaluated three pure functionals (PBE^{16,17}, BLYP,^{18,19} and TPSS²⁰), four hybrid functionals (PBE0,²¹ B3LYP,^{19,22,23} M06,²⁴ and TPSSH²⁰), and four range-separated hybrid functionals (CAM-B3LYP,²⁵ LC- ω PBE,^{26–28} BNL,^{29,30} and ω B97X-D³¹). Supplementary calculations were also performed with additional quantum

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Scheme 1. General reaction Scheme for the Michael-Type Addition of a Thiol to a Substituted Olefin



chemical methods: AM1, PM3, PM6, HF, MP2, M06-2X, M06-HF, and ω B97X. These data are collected in Table S1 of the Supporting Information.

All calculations employed the aug-cc-pVTZ correlation-consistent Dunning basis set.^{32,33} All DFT calculations were performed using the Gaussian 09 Version A.01 suite of programs,³⁴ with exception of the calculations performed with the BNL functional, where Q-Chem Version 3.2 was used.³⁵ MP2 and CCSD(T) calculations were performed with TURBOMOLE 6.5³⁶ using the resolution of identity approximation.³⁷

RESULTS AND DISCUSSION

Trends in Carbanion Stability. The relative stabilities of the carbanion with respect to the thiolate and olefin are presented in Table 1. Generally, the CCSD(T)//MP2 calculated stability of the carbanion reflects electron withdrawing ability of the olefin substituent. The carbanion of nitroethylene is exceptionally stable, reflecting the high electron withdrawing character of the nitro functional group. The stability of this intermediate decreases as the electron withdrawing character of the substituent is decreased, resulting in a ranking of $\text{NO}_2 > \text{COOH} > \text{CO}(\text{CH}_3) > \text{CN}$. The nitro-substituted carbanion also has the shortest S–C(β) bond length ($r_{\text{C-S}} = 1.88 \text{ \AA}$), while the S–C(β) bonds of the three other carbanions are elongated by 0.02–0.11 \AA .

The DFT methods considered predict a wide range of carbanion S–C(β) bond lengths and energies. All functionals perform reasonably well for nitroethylene; however, these methods have inconsistent predictions for the other substituents. While CCSD(T)//MP2 predicts the existence of a stable carbanion with a S–C(β) bond length in the range from 1.88 to 1.99 \AA for all the reactions that were investigated, many functionals predict that there is no potential energy minimum associated with the carbanion. Instead, the structures optimize to a noncovalent complex of the thiolate and the olefin. Even for methyl vinyl ketone ($R = \text{CO}(\text{CH}_3)$), one of the more electrophilic olefins considered, the PBE, BLYP, TPSS, TPSSH, and B3LYP functionals predict that there is no potential energy minimum associated with the carbanion. The PBE0 hybrid functional, which has a high component of exact exchange (25%), reliably predicts carbanions with reasonable S–C(β) distances but tends to overestimate the stability of these intermediates by 2–5 kcal mol^{-1} .

The range-separated functionals (LC- ω PBE, BNL, ω B97X, and ω B97X-D) consistently predict stable carbanion intermediates, with typical $\sigma(\text{C-S})$ bond lengths for the S–C(β) bond. The LC- ω PBE functional tends to overestimate the stability of these intermediates by 1–3 kcal mol^{-1} while CAM-B3LYP underestimates the stabilities of these intermediates by

Table 1. Carbanion S–C(β) Bond Lengths and Energies Relative to the Olefin and Methylthiolate Reactants Calculated Using DFT and Ab Initio Methods

R	method	$r_{\text{C-S}} (\text{\AA})$	$\Delta E_{\text{carbanion}} (\text{kcal mol}^{-1})$
$-\text{NO}_2$	PBE	1.95	–34.8
	BLYP	2.04	–27.2
	TPSS	1.98	–30.6
	B3LYP	1.93	–28.6
	PBE0	1.89	–35.0
	M06	1.90	–34.3
	TPSSH	1.94	–30.8
	BNL	1.86	–34.2
	CAM-B3LYP	1.87	–31.0
	LC- ω PBE	1.84	–34.7
$-\text{CO}_2\text{H}$	ω B97X-D	1.88	–32.6
	CCSD(T)//MP2	1.88	–32.4
	PBE	2.01	–22.5
	BLYP	no intermediate	
	TPSS	2.07	–18.4
	B3LYP	1.98	–14.6
	PBE0	1.91	–21.5
	M06	1.93	–20.0
	TPSSH	1.99	–18.0
	BNL	1.87	–19.9
$-\text{COCH}_3$	CAM-B3LYP	1.90	–16.5
	LC- ω PBE	1.85	–21.3
	ω B97X-D	1.91	–18.5
	CCSD(T)//MP2	1.90	–19.8
	PBE	no intermediate	
	BLYP	no intermediate	
	TPSS	no intermediate	
	B3LYP	no intermediate	
	PBE0	1.95	–20.5
	M06	2.04	–19.2
$-\text{CN}$	TPSSH	no intermediate	
	BNL	1.89	–16.5
	CAM-B3LYP	1.93	–14.1
	LC- ω PBE	1.87	–18.5
	ω B97X-D	1.96	–17.0
	CCSD(T)//MP2	1.94	–17.7
	PBE	no intermediate	
	BLYP	no intermediate	
	TPSS	no intermediate	
	B3LYP	no intermediate	
	PBE0	2.00	–20.4
	M06	2.02	–18.9
	TPSSH	no intermediate	
	BNL	1.90	–16.7
	CAM-B3LYP	1.97	–14.1
	LC- ω PBE	1.89	–18.7
	ω B97X-D	1.97	–16.8
	CCSD(T)//MP2	1.99	–15.9

1–4 kcal mol^{-1} . ω B97X-D is in close agreement with CCSD(T)//MP2 for both the relative energies and structures for the full range of functional groups examined.

Potential Energy Surface of Thiolate Addition. To explore the origin of the difference between functionals, we calculated the relaxed potential energy surface of the S–C(β) distance for the reaction of methyl vinyl ketone (MVK) with methylthiolate using CCSD(T)//MP2, B3LYP, and ω B97X-D (Figure 1).³⁸ The CCSD(T)//MP2 surface shows a stable

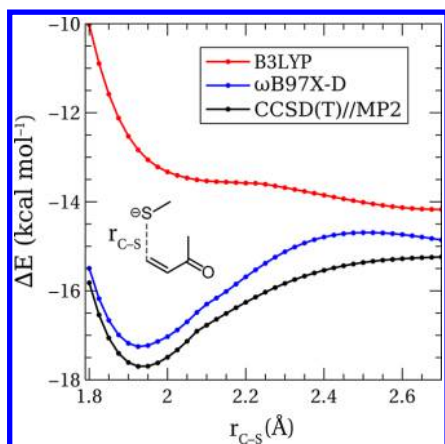


Figure 1. Relaxed potential energy surface for the addition of methylthiolate to MVK along the $S-C(\beta)$ coordinate.

intermediate with a minimum around $r_{C-S} = 1.92$ Å. There is no potential energy barrier associated with the formation of this intermediate; the surface is attractive at distances up to 2.7 Å. In contrast, the B3LYP surface shows no minimum corresponding to the carbanion, as the MVK–thiolate interaction is repulsive at all distances up to 2.7 Å. The ω B97X-D surface is in good agreement with CCSD(T)//MP2, with a stable minimum for the carbanion intermediate around $r_{C-S} = 1.91$ Å, although it predicts a potential energy that is too high by roughly 0.5 kcal mol^{−1} over the full surface.

Spurious Charge Transfer Stabilization of the Thiolate-Olefin Complex. Delocalization error is a significant problem in many popular DFT functionals.³⁹ This error is caused by electron self-repulsion in the Coulomb functional. Formally, the exchange-correlation functional should correct for this self-repulsion; however, as these functionals are inexact, this is not achieved consistently, leading to a tendency for some functionals to predict excessively delocalized distributions. This type of error has been noted in the calculation of reaction barriers,²⁷ charge-transfer excitations,^{40–42} radical dissociations,^{43,44} and donor–acceptor complexes.^{45–47}

Range-separated functionals have emerged as a promising strategy to address delocalization error.^{31,48} These functionals interpolate between two forms as a function of distance. At short distances, the exchange functional is described using a conventional generalized gradient approximation functional (GGA). At long-range, a greater proportion of Hartree–Fock exchange is used. The success of these range-separated functionals in describing the potential energy surface of Michael-type additions can be attributed to correcting delocalization error; functionals such as PBE and B3LYP favor long-range anion-to- π^* charge transfer to reduce electron self-repulsion. This charge transfer distorts the potential energy surface to favor the noncovalent complex instead of the carbanion.

This type of spurious charge transfer is evident in the energy curve corresponding to the vertical attachment of an electron to MVK and the vertical ionization of methylthiolate. This curve can be approximated at fractional electron occupancies with a cubic polynomial using generalized Janak's theorem,⁴⁹ where the end points are defined by the vertical ionization potentials and electron affinities of methylthiolate and MVK, respectively, and the initial slopes are determined from the highest occupied and lowest unoccupied Kohn–Sham eigenvalues (Figure 2).⁵⁰ For the exact functional, the electronic energy should change

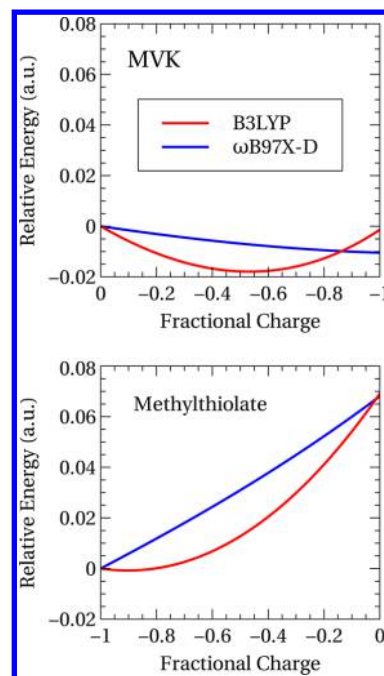


Figure 2. Estimated energy surfaces for the addition (MVK, top) or removal (methylthiolate, bottom) of an electron for the B3LYP and ω B97X-D functionals.

linearly between these two states.⁵¹ The surface calculated using ω B97X-D is in good agreement with this, with nearly linear slopes for both MVK and methylthiolate. The curvature of the B3LYP surfaces is significant, leading to a sizable stabilization when a fraction of an electron is removed from the methylthiolate and transferred to the olefin.

This effect can also be observed by examining the net charge on the olefin fragment at a distance corresponding to a noncovalent complex. We optimized the MVK–methylthiolate complex with the $S-C(\beta)$ distance constrained to 3.0 Å using the PBE, B3LYP, and ω B97X-D functionals and calculated the net charges of the two molecules using natural population analysis.⁵² For the pure PBE functional, MVK has a net charge of $-0.38 e$, indicating a large degree of charge transfer. This is decreased to $-0.29 e$ when the hybrid B3LYP functional is used, and decreases to only $-0.18 e$ when the range-separated hybrid ω B97X-D functional is used. This spurious charge transfer is an example of density-driven error, due to the use of an approximate density rather than error due to the use of approximate one electron functionals.⁴⁷ Notably, this occurs even with weak acceptors such as the olefins used in this study, suggesting that this problem may occur in many systems that contain a weakly bound anion when these popular pure and hybrid functionals are used.

Net Reaction Energies. The thermodynamic reversibility of the thiol addition has been identified as a key design characteristic in the development of irreversible inhibitors,⁷ so the ability of a quantum chemical method to accurately predict the reaction energy of a thiol addition is also important. The net reaction energies for the addition of methanethiol with the olefins to form a neutral thioether, calculated using the DFT and ab initio methods, are collected in Table 2. The CCSD(T)//MP2 results are only modestly sensitive to the functional group on the olefin; the reaction of the highly electron deficient nitroethylene is most favorable ($\Delta E_{\text{net}} =$

Table 2. Energy of the Thioether Products Relative to the Olefin and Methanethiol Reactants Calculated Using the DFT and Ab Initio Methods

R	method	ΔE_{net} (kcal mol ⁻¹)
-NO ₂	PBE	-22.8
	BLYP	-14.9
	TPSS	-20.2
	B3LYP	-18.3
	PBE0	-25.5
	M06	-24.4
	TPSSh	-21.4
	BNL	-25.7
	CAM-B3LYP	-21.9
	LC- ω PBE	-27.7
	ω B97X-D	-25.2
	CCSD(T)//MP2	-25.4
-CO ₂ H	PBE	-21.0
	BLYP	-12.5
	TPSS	-17.7
	B3LYP	-16.2
	PBE0	-23.9
	M06	-22.9
	TPSSh	-19.1
	BNL	-24.6
	CAM-B3LYP	-20.1
	LC- ω PBE	-26.3
	ω B97X-D	-23.5
	CCSD(T)//MP2	-23.5
-COCH ₃	PBE	-21.0
	BLYP	-12.4
	TPSS	-17.8
	B3LYP	-16.2
	PBE0	-23.9
	M06	-21.5
	TPSSh	-19.1
	BNL	-24.6
	CAM-B3LYP	-20.1
	LC- ω PBE	-26.3
	ω B97X-D	-23.6
	CCSD(T)//MP2	-22.9
-CN	PBE	-21.4
	BLYP	-13.0
	TPSS	-18.3
	B3LYP	-16.8
	PBE0	-24.5
	M06	-23.1
	TPSSh	-19.8
	BNL	-25.2
	CAM-B3LYP	-20.8
	LC- ω PBE	-27.0
	ω B97X-D	-24.0
	CCSD(T)//MP2	-23.9

-25.4 kcal mol⁻¹), while the other reaction energies fall in a narrow range between -23.9 and -22.9 kcal mol⁻¹.

There is considerable diversity in the predictions of the net reaction energies by the DFT methods. The BLYP and B3LYP functionals tend to underestimate the stability of the products by a significant margin, a feature recently noted by Krenske et al.⁵³ The PBE0, M06, BNL, and ω B97X-D functionals are all in good agreement with the CCSD(T)//MP2 energies. ω B97X-D

is in closest agreement, deviating from the CCSD(T)//MP2 reaction energies by only 0.0–0.7 kcal mol⁻¹.

CONCLUSION

In this study, we evaluated a range of quantum chemical methods for modeling Michael-type addition reactions of thiols with electron deficient olefins. High level ab initio calculations using CCSD(T)//MP2 show that a methylthiolate anion will react with substituted olefins to form a stable carbanion intermediate. Many pure and hybrid DFT functionals incorrectly predict that there is no such intermediate due to spurious stabilization of a noncovalent charge-transfer complex. Range-separated DFT functionals, such as ω B97X-D, correct this failure and predict stable carbanions in good agreement with the CCSD(T)//MP2 results. This shows that the canonical mechanism for a thio-Michael-type addition is viable and can be described realistically using range-separated DFT functionals. These range-separated functionals will allow for rigorous modeling of the chemical modification of cysteine side chains by electrophilic drugs.

ASSOCIATED CONTENT

Supporting Information

Potential energy surfaces for the addition of methylthiolate to MVK calculated using the LC- ω PBE, PBE, and PBE0 functionals; tables of carbanion and product stabilities for wider set of ab initio methods. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: crowley@mun.ca.

Notes

The authors declare no competing financial interest.

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