ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Influence of Base and Structure in the Reversible Covalent Conjugate Addition of Thiol to Polycyclic Enone Scaffolds

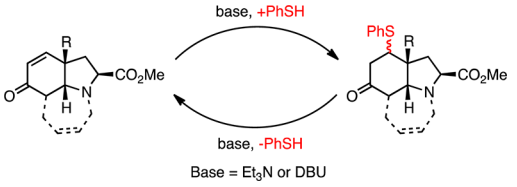
Christopher J. Rosenker,[‡] Elizabeth H. Krenske,*[,†] K. N. Houk,*[,§] and Peter Wipf*[,‡]

School of Chemistry, University of Melbourne, VIC 3010, Australia, and Australian Research Council Centre of Excellence for Free Radical Chemistry and Biotechnology, Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States, and Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

e.krenske@uq.edu.au; houk@chem.ucla.edu; pwipf@pitt.edu

Received January 11, 2013

ABSTRACT



The energetics of thiol addition and elimination reactions to bicyclic enones derived from an indole core structure were explored using ^{1}H NMR and density functional theory (DFT) calculations. The agreement between experiment and theory is excellent, and the combined results reveal that even minor changes in the conformation of the enone, substituents on the scaffold, and the use of different bases have a signficant influence on product distribution. A potential application of these principles is in the rational design of new reversible covalent enzyme inhibitors.

Interest in irreversible inhibitors of enzymatic transformations or receptor mediated events has surged in recent years, in part due to a better understanding of the mechanism of action of biologically active natural products, which often act as covalent modifiers.[1] In addition to α-halo carbonyl groups, oxiranes, acylamides, and vinyl sulfones, enones are increasingly valuable as tunable covalent inhibitors,[2] and the potential use of enones as selective thiol capture agents in enzyme active sites and allosteric hot spots has encouraged mechanistic studies.[3] Spectroscopic and computational methods have been developed to rapidly classify thiol acceptors,[4] and many synthetic protocols are available to effect Michael reactions of sulfur donors.[5]

In previous studies, we have identified thiol capture pathways in epoxyketones and used reversible thiol additions to enones in natural products total synthesis.[6,7] For example, the synthesis of (−)-tuberostemonine **1** required

[†] University of Melbourne and Australian Research Council Centre of Excellence for Free Radical Chemistry and Biotechnology. Current address: School of Chemistry and Molecular Biosciences, University of Queensland, Brisbane, QLD 4072, Australia.

[‡] University of Pittsburgh.

[§] University of California.

(1) (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311. (b) Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053. (c) Drahl, C.; Cravatt, B. F.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5788.

(2) For reviews and recent examples: (a) Amslinger, S. *ChemMedChem* **2010**, *5*, 351. (b) Singh, J.; Petter, R. C.; Baillie, T. A.; Whitty, A. *Nat. Rev. Drug Discovery* **2011**, *10*, 307. (c) Zheng, S.; Santosh Laxmi, Y. R.; David, E.; Dinkova-Kostova, A. T.; Shiavoni, K. H.; Ren, Y.; Zheng, Y.; Trevino, I.; Bumeister, R.; Ojima, I.; Wigley, W. C.; Bliska, J. B.; Mierke, D. F.; Honda, T. *J. Med. Chem.* **2012**, *55*, 4837. (d) Serafimova, I. M.; Pufall, M. A.; Krishnan, S.; Duda, K.; Cohen, M. S.; Maglathlin, R. L.; McFarland, J. M.; Miller, R. M.; Frödin, M.; Taunton, J. *Nat. Chem. Biol.* **2012**, *8*, 471.

(3) (a) van Axel Castelli, V.; Bernardi, F.; Dalla Cort, A.; Mandolini, L.; Rossi, I.; Schiaffino, L. *J. Org. Chem.* **1999**, *64*, 8122. (b) Castelli, V.; Dalla Cort, A.; Mandolini, L.; Reinhoudt, D.; Schiaffino, L. *Eur. J. Org. Chem.* **2003**, 627. (c) Krenske, E. H.; Petter, R. C.; Zhu, Z.; Houk, K. N. *J. Org. Chem.* **2011**, *76*, 5074.

(4) (a) Suzuki, M.; Mori, M.; Niwa, T.; Hirata, R.; Furuta, K.; Ishikawa, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 2376. (b) Cusack, K. P.; Arnold, L. D.; Barberis, C. E.; Chen, H.; Ericsson, A. M.; Gaza-Bulseco, G. S.; Gordon, T. D.; Grinnell, C. M.; Harsch, A.; Pellegrini, M.; Tarcsa, E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5503. (c) Gacche, R.; Khsirsagar, M.; Kamble, S.; Bandgar, B.; Dhole, N.; Shisode, K.; Chaudhari, A. *Chem. Pharm. Bull.* **2008**, *56*, 897. (d) Avonto, C.; Taglialatela-Scafati, O.; Pollastro, F.; Minassi, A.; Di Marzo, V.; De Petrocellis, L.; Appendino, G. *Angew. Chem., Int. Ed.* **2010**, *50*, 467.

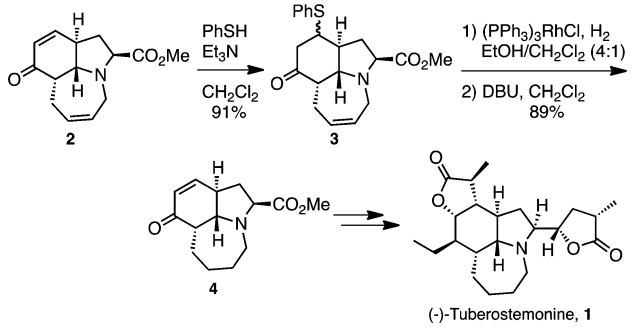
(5) (a) Enders, D.; Luettgen, K.; Narine, A. A. *Synthesis* **2007**, 959. (b) Breman, A. C.; Smits, J. M. M.; De Gelder, R.; Van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *Synlett* **2012**, *23*, 2195.

(6) Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351.

10.1021/ol400094k

the differentiation of the alkene moieties in the six- and seven-membered rings of intermediate **2**, which was accomplished by masking the enone as thioether **3** (Scheme 1).[7,8a] The azepine was then hydrogenated using Wilkinson's catalyst, and the enone was regenerated by a DBU-mediated thiophenol elimination to give **4**.[8b]

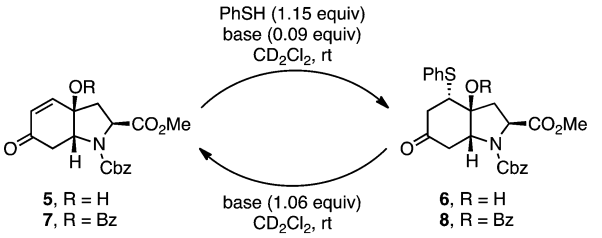
Scheme 1. Thiol Addition/Elimination in the Synthesis of Tuberostemonine (**1**)



We were intrigued by the ability to move the equilibrium between enone **2** and β-thiophenylketone **3** back to enone **4**, but we could only speculate about the influence of conformational changes in the tricycle (azepine vs azepane) or the effect of base (Et_3N vs DBU) in this conversion. Accordingly, we explored, experimentally and computationally, the energetics of several related indole derived enones. While the equilibrium constant was of major interest to us in the current study, we have studied transition states for related simpler systems elsewhere.[3c] The barriers of addition of thiolate to enones are quite low in aprotic solvents. The amine bases serve to form thiolates, and the ammonium cations then protonate the enolate generated by thiolate addition to enone.[9]

Thiophenol addition reactions were performed in the presence of a slight excess of thiol (1.15 equiv) and catalytic base (0.09 equiv of Et_3N or DBU), while the thiol eliminations used stoichiometric base (1.06 equiv of Et_3N or DBU). The ratio of starting material to product was analyzed by ^{1}H NMR and used to determine the ΔG of the thiol addition/elimination processes.

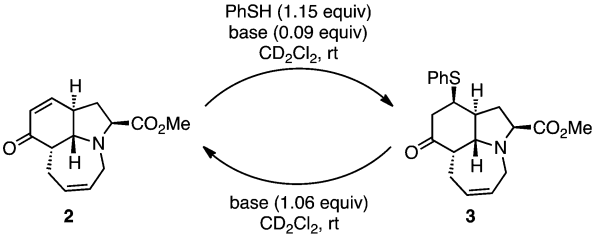
The determination of the equilibrium in the addition of thiophenol to bicyclic enone **5**[10] in the presence of either Et_3N or DBU gave a $\Delta G \leq -4.6$ kcal/mol for this conversion (Figure 1). Thiol elimination from the major stereoisomer of thioether **6** in the presence of Et_3N was found to result in a ΔG of +1.8 kcal/mol, while the thiol elimination of **6** using DBU yielded a **5:6** ratio of ≥50:1 by ^{1}H NMR with a $\Delta G \leq -3.8$ kcal/mol. The thiol addition reaction to provide thioether **8** provided a 2.0−2.3:1 ratio of stereoisomers and was favored by $\Delta G = -4.1$ to −4.0 kcal/mol in the presence of catalytic Et_3N or DBU. Additionally, thiol elimination of **8** to afford **7** was unfavorable by +1.0 kcal/mol using Et_3N, but favorable by ≤ −3.8 kcal/mol in the presence of DBU.



reaction	base	ΔG [kcal/mol]
5 to **6**	Et_3N	≤ −4.6
5 to **6**	DBU	≤ −4.6
6 to **5**	Et_3N	+1.8 ± 0.03
6 to **5**	DBU	≤ −3.8
7 to **8**	Et_3N	−4.1 ± 0.06
7 to **8**	DBU	−4.0 ± 0.02
8 to **7**	Et_3N	+1.0 ± 0.001
8 to **7**	DBU	≤ −3.8

Figure 1. Thiol addition/elimination reactions with enones **5** and **7** using Et_3N and DBU.

Addition of thiophenol to tricyclic enone **2** was highly favorable and exceeded the limits of detection by ^{1}H NMR (≤−4.6 kcal/mol) using either catalytic Et_3N or DBU (Figure 2). Thiol elimination in thioether **3** was unfavorable by +3.4 kcal/mol in the presence of Et_3N; however, the thiol elimination proved favorable by ≤ −2.6 kcal/mol in the presence of DBU.



reaction	base	ΔG [kcal/mol]
2 to **3**	Et_3N	≤ −4.6
2 to **3**	DBU	≤ −4.6
3 to **2**	Et_3N	+3.4 ± 0.1
3 to **2**	DBU	≤ −2.6

Figure 2. Thiol addition/elimination reactions with enone **2** using Et_3N and DBU.

Et_3N and DBU catalyzed thiophenol additions to tricyclic enone **4** were favorable with a $\Delta G \leq -4.6$ kcal/mol

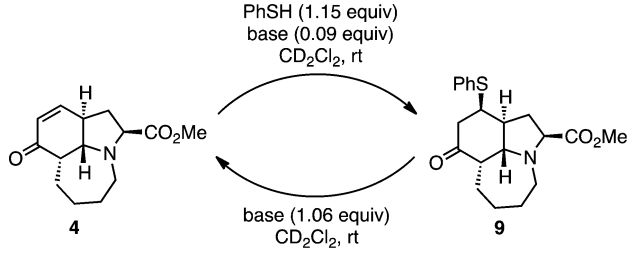
(7) (a) Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225.

(8) (a) De Groot, A.; Peperzak, R. M.; Vader, J. *Synth. Commun.* **1987**, *17*, 1607. (b) Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757.

(9) For other studies of the mechanism of reversible sulfa-Michael reactions, see: (a) Dmuchovsky, B.; Vineyard, B. D.; Zienty, F. B. *J. Am. Chem. Soc.* **1964**, *86*, 2874. (b) Friedman, M.; Cavins, J. F.; Wall, J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3672. (c) De Maria, P.; Fini, A. *J. Chem. Soc. (B)* **1971**, 2335.

(10) For additional examples of conjugate addition reactions with enone **5**, see: (a) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576. (b) Wipf, P.; Mareska, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723.

(Figure 3). The thiol elimination reaction of **9** was unfavorable by 2.3 kcal/mol using Et_3N and favorable by −2.9 kcal/mol using DBU.

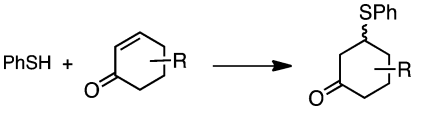


reaction	base	ΔG [kcal/mol]
4 to **9**	Et_3N	≤ −4.6
4 to **9**	DBU	≤ −4.6
9 to **4**	Et_3N	2.3 ± 0.03
9 to **4**	DBU	−2.9 ± 0.2

Figure 3. Thiol addition/elimination reactions with enone **4** using Et_3N and DBU.[11]

We used density functional theory calculations[12] to analyze the effect of base on the thiol addition/elimination equilibria. Geometries of the enones and their PhSH adducts were optimized at the B3LYP/6-31G(d) level,[13] and single-point energies were then computed at the M06-2X/6-311G(2d,p) level.[14,3c] The theoretical values of ΔH and ΔG for the addition of thiophenol to the four enones are shown in Table 1.

Table 1. Computed Thermodynamics for Additions of PhSH to Enones [kcal/mol][a]



enone	adduct	ΔH (gas)	ΔG (gas)	ΔG (soln)	ΔG (expt)
5	**6**	−18.1	−2.9	−0.1	≤−4.6
7	**8**	−18.1	−2.9	0.0	−4.1, −4.0
2	**3**	−20.1	−6.3	−4.1	≤−4.6
4	**9**	−20.2	−6.2	−3.9	≤−4.6

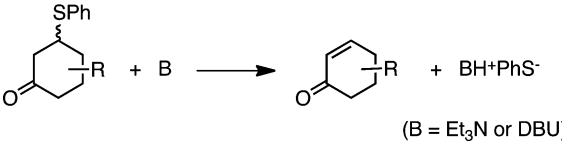
[a] M06-2X/6-311G(2d,p)//B3LYP/6-31G(d), 1 mol/L, 298.15 K, kcal/mol; solution-phase data include SMD solvation energies in CH_2Cl_2 computed at the B3LYP/6-31G(d) level.

The computed values of ΔH predict that the tricyclic enones **2** and **4** should be considerably more reactive toward the addition of PhSH than the OH- and OBz-substituted enones **5** and **7**. The gas-phase ΔG values predict the same trend, although the reactivities of the more conformationally flexible enones **5** and **7** appear to diminish somewhat owing to the larger predicted values of $-T\Delta S$. We explored the use of several solvation models to estimate the free energies in dichloromethane and found that SMD[15] solvation energies computed at the B3LYP/6-31G(d) level gave the best agreement with experiment. The solution-phase ΔG values are 2−3 kcal/mol higher than those in the gas phase and underestimate the experimental reactivities. This is likely due to the tendency of continuum solvation to overestimate solute entropies.

Among the base-catalyzed thiol additions to enones investigated, our experiments show that additions of PhSH to enones **5**, **2**, and **4** are highly favorable. The thiol addition to enone **7** is slightly less favorable, possibly due to the increased steric bulk placed on the tertiary alcohol by the benzoyl group, although the computed energetics do not fully capture this decreased reactivity.

Computed energetics for the deprotection of the thioethers by stoichiometric Et_3N or DBU are presented in Table 2. The structure of the byproduct ion pair $Et_3NH^+PhS^-$ could not be located in the gas phase, and therefore the structures of both ion pairs ($Et_3NH^+PhS^-$ and $DBUH^+PhS^-$) were optimized in solvent.

Table 2. Computed Thermodynamics for Elimination of PhSH from Enone Adducts by Stoichiometric Et_3N or DBU [kcal/mol][a]



adduct	enone	base	ΔH (gas)	ΔG (gas)	ΔG (soln)	ΔG (expt)
6	**5**	Et_3N	21.0	17.1	1.1	1.8
		DBU	19.0	15.8	−2.7	≤−3.8
8	**7**	Et_3N	21.1	17.1	1.1	1.0
		DBU	19.1	15.7	−2.7	≤−3.8
3	**2**	Et_3N	23.1	20.4	5.1	3.4
		DBU	21.1	19.1	1.4	≤−2.6
9	**4**	Et_3N	23.1	20.3	5.0	2.3
		DBU	21.1	19.0	1.2	−2.9

[a] M06-2X/6-311G(2d,p)//B3LYP/6-31G(d), 1 mol/L, 298.15 K, kcal/mol; solution-phase data include SMD solvation energies in CH_2Cl_2 computed at the B3LYP/6-31G(d) level.

The calculated ΔG values for the deprotection reactions in solution lie within ~1 kcal/mol of experiment for bicyclic thioethers **6** and **8** but are 2−4 kcal/mol too positive for tricyclic **3** and **9**. Theory predicts that the elimination of PhSH from any thioether by stoichiometric DBU should be 3.8 kcal/mol more favorable than

(11) During the thiol elimination of **9** in the presence of DBU, enone **4** epimerizes to a 2.5:1 mixture of epimers α to the carbonyl group.

(12) Calculations were performed with Gaussian 09 (Frisch, M. J., et al.); see Supporting Information.

(13) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(14) (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

(15) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.

deprotection by Et_3N, in good agreement with the experimental measurements. The experiment shows the DBU deprotections to be 4.8−6.0 kcal/mol more favorable than the corresponding Et_3N deprotections.

The investigations described herein demonstrate that the conversion of a substituted cyclohexenone to its PhSH adduct is a weakly exergonic reaction, and the elimination of the thiol from the adduct depends on the strength of the base. In an ion-pairing solvent such as CH_2Cl_2, the equilibrium Base + RSH $\leftrightarrows$ $BaseH^+RS^-$ determines whether elimination of the thiol is favored or not, and the use of DBU rather than Et_3N in CH_2Cl_2 provides approximately 4 kcal/mol of driving force. In a polar solvent, the relevant equilibrium is Base + H^+ $\leftrightarrows$ $BaseH^+$. The pK_a values of DBU and Et_3N in DMSO,[16] for example, indicate a 4.1 kcal/mol greater driving force for deprotection when using DBU. Accordingly, the fine control exerted over the enone/thioether equilibrium by base strength and, in particular, the effect of the enone substitution pattern is an important consideration in the design of enones as tunable covalent modifiers of enzyme thiol groups.

Acknowledgment. This work was supported by the National Science Foundation (CHE 1059084 to K.N.H.), Australian Research Council (DP0985623 to E.H.K.), ARC Centre of Excellence for Free Radical Chemistry and Biotechnology (funding to E.H.K.), and the National Institutes of Health (GM067082 to P.W.). Computing resources were provided by the National Computational Infrastructure National Facility (Australia) and the University of Melbourne.

Supporting Information Available. Experimental procedures and spectral data for all new compounds, including copies of ^1H and ^{13}C NMR spectra, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) pK_a values in DMSO: $DBUH^+$ 12, $TEAH^+$ 9.

The authors declare no competing financial interest.