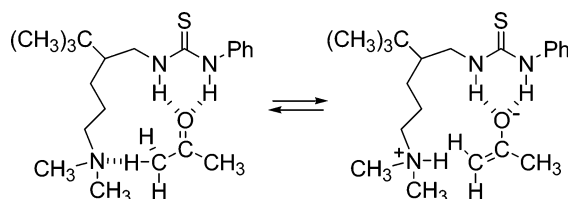# Transition State Modeling and Catalyst Design for Hydrogen Bond-Stabilized Enolate Formation

Yimin Zhu and Dale G. Drueckhammer*

Department of Chemistry, Stony Brook University, Stony Brook, New York 11794

dale.drueckhammer@sunysb.edu

Received July 4, 2005

A catalyst for enolate formation was designed that incorporates an amine base along with a thiourea to bind to the oxygen atom of the substrate and enolate through hydrogen bonding. A computational model of the transition state was developed in which the thiourea (modeled initially as a urea) and amine were separate molecules. This model and models incorporating one or two methanol molecules in place of the urea showed an out-of-plane hydrogen bond, apparently to the carbonyl π-bond, in addition to an in-plane hydrogen bond to an unshared electron pair. In contrast, optimized complexes of the ketone and the fully formed enolate showed only in-plane hydrogen bonding. The transition state model with the urea and amine was used to define a database search with the computer program CAVEAT to identify structures suitable for linking the amine and urea/thiourea moieties in the transition state. On the basis of a group of structures identified from this search, a flexible but conformationally biased linker was designed to connect the two catalytic moieties. The molecule having the amine and thiourea moieties connected by this linker was synthesized and was shown to catalyze proton exchange between methanol and deuterated acetone. The catalyst was about 5-fold more efficient than the amine and thiourea as separate molecules and relative to a similar but less conformationally biased catalyst.

Introduction

The design of simple catalysts that in a general way mimic the action of enzymes is a longstanding and continuing goal of organic chemistry.[1-4] A recent very successful example is the use of proline and analogues as simple catalysts for aldol condensation and related reactions.[5-8] Catalysis is achieved via an enamine mechanism related to the mechanism of the class I aldolases.[9] Other enzymes such as the class II aldolases and citrate synthase catalyze similar reactions via enolate intermediates.[10-12] Simple catalysts for enolate formation could potentially be applied to esters and other carboxylic acid derivatives, for which enamine formation is not viable, and could have practical use in carbon–carbon bond forming and racemization reactions.[13,14] Several catalysts for formation of enolates or enols have been described, including cyclodextrins having appended basic groups,[15-19]

(1) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532.

(2) Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635–3638.

(3) French, R. R.; Holzer, P.; Leuenberger, M. G.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1267–1269.

(4) Yan, J.; Breslow, R. *Tetrahedron Lett.* **2000**, *41*, 2059–2062.

(5) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

(6) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557.

(7) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579.

(8) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591.

(9) Morris, A. J.; Tolan, D. R. *Biochemistry* **1994**, *33*, 12291–12297.

(10) Hall, D. R.; Leonard, G. A.; Reed, C. D.; Watt, C. I.; Berry, A.; Hunter, W. N. *J. Mol. Biol.* **1999**, *287*, 383–394.

(11) Kurz, L. C.; Shah, S.; Crane, B. R.; Donald, L. J.; Duckworth, H. W.; Drysdale, G. R. *Biochemistry* **1992**, *31*, 7899–7907.

(12) Kluger, R. *Chem. Rev.* **1990**, *90*, 1151–1169.

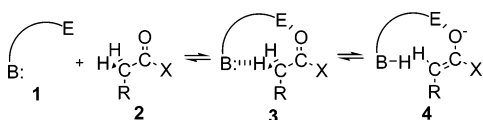(13) Um, P.-J.; Drueckhammer, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 5605–5610.

(14) Dinh, P. M.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1999**, *40*, 749–752.

(15) Siegel, B.; Pinter, A.; Breslow, R. *J. Am. Chem. Soc.* **1977**, *99*, 2309–2312.

(16) Breslow, R.; Graf, A. *J. Am. Chem. Soc.* **1993**, *115*, 10988–10989.

(17) Desper, J. M.; Breslow, R. *J. Am. Chem. Soc.* **1994**, *116*, 12081–12082.

SCHEME 1

SCHEME 2

aza-crown ethers,[20] and a modified Kemp's triacid.[21] Such catalysts are typically designed to have distinct functional groups for deprotonation and for stabilization or protonation of enolate oxygen. A recognized challenge in the design of such catalysts is making the backbone structure sufficiently rigid or constrained to prevent collapse into a conformation in which the catalytic groups simply bind to each other.[21,22] Several receptors have been reported that selectively bind and stabilize enolates.[22−27] These receptors usually bind the enolate via hydrogen-bonding interactions to the enolate oxygen, though acidity enhancement by intramolecular coordination to Zn(II) ion has also been demonstrated.[25]

The goal of this project was to use computer-guided design methods based on the computer program CAVEAT to design a simple enolate-forming catalyst. CAVEAT is a unique program developed by Bartlett and co-workers that searches a virtual molecular database to identify structures having bonds that match a set of defined vectors.[28,29] Each vector defines a starting point and a direction, with compounds identified using CAVEAT having sets of atoms and associated bonds corresponding to each vector. This program has been used in the design of enzyme inhibitors and conformationally constrained peptides[28,29] and more recently in the design of chiral ligands for asymmetric catalysis[30] and a boronic acid-based receptor and sensor for glucose.[31]

The general approach of this project is illustrated in Scheme 1. The catalyst **1** is envisioned having an electrophilic group (E) that will coordinate to the carbonyl oxygen of the substrate **2** and stabilize the enolate during

catalysis, linked to a basic group (B) positioned to deprotonate the α-carbon. The linker should hold the electrophilic and basic groups in proper relative position for optimal transition state stabilization in conversion of the substrate complex **3** to the enolate complex **4**. Described here are the computational modeling of the transition state for this reaction, the design of an appropriate linker, and synthesis and testing of the designed catalyst.

Results

For this initial study, an amine was chosen as the basic group and a urea or thiourea as the electrophilic group. The development of a computer model for the transition state began with location of the transition state **5** for proton transfer from the protonated form of acetone to trimethylamine (Scheme 2). The transition state for this reaction was located and optimized at the HF/6-31+G-(d) level using the QST2 method in Gaussian03.[32] The resulting structure was modified by deletion of the proton on the oxygen and introduction of *N,N′*-dimethylurea in position to form two hydrogen bonds to this oxygen. One of the amine methyl groups was replaced with a hydrogen atom to simplify the structure.
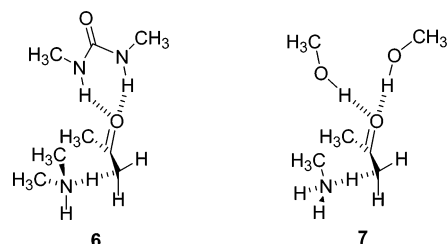
FIGURE 1. Complexes used in transition state models.

The atoms of the amine, the enolate, and the transfer-ring proton were frozen, and the position and structure of the urea moiety was optimized at the B3LYP/6-31+G-(d) level to give the approximate transition state structure **6** shown in Figures 1 and 2. In complexes with acetone or its enolate, the urea aligned in approximately the same plane as the non-hydrogen atoms of the ketone

(18) Breslow, R.; Desper, J. M.; Huang, Y. *Tetrahedron Lett.* **1996**, *37*, 2541−2544.

(19) Binder, W. H.; Menger, F. M. *Tetrahedron Lett.* **1996**, *37*, 8963−8966.

(20) Fenniri, H.; Lehn, J.-M.; Marquis-Rigault, A. *J. Am. Chem. Soc.* **1996**, *35*, 337−339.

(21) Wolfe, J.; Muehldorf, A.; Rebek, J. *J. Am. Chem. Soc.* **1991**, *113*, 1453−1454.

(22) Snowden, T. S.; Bisson, A. P.; Anslyn, E. V. *Bioorg. Med. Chem.* **2001**, *9*, 2467−2478.

(23) Chin, T.; Gao, Z.; Lelouche, I.; Shin, Y. K.; Purandare, A.; Knapp, S.; Isied, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 12849−12858.

(24) Kimura, E.; Kitamura, H.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1997**, *119*, 10909−10919.

(25) Kimura, E.; Gotoh, T.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 1267−1274.

(26) Kelly-Rowley, A. M.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1995**, *117*, 3438−3447.

(27) Snowden, T. S.; Bisson, A. P.; Anslyn, E. V. *J. Am. Chem. Soc.* **1999**, *121*, 6324−6325.
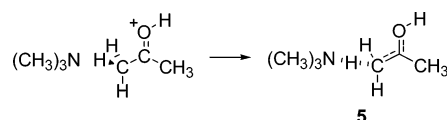
(28) Lauri, G.; Bartlett, P. A. *J. Comput.-Aided Mol. Des.* **1994**, *8*, 51−66.

(29) (a) Bartlett, P. A.; Shea, G. T.; Telfer, S. J.; Waterman, S. In *Molecular Recognition: Chemical and Biological Problems*; Roberts, S. M., Ed.; Royal Society of Chemistry: London, 1989; pp 182−196. (b) Bartlett, P. A.; Etzkorn, F. A.; Guo, T.; Lauri, G.; Liu, K.; Lipton, M.; Morgan, B. P.; Shea, G. T. In *Chemistry at the Frontiers of Medicine*, Proceedings of the Robert A. Welch Foundation Conference on Chemical Research XXXV, Houston, TX, Oct 28−29, 1991; Robert A. Welch Foundation: Houston, TX, 1991; pp 45−68.

(30) Kozlowski, M. C.; Panda, M. *J. Mol. Graphics Modell.* **2002**, *20*, 399−409.

(31) Yang, W.; He, H.; Drueckhammer, D. G. *Angew. Chem., Int. Ed.* **2002**, *40*, 1714−1718.

(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision A.1; Gaussian, Inc.: Wallingford, CT, 2004.
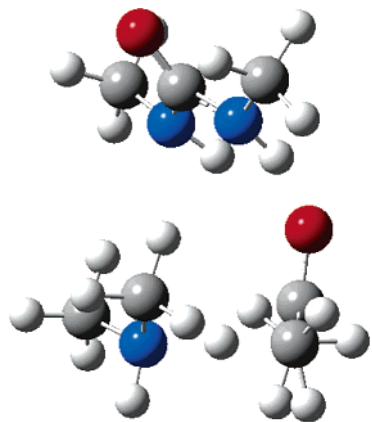
FIGURE 2. Transition state model **6** for the deprotonation of the acetone−dimethylurea complex by dimethylamine.
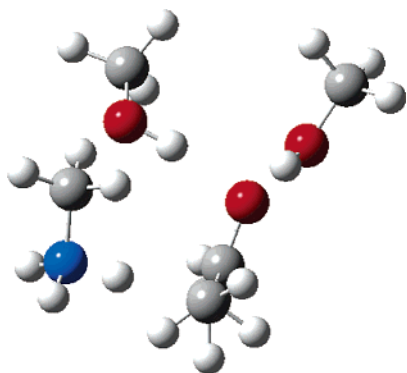

FIGURE 3. Transition state model **7** for the deprotonation of the acetone−bis-methanol complex by methylamine.

or enolate. However, in this and other transition state-like structures, the urea is always significantly tilted out of the plane of the developing enolate toward the side on which deprotonation is occurring. To further investigate this issue, structures with one or two methanol molecules hydrogen-bonded to the frozen transition state were also calculated at the B3LYP/6-31+G(d) level. The optimized structure with a single methanol molecule had the hydrogen bond from methanol directed perpendicular to the plane of the developing enolate on the face nearest the base. When a second methanol molecule was introduced, the first methanol molecule remained in the same position while the second formed a hydrogen bond in the plane of the developing enolate (**7**, Figures 1 and 3).

The later steps in the catalyst design are illustrated in Scheme 3. The C−N bonds of the amine and urea shown in bold of the transition state complex **6** were used to define a vector pair for a CAVEAT search. Structure **8** was found from a recently developed virtual library of trisubstituted cyclic hydrocarbon structures, with the C−H bonds of **8** shown in bold matching the vector pair defined by **6**. Replacement of these hydrogens by the urea and amine groups leads to the potential catalyst structure **9**. While this structure has a good deal of flexibility, it was observed that, in the conformation that matches the vectors defined by **6**, the two C−C bonds extending from the ring to the urea are both in gauche conformations relative to the other carbons of the chain connecting the urea and amine groups. In contrast, the two C−C bonds extending to the amine group are both in the preferred
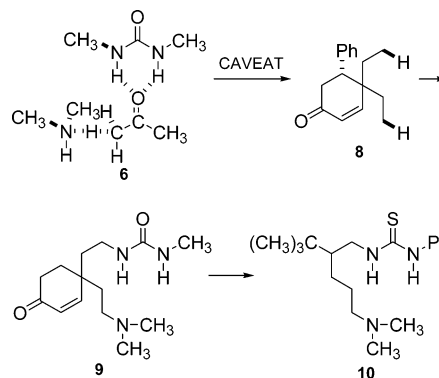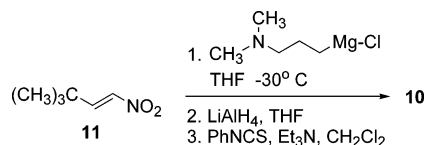
anti conformation. The structure was further simplified by deleting the ring and introducing a *tert*-butyl group at the carbon connecting the two gauche carbon−carbon bonds. The *tert*-butyl group is expected to induce the gauche conformation of the main chain at both C−C bonds extending from the *tert*-butyl substituted carbon, as both methylene groups will prefer to be anti to the *tert*-butyl group. Also, the methyl urea moiety was replaced with the phenylthiourea to form **10**.

A conformational search of **10** by AM1 identified a structure in which the amine group is positioned to form a somewhat distorted hydrogen bond with the more internal N−H of the thiourea. In calculations not considering solvation (B3LYP/6-311+G(d,p)//B3LYP/6-31G-(d)), this internally hydrogen-bonded structure was more stable than the proposed active structure of the catalyst. However, when a solvation model (PCM) was included in the calculations, initially with chloroform as the solvent, the proposed active conformation was calculated to be more stable than the somewhat strained hydrogen-bonded structure by about 0.3 kcal/mol.

The synthesis of the designed catalyst was completed as shown in Scheme 4. The nitroolefin **11** was prepared by a base-catalyzed Henry reaction of trimethylacetaldehyde and nitromethane followed by dehydration of the resulting nitro alcohol as previously described.[33] Addition of the Grignard reagent derived from commercially available 3-(*N*,*N*-dimethylamino)-1-chloropropane and reduction of the nitro group to the amine was followed by phenylthiourea formation to make the proposed catalyst **10**. For comparison purposes, the equivalent structure **13** lacking the *tert*-butyl group was prepared by reduction of the nitrile **12**[34] and thiourea formation as shown in Scheme 5.

The ^{1}H NMR spectrum of **10** was compared to that of *N*-butyl-*N*′-phenylthiourea to evaluate possible intramolecular hydrogen-bonding interactions.[35] The proton on

(33) Lucet, D.; Sabelle, S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583−2591.

(34) Park, S.; Hayes, B. L.; Marankan, F.; Mulhearn, D. C.; Wanna, L.; Mesecar, A. D.; Santarsiero, B. D.; Johnson, M. E.; Venton, D. L. *J. Med. Chem.* **2003**, *46*, 936−953.

SCHEME 5
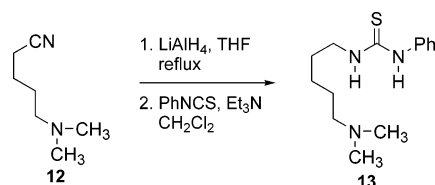
TABLE 1. Rate Constants for the Catalyzed Proton Exchange Reactions

catalyst	rate constant (min^{-1})[a]
BuNMe2	0.009
BuNMe2 + BuNHCSNHPh	0.009
10	0.046
13	0.011

[a] Conditions: 0.1 mmol catalyst, 0.05 mL of methanol, in 0.5 mL of acetone-d_6 at room temperature.

the internal alkyl nitrogen of **10** was shifted to about 6.6 ppm from 6.0 ppm for the equivalent proton of the model thiourea. The proton on the phenyl-substituted nitrogen at 8.2 ppm was not shifted significantly. Compound **13** exhibited a smaller shift of the internal alkyl nitrogen and a larger downfield shift of the phenyl-substituted nitrogen relative to **10**. Addition of 1 equiv of butyl dimethylamine to the model thiourea (both 0.2 M) resulted in no change in chemical shift of either of the thiourea protons. Attempts were made to evaluate binding of acetone to **10** from the change in chemical shift of the thiourea protons. A downfield shift of these protons was observed in acetone-d_6 compared to CDCl$_3$, the *N*-phenyl proton moving from 8.2 to 8.9 ppm and the *N*-alkyl proton moving from 6.6 ppm to the region overlapping with the phenyl protons at 7.2–7.4 ppm. As the percentage of acetone in an acetone/CDCl$_3$ mixture was increased, a gradual shift of the thiourea protons was observed but a point of saturation was not observed.

The catalysis of enolate formation by **10** was determined by deuterium exchange experiments in deuterated acetone using methanol as a source of exchangeable proton. The reaction was monitored by ^{1}H NMR following the disappearance of the methanol OH peak and appearance of the acetone peak over time. For comparison catalysis by *N,N*-dimethylbutylamine, a model for the amine component of catalyst **10** was studied. Also studied was catalysis by the same model amine in the presence of *N*-butyl-*N'*-phenylthiourea and by the catalyst structure **13** lacking the *tert*-butyl group. The results are summarized in Table 1. While no detectable exchange was observed in the absence of any catalyst, significant reaction was observed in the presence of butyldimethylamine. No detectable enhancement of this rate was observed when a molar equivalent of *N*-butyl-*N'*-phenylthiourea relative to the amine was included. The rate of exchange catalyzed by **10** was 5-fold greater than that of the simple amine. In contrast, the catalyst **13** lacking the *tert*-butyl group exhibited only slight rate enhancement relative to the simple amine. An experiment was also done to measure the exchange reaction between deuterated methanol and nondeuterated acetone. The rate was faster than that with deuterated acetone by a factor of 1.4.

Discussion

This work was directed at the development of a catalyst for enolate formation designed to function in non-hydrogen-bonding organic solvent, such that binding of the catalyst to the carbonyl substrate could be driven by hydrogen-bonding interactions. Urea, thiourea, and related guanidinium functionality have been used extensively in catalysts for nucleophilic addition to carbonyl groups, conjugate additions, and related reactions and thus were chosen as simple and easily prepared enolate-stabilizing groups for this work.[36–40] A urea was used in initial modeling, but in the actual catalyst was replaced by the phenylthiourea, which is easily synthesized, is expected to be more acidic and thus a better hydrogen bond donor than the urea, and should be less prone to self-association due to the poorer hydrogen-bonding ability of the sulfur atom. In initial modeling, it was expected that the urea would hydrogen bond to the lone pairs on oxygen in the substrate complex and in the transition state and, thus, that the urea would lie in the same plane as the carbon and oxygen atoms of the ketone and developing enolate. While this was indeed observed in the acetone and enolate complexes, the approximate transition state structure gave a very nonplanar structure. Anslyn and co-workers have proposed and demonstrated evidence for enolate stabilization by hydrogen bond donors directed toward the π-bond rather than the lone electron pairs.[22,27] They also pointed out that hydrogen bonds in the enzyme *p*-chlorobenzoyl-CoA dehalogenase are directed perpendicular to the plane of the enolate, consistent with enzymatic stabilization of the intermediate Meisenheimer complex by hydrogen bonds directed toward the π-bond.[41] Similar out-of-plane hydrogen bonding is observed in crotonase[42] and likely in the other members of the crotonase superfamily,[22,43] and in the acyl-CoA dehydrogenases.[44,45] In contrast, the hydrogen bonds that stabilize the enolate intermediate in citrate synthase are in the plane of the enolate directed toward the lone electron pairs on oxygen.[46] Our calculations on the urea transition state complex are consistent with the enzymes that exhibit out-of-plane hydrogen bonding. In calculations in which the urea was replaced by a pair of methanol molecules, it was found that one methanol formed a hydrogen bond directed perpendicular

(35) Novak, L.; Hanania, M.; Kovacs, P.; Kovacs, C. E.; Kolonits, P.; Szantay, C. *Synth. Commun.* **1999**, *29*, 1757–1766.

(36) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062–2064.

(37) Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, 713–719.

(38) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589–5592.

(39) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.

(40) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

(41) Benning, M. M.; Taylor, K. L.; Liu, R.; Yang, G.; Xiang, H.; Wesenberg, G.; Dunaway-Mariano, D.; Holden, H. M. *Biochemistry* **1996**, *35*, 8103–8109.

(42) Bahnson, B. J.; Anderson, V. E.; Petsko, G. A. *Biochemistry* **2002**, *41*, 2621–2629.

(43) (a) Babbit, P. C.; Gerlt, J. A. *J. Biol. Chem.* **1997**, *272*, 30591–30594. (b) Xiang, H.; Luo, L.; Taylor, K. L.; Dunaway-Mariano, D. *Biochemistry* **1999**, *38*, 7638–7652.

(44) Kim, J. J.; Wang, M.; Paschke, R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 7523–7527.

(45) Djordjevic, S.; Pace, C. P.; Stankovich, M. T.; Kim, J. J. *Biochemistry* **1995**, *34*, 2163–2171.

(46) (a) Usher, K. C.; Remington, S. J.; Martin, D. P.; Drueckhammer, D. G. *Biochemistry* **1994**, *33*, 7753–7759. (b) Yang, W.; Drueckhammer, D. G. *J. Phys. Chem. B* **2003**, *107*, 5986–5994.

to the plane of the developing enolate directed from the face on which deprotonation is occurring, while the second methanol molecule formed an in-plane hydrogen bond. It appears that the urea complex of the transition state approximates this mode of binding to the extent that the constraints of the urea allow. One of the hydrogen bonds is directed approximately perpendicular to the plane and the other approximately in the plane of the developing enolate. This also permits the hydrogen bonds to be more linear than would be possible if both hydrogen bonds were directed toward the oxygen lone electron pairs. These results support Anslyn's observations and further suggest that the π-bond directed hydrogen bonding may be even more important in the transition state than in the enolate complex.

Calculations on the catalyst structure predict that a collapsed intramolecular hydrogen-bonded structure is possible but that such a structure should not dominate the catalyst conformation in solution. The NMR results are consistent with some degree of intramolecular hydrogen bonding between the amine and the internal thiourea proton in **10**, but with no significant intermolecular hydrogen bonding at this concentration. Further NMR shifts are observed in the presence of acetone, as expected due to hydrogen bonding between acetone and the thiourea. This indicates that intramolecular hydrogen bonding of the catalyst does not prevent hydrogen bonding to substrate, and substrate binding likely breaks up the intramolecular hydrogen bonding. The absence of a point of saturation in thiourea proton shifts upon addition of acetone suggests fairly weak binding of acetone to the catalyst, though an actual association constant could not be determined. The solvent-dependent shift could also be due in part to more general solvent effects in addition to hydrogen bonding.

The proton exchange reactions used to demonstrate catalysis require an exchange reaction of the protonated amine with solvent in the enolate complex. This proton exchange between heteroatoms is expected to be very fast relative to the proton exchange from and to carbon. While this was not verified in the present study, such exchange is a classic observation in enzyme catalysis where the intermediates are expected to be very short-lived and the basic group in the enzyme active site could be somewhat shielded from solvent.[47] Comparison of the exchange reaction of deuterated versus nondeuterated acetone indicates a kinetic isotope effect that is quite small for a reaction in which a proton is being transferred in the slow step. The protonated versus deuterated state of the thiourea moiety of the catalyst and the secondary effect of the other deuterium atoms on acetone may also have some influence on these relative rates. However, these effects are likely to be small such that the actual primary kinetic isotope effect is still probably much less than two. This small kinetic isotope effect likely indicates a very late transition state, in which the N−H (N−D) bond is almost fully formed.

The exchange rates indicate that the proper arrangement of electrophilic and basic groups can provide enhanced catalysis relative to the two groups as separate entities. The comparison of results with **10** versus **13** also indicates the importance of proper conformation of the catalyst. The rates compare favorably with previously reported bifunctional catalysts for enolate or enol formation, with rate constants of about 10^{-3} min^{-1} typically observed.[15,16] An exception is the Kemp's triacid-based catalyst of Rebek and co-workers, in which a protonated α-amino group of the substrate facilitates binding and transition state stabilization, and a kcat of 0.15 min^{-1} was observed.[21] A macrocyclic polyamine was shown by Lehn and co-workers to catalyze H/D exchange in malonate ion at a rate of 13.2 min^{-1}, though with other catalysts the deprotonation of acetone has been shown to be about 1000-fold slower than deprotonation of the more acidic malonate ion.[19,20]

The catalyst designed in this work and previously reported catalysts for enolate formation all fall woefully short of the ideal of mimicking the rates of enzyme catalysis. A well-known challenge in enolate formation is that the charge in the transition state resides largely on carbon rather than oxygen due to nonperfect synchronization.[48,49] Computational studies modeled after enzyme active sites support the potential for hydrogen bonding to carbonyl oxygen in stabilizing the transition state for enolate formation, and indeed it appears that such hydrogen bonding is the primary means of transition state stabilization in enolate-forming enzymes.[50] However, most simple/designed enolate receptors provide only about a 1 pK_a unit increase in acidity of the conjugate acid of their enolate ligands, though Anslyn's receptor having hydrogen-bonding groups directed at the π-system showed a 2.9 pK_a unit enhancement.[22,27] The nonperfect synchronization concept would suggest an even smaller effect on the transition state for enolate formation. An intramolecular hydrogen bond donor was shown to provide a 10−100-fold increase in the rate of enolate formation in a model system.[48] The 5-fold enhancement in the rate exhibited by the thiourea moiety in the catalyst reported in this work, though generally disappointing, is reasonably good based on these comparisons. The nonlinearity of the hydrogen bonds between the oxygen and the thiourea probably diminishes their ability to stabilize the enolate and transition state for its formation, and groups that allow more linear hydrogen bonds could offer some improvement. While an even more optimal and perhaps more rigid linker might provide some further enhancement in catalysis, other kinds of enolate-stabilizing groups such as metal complexes might be more effective than hydrogen-bonding groups and could be amenable to the same design strategy for linking catalytic groups.

The work described here demonstrates that a simple linker designed using CAVEAT can provide an appropriate relative positioning of a pair of functional groups for bifunctional catalysis. This approach may be useful for designing more effective catalysts for reactions that are more easily catalyzed by a pair of properly positioned functional groups and may thus provide a basis for future developments in bifunctional catalysis.

(47) Dinovo, E. C.; Boyer, P. D. *J. Biol. Chem.* **1971**, *246*, 4586−4593.

(48) Zhong, Z.; Snowden, T. S.; Best, M. D.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3488−3495.
(49) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9−16.
(50) Bach, R. D.; Thorpe, C.; Dmitrenko, O. *J. Phys. Chem. B* **2002**, *106*, 4325−4335.

Experimental Section

3-Dimethylaminopropylmagnesium Chloride. To an aqueous solution of sodium hydroxide (105 mL, 1 M) and diethyl ether (50 mL) at 0 °C was slowly added 1-chloro-3-(dimethylamino)propane hydrochloride (15.8 g, 100 mmol). The layers were separated, and the aqueous phase was extracted with diethyl ether (50 mL × 2). The combined organic layers were washed with brine (30 mL) and carefully concentrated under vacuum to a volume of around 20 mL. The solution was then diluted with 50 mL of THF. To a three-necked flask equipped with a condenser and an addition funnel under nitrogen was added freshly ground magnesium turnings (1.9 g, 78 mmol), a crystal of iodine, THF (5 mL), a drop of ethylene bromide, and a few drops of the 1-chloro-3-(dimethylamino)-propane solution. The mixture was gently heated to reflux until the color of the solution disappeared. The solution of 1-chloro-3-(dimethylamino)propane in THF was then added at a rate sufficient to maintain reflux. The solution was heated at reflux for an additional hour before cooling to room temperature. The clear solution was transferred to a flask containing a few crystals of 1,10-phenanthroline. The solution became red after storing in the refrigerator overnight. The red solution was titrated with 2-butanol to give a concentration of 0.81 M.

***N*-5-(Dimethylamino)-2-*tert*-butyl-pentyl *N′*-Phenyl Thiourea 10.** To a solution of **11**[33] (0.646 g, 5 mmol) in THF (10 mL) at −30 °C was added dropwise a solution of 3-di-methylaminopropylmagnesium chloride in THF (7 mL, 0.81 M, 5.7 mmol). The solution was slowly warmed to −20 °C and stirred for 1 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated to give *N,N*,5,5-tetramethyl-4-nitromethyl-1-hexaneamine (0.778 g, 3.6 mmol), which was used in the following step without further purification.

To a solution of *N,N*,5,5-tetramethyl-4-nitromethyl-1-hexaneamine (0.778 g, 3.6 mmol) in THF (15 mL) was added lithium aluminum hydride (0.27 g, 7.1 mmol). The mixture was heated at reflux for 3 h and carefully quenched at 0 °C with aqueous sodium hydroxide solution (20 mL, 4 M). The solution was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, and concentrated to give *N,N*,5,5-tetramethyl-4-aminomethyl-1-hexaneamine (0.649 g, 3.48 mmol), which was used in the following step without further purification.

To a solution of phenyl isothiocyanate (0.49 g, 3.62 mmol) in methylene chloride (3 mL) was added a solution of *N,N*,5,5-tetramethyl-4-aminomethyl-1-hexaneamine (0.649 g, 3.48 mmol) in methylene chloride (3 mL). The solution was stirred at room temperature for 3 h. The solvent was removed under vacuum, and the product was purified by chromatography on silica gel (2:1 ethyl acetate/methanol) to give **10** (0.838 g, 2.6 mmol) in 53% yield over three steps. R_f 0.25 in 2:1 ethyl acetate/methanol. ^{1}H NMR in CDCl$_3$: 8.20 (br, 1H), 7.37 (m, 2H), 7.25 (m, 3H), 6.58 (br, 1H), 3.77 (br, 1H), 3.49 (br, 1H), 2.33 (m,

2H), 2.22 (s, 6H), 1.52 (m, 3H), 1.25 (m, 1H), 1.16 (m, 1H), 0.86 (s, 9H). ^{13}C NMR in CDCl$_3$: 180.1, 136.6, 129.7, 126.7, 125.0, 59.5, 47.7, 46.6, 45.1, 33.2, 27.7, 26.8, 26.3. HRMS calcd for C$_{18}$H$_{32}$N$_3$S 322.2317, found 322.2322.

***N*-5-Dimethylaminopentyl *N′*-Phenyl Thiourea 13.** To a solution of 5-dimethylaminovaleronitrile **12**[34] (0.63 g, 5 mmol) in THF (20 mL) was slowly added lithium aluminum hydride (0.38 g, 10 mmol). The mixture was heated at reflux overnight. The remaining lithium aluminum hydride was carefully quenched with aqueous sodium hydroxide solution (10 mL, 4 M). The solution was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, and concentrated to give the crude 5-dimethylaminopentylamine (0.43 g, 3.3 mmol). The crude amine was dissolved in methylene chloride (3 mL) and then added to a solution of phenyl isothiocyanate (0.47 g, 3.5 mmol) in methylene chloride (3 mL). The solution was stirred at room temperature for 5 h. The solvent was removed under vacuum, and the product was purified by chromatography on silica gel (1:1 ethyl acetate/methanol) to give **13** (0.62 g, 2.34 mmol, 47% yield over two steps). R_f 0.12 in 1:1 ethyl acetate/methanol. ^{1}H NMR in CDCl$_3$: 9.16 (br, 1H), 7.37 (m, 2H), 7.23 (m, 3H), 6.41 (br, 1H), 3.57 (q, 2H), 2.25 (t, 2H), 2.19 (s, 6H), 1.56 (m, 2H), 1.45 (m, 2H), 1.32 (q, 2H). ^{13}C NMR in CDCl$_3$: 179.7, 136.5, 129.3, 126.1, 124.4, 58.9, 44.8, 44.5, 28.3, 26.5, 24.0. HRMS calcd for C$_{14}$H$_{24}$N$_3$S 266.1691, found 266.1684.

Typical Procedure for Deuterium Exchange Experiments. The catalyst **10** (32.1 mg, 0.1 mmol) was dissolved in acetone-d_6 (0.5 mL), and methanol (50 μL, 1.23 mmol) was added. The exchange reaction was monitored by ^{1}H NMR with the disappearing OH peak of methanol and the emerging proton peak of acetone over time. The methyl protons of methanol were used as the internal standard.

Deuterium Exchange of Nondeuterated Acetone with Methanol-d_4. The catalyst **10** (32.1 mg, 0.1 mmol) was dissolved in 0.5 mL of acetone, and methanol-d_4 (50 μL) was added. NMR conditions were optimized with a solution of 0.5 mL of acetone-d_6 and 50 μL of methanol. The exchange reaction was monitored by ^{1}H NMR in the unlock mode following the emerging OH peak of methanol over time. Both the *tert*-butyl protons and the proton at δ 3.70 in the thiourea were used as the internal standard.

Supporting Information Available: General experimental methods, complete descriptions of the calculated geometries of **5**−**7**, and ^{1}H NMR spectra for **10** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0513818