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Molecular mechanics calculations as predictors of enantioselectivity for chiral nucleophile catalyzed reactions

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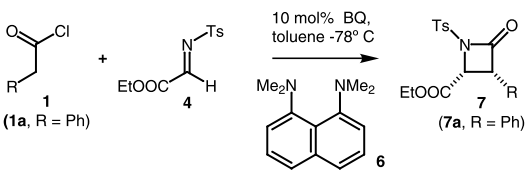
Abstract—We present molecular mechanics (MM) calculations as models of activated complexes for the β-lactam forming [2+2] cycloaddition between imino ester **4** and the zwitterionic intermediates derived from ketenes and various chiral nucleophilic catalysts. Our method employs the use of Monte Carlo conformational searches utilizing the MMFF force field contained within the Macromodel program. These models accurately predict the sense of stereochemical induction observed experimentally. Also, the predicted energetic differences for minima leading to (*R*) or (*S*)-derived ketene facial selectivity correlate in a general sense with the magnitude of the enantioselectivity. This work establishes that our approach represents a viable method for the design of new nucleophilic catalysts a priori using MM calculations.

1. Introduction

The design and screening of new catalysts for asymmetric synthesis is a very important, yet extremely time consuming undertaking. Often the search for a new catalyst involves running an extensive number of reactions followed by chiral HPLC or GC analysis to determine its efficacy, which amounts to a very tedious undertaking. Recently, there have been many developments intended to increase the speed of this process by employing high throughput screening techniques during the search for new catalysts.[1] This process could also be accelerated through the development of a straightforward computational model for the catalytic system being examined. Potential catalysts could then be screened computationally to remove the least likely candidates before the catalyst is screened experimentally. In some cases, especially where researchers often do not have access to the expensive equipment required to perform some of the latest screening techniques, this pre-screen could save valuable time and resources. Not only would this expedite the screening process, it would also provide information as to what controls the sense of induction in the catalyst system. This additional information could be utilized to determine which catalyst motifs can be best exploited. A simple but effective computational technique is expected to work best on metal-free catalyst systems that lead to all-organic activated complexes. In this paper, we propose the use of molecular mechanics (MM) calculations to model activated complexes for reactions catalyzed by chiral nucleophiles and to account for both the sense and relative degree of optical induction.

The sheer importance of β-lactams has made this structural motif a worthwhile goal for the synthetic organic chemist.[2] Recently β-lactams (especially non-natural ones) have achieved many important non-antibiotic uses such as their development as mechanism-based serine protease inhibitors,[3] as well as being useful precursors to β-amino acids. As a testament to the continuing importance of β-lactams to pharmaceutical science, a recent issue of *Tetrahedron* was devoted exclusively to β-lactam chemistry and synthesis.[4] We recently reported a mechanistically distinct, chiral nucleophile catalyzed β-lactam forming reaction[5] by making the ketene nucleophilic (through generation of a zwitterionic intermediate),[6] and the imine component electrophilic (Eq. (1)).[7–9] Herein we expand upon our initial discussion by modeling ketenes with different substituents through a series of MM calculations using the Macromodel program,[10] and by screening other chiral nucleophiles with the intent to lead to the de novo design of a novel nucleophilic catalyst for asymmetric synthesis of β-lactams. By comparing the results of our 'theoretical screening' to our experimental results, we establish the overall validity of the process.



(1)

Keywords: molecular mechanics; Monte Carlo conformational searches; β-lactams; enantioselective; ketenes.

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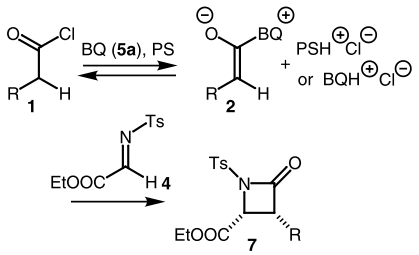


Scheme 1. Proposed mechanism for the BQ catalyzed β-lactam synthesis.

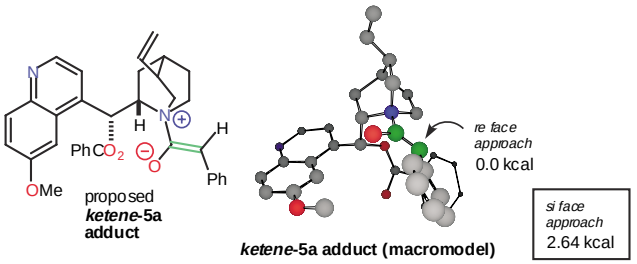
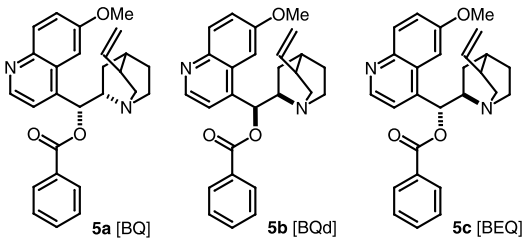


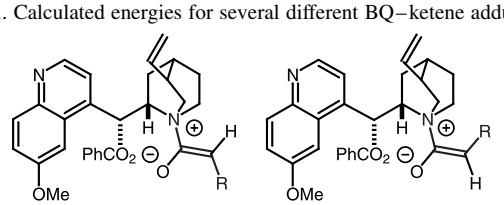
Figure 1. Stereochemical model of the putative zwitterionic intermediates of BQ and phenylketene.



2. Results and discussion

Based on experimental evidence and the known reactivity of ketenes, we have postulated a reaction mechanism that is consistent with the pathway depicted in Scheme 1.[6] An acid chloride (**1**) reacts with benzoylquinine (**5a**, BQ), or another amine-based nucleophilic catalyst (**5b**–**e**, **8**–**11**), to form an acylammonium salt that is subsequently deprotonated to form a zwitterionic enolate **2**, generating 1 equiv. of the hydrochloride of proton sponge (**6**, PS) which precipitates from the reaction solution (free ketenes may not be involved in the reaction).[11] The putative enolate then reacts with imine **4** to form the β-lactam (**7**). Within this mechanism, the nucleophilic cinchona alkaloid-derived catalyst serves a dual role, acting as both a proton shuttle for the in situ generation of ketenes from acid halides as well as an asymmetric catalyst for β-lactam formation. Central to this reaction scenario is the generation of a reactive zwitterionic intermediate **2**, formed by the addition of the nucleophilic cinchona alkaloid nitrogen to the electrophilic carbon of a ketene. To understand which specific structural aspects of the catalyst engendered asymmetry to this process, we sought a simple computational procedure that would accurately predict product selectivities. The use of Monte Carlo MM calculations was judged to be a superior method of analysis based on the conformational flexibility and all-organic nature of this system.[12]

Table 1. Calculated energies for several different BQ–ketene adducts



Entry	R	E_1 (kcal)	E_2 (kcal)	$\lvert\Delta E\rvert$ (kcal)
1	Ph (*Z*)	73.03 *re*	75.66 *re*	2.64
2	Ph (*E*)	78.69 *si*	78.75 *si*	0.06
3	Et (*Z*)	36.38 *re*	38.36 *re*	1.98
4	Et (*E*)	38.36 *si*	38.59 *si*	0.23
5	Br (*Z*)	70.33 *re*	73.78 *re*	3.46
6	Br (*E*)	74.16 *si*	74.56 *si*	0.39

Initially, we investigated the energetic importance of the ketene geometry in the putative zwitterionic intermediates formed between BQ and ketenes using the MMFF force field of Macromodel.[13] In all the cases that we studied, the bridgehead (quinuclidine) nitrogen is preferably *trans* to the ketene substituent across the C=C bond (Table 1). Inspection of the lowest conformational structures of each entry in Table 1 reveals that the *E*-ketene geometry is energetically less favored due to repulsive van der Waals interactions between the ketene and the adjacent quinoline ring of the catalyst. Additionally, the presence of noticeable $A_{1,3}$ interactions between the terminal substituent of the ketene and the bridging carbon framework of the quinuclidine nucleus are expected to play a role. The energetic preference for the *Z*-ketene geometry arises from a favorable placement of the terminal ketene substituent away from the quinoline and benzoyl groups of catalyst **5a**, effectively creating a pocket that shields one face of the ketene. The predominant $A_{1,3}$ interactions that were present in the *E* geometry have also been alleviated in the *Z* conformer.

Inspection of the *Z* isomers of these same models thus reveals that the *re*-face of the ketene C=C bond is open to the approach of an electrophile. A specific example of this trend is shown in Fig. 1 where the model derived from *re*-face (top face) exposure of the *Z*-BQ–phenylketene adduct derived from phenylacetyl chloride and BQ is calculated to be 2.64 kcal/mol lower in energy than the corresponding model containing the exposed *si*-face. Importantly, the observed sense of induction of the β-lactam products isolated experimentally is consistent with these models and in accord with other models proposed for cinchona alkaloid catalyzed processes.

Previously we had found that the use of benzoylquinidine (**5b**, BQd) as the catalyst inverts the stereochemistry of both chiral centers in the resultant β-lactam.[6] In BQ, the bridgehead chiral center alpha to the quinuclidine amine and the center attached to the ester are of opposite configuration to those in BQd. To determine whether one or both chiral centers are controlling the sense of induction,

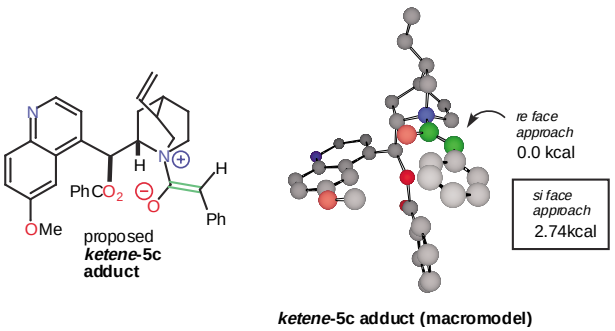


Figure 2. Stereochemical model of the putative zwitterionic intermediate of BEQ and phenylketene.

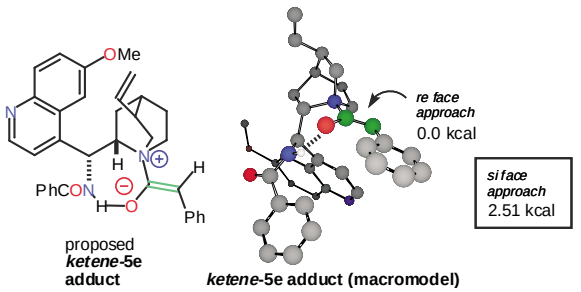


Figure 4. Stereochemical model of the zwitterionic intermediate when using benzamidoquinine **5e**.

we investigated the consequence of epimerizing the 'oxy' stereogenic center alpha to the ester oxygen (affording benzoylepiquinine, or BEQ, **5c**). Macromodel calculations in this case predict the same sense of induction as that seen in BQ catalyzed reactions. As seen in model ketene–**5c**, the *re*-face of the ketene zwitterion is still exposed (Fig. 2). The lowest energy corresponding *si*-face exposed conformer is some 2.74 kcal/mol higher in energy. When we performed the reaction using BEQ (phenylacetyl chloride **1a**, imino ester **4**) under standard conditions with proton sponge as the stoichiometric base, we obtained the *cis*-diastereomer **7a** in 97% ee, confirming our prediction.

Carrying our investigation one step further, we removed the benzoyl group altogether, resulting in deoxyquinine (**5d**, DOQ) which now has an achiral center where the ester was attached. Calculations on the adduct of phenylketene and DOQ predict the same sense of induction (as observed, Fig. 1) except for the fact that the lowest *si*-face conformation is now about 1.31 kcal/mol higher in energy, a smaller gap reflected in the diminished ee (72%) that we observed (Fig. 3). This calculation suggests that the presence of the oxy stereogenic center in BQ is not critical to the sense of induction, and it is the steric bulk of the benzoyl group that is most critical in enhancing selectivity.

We have proposed that quinine amide **5e** engages in hydrogen bonding with the ketene enolate in the activated complex ketene–**5e**,[14] yielding product with the same sense of induction as BQ. Macromodel calculations were performed on model complex ketene–**5e**, and a low energy complex was found in which an intramolecular hydrogen bond stabilized the oxygen of the ketene enolate, leaving the *re* face exposed to attack of an electrophile (Fig. 4). The corresponding low energy structure with the *si*-face exposed is 2.51 kcal/mol higher in energy. The energy difference between the two faces is smaller than that of BQ, explaining the decreased selectivity when using **5e** (89% ee). This calculation suggests, however, that hydrogen bonding can be used as an organizing principle in the catalyst design of ketene reactions.

New catalysts. To test our model of the catalyst–ketene complex, we chose several nucleophilic catalysts and calculated the relative energy differences between approach from the *re* and *si* faces. The catalysts were then screened under standard reaction conditions to determine the predictive power of our model. We discuss the results from natural, semi-synthetic and entirely synthetic nucleophiles. As our first example we examined (*S*)-(−)-nicotine (**8**), an inexpensive and readily available alkaloid. Nicotine shares some similarities with BQ in that it has a tertiary amine as well as a less nucleophilic pyridine nitrogen. Unlike BQ, the tertiary amine is not part of a bicyclic system, and additionally, there is considerably less steric bulk associated with the molecule. When we ran the MMFF calculation, we found there to be a small energy difference of 0.51 kcal/mol between *re* and *si* approach (where the energy difference for BQ was 2.64 kcal/mol) thus predicting minimal enantioselectivity (Fig. 5). Visual inspection of the model also suggests that there should be minimal enantioselectivity. The catalyst is contained in the vertical plane while the ketene is projected outward from the assembly, allowing reaction to occur from either face. Experimentally, this model held true, yielding β-lactam **7a** in 6% ee and 2:1 diastereomeric ratio (dr, *cis*/*trans*).

We also investigated brucine (**9**), another inexpensive commercially available alkaloid.[15] Brucine is a considerably larger molecule than nicotine and has a nucleophilic tertiary amine in a bridgehead position, like BQ. The transition state model shows a preference for *re* face attack

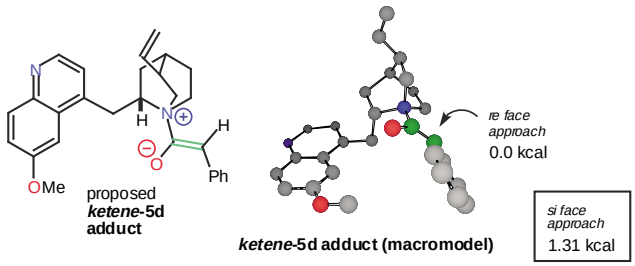


Figure 3. Stereochemical model of the putative zwitterionic intermediate of DOQ.

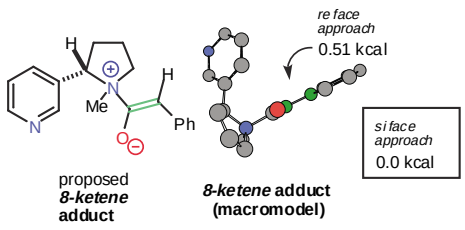


Figure 5. Proposed stereochemical model of the nicotine–phenylketene adduct.

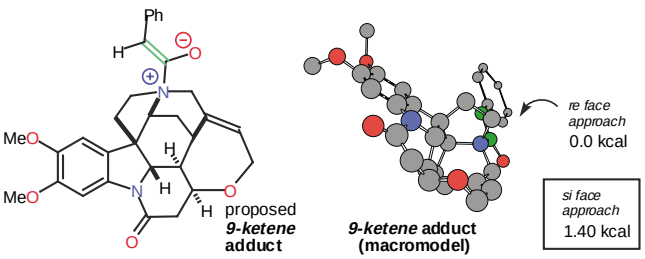


Figure 6. Proposed stereochemical model of the putative zwitterionic intermediates of brucine and phenylketene.

of 1.40 kcal (Fig. 6). When used in our system, **7a** was produced in 77% ee and 10/1 dr. Of all our calculations, this one is the most surprising, as in no case does shielding of either the *re* or the *si*-face look extensive enough to lead to a compelling result.

As our next test, we chose to examine the semi-synthetic quinidine derivative **10**, which is synthesized in one step from quinidine.[16] This catalyst has been used very effectively for a catalytic asymmetric Baylis–Hillman reaction, forming α-methylene-β-hydroxy esters in high enantioselectivity.[17] When we modeled **10** we found a larger energy difference (1.79 kcal) between the two possible modes of attack by the ketene, suggesting higher enantioselectivity than with nicotine, but less than that from BQ (Fig. 7). This was confirmed experimentally with the formation of **7a** in 33% ee and 10/1 dr. An interesting point about this catalyst system is the observed sense of induction. The β-lactam product has the opposite chirality (*R*,*R*) than the resultant product from the benzoylquinidine reaction (*S*,*S*), even though the two catalysts have the same configuration at the aforementioned chiral centers. While somewhat surprising at first inspection, the sense of induction was in fact predicted by our model.

Finally, we chose to study the designed synthetic amidine catalyst **11**, which we predicted upon reaction with phenylketene would afford a reactive complex in which the *si*-face is blocked to approach of an electrophile. Catalyst **11** is readily made from optically pure phenylenediamine. Unlike all of our previous models, this catalyst uses an imino nitrogen as the nucleophile with a proposed hydrogen bond donor included in the catalyst to provide additional rigidity, similar to benzamidoquinine **5e**.[14] When calculated, **11** shows a strong preference for *re*-approach (2.45 kcal), predicting fairly good enantioselectivity (Fig. 8), a prediction which is confirmed experimentally (73% ee, 3/1 dr). Modifications are being made to the skeleton of the amidine catalyst system to optimize the enantioselectivity.

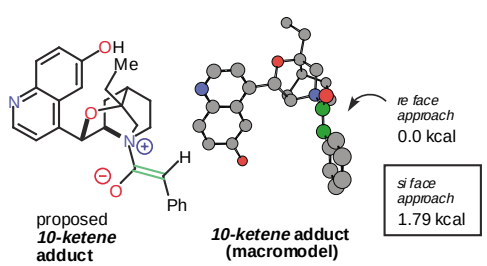


Figure 7. Proposed stereochemical model of semi-synthetic **10**–phenylketene adduct.

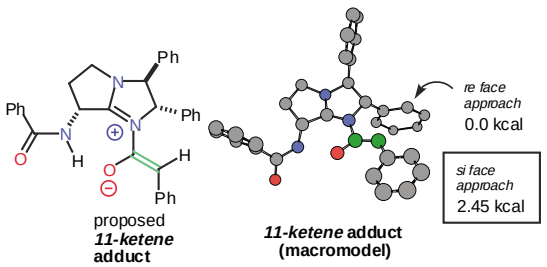


Figure 8. Stereochemical model of the synthetic catalyst **11**–phenylketene adduct.

Overall, the molecular models (except for that of brucine) and the empirical results show good correlation, correctly predicting the magnitude of the enantioselectivity and the sense of induction. The model held for both cinchona derived catalysts as well as other tertiary amine systems and a de novo designed synthetic amidine catalyst as well (Table 2).

Table 2. A summary of the calculated and empirical results using phenylacetyl chloride with several catalysts

Entry[a]	Catalyst	E_1 (kcal)	E_2 (kcal)	$\lvert\Delta E\rvert$ (kcal)	% ee[b]
1	(*S*)-Nicotine **8**	−38.91 *si*	−38.40 *si*	0.51	6 (*R*,*R*)
2	Brucine **9**	15.06 *si*	16.46 *si*	1.40	77 (*R*,*R*)
3	Mod-quinidine **10**	67.42 *si*	69.21 *si*	1.79	33 (*R*,*R*)
4	Amidine **11**	53.72 *si*	56.17 *si*	2.45	73 (*R*,*R*)
5	Benzoylquinine **5a**	73.03 *si*	75.66 *si*	2.64	99 (*R*,*R*)

[a] Reactions run under standard reaction conditions outlined in Section 4.
[b] % ee determined by chiral HPLC.

To make models like this useful, one must develop a scale to give the relative energies meaning. Logically, there must exist a ΔE (energy *X*) at which the catalyst will start to become selective, and consequently there will be a point (energy *Y*) where any further increase in energy will not result in a measurable increase in selectivity (Fig. 9). Between these two energies is the scale (depicted as, but not necessarily linear) that relates the relative energy difference to the theoretical selectivity of the catalyst. These points or barriers can be approximated experimentally for each system, resulting in a scale which calculated energies of new catalysts can be compared to predict selectivity.

3. Conclusion

We have found that molecular mechanics transition state

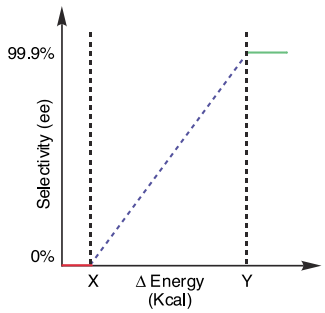


Figure 9. A diagram of the relationship between the ΔE of two transition state models and the resultant selectivity.

calculations on nucleophilic catalyst–ketene adducts give insight into the physical reason for the observed sense of induction observed experimentally with the benzoylquinine catalyzed β-lactam forming reaction. This model system was then used to predict the magnitude of stereoselectivity induced by several chiral nucleophilic catalysts with different structural motifs. Future studies will expand on the rational design of novel nucleophilic catalysts.

4. Experimental

4.1. General procedure for β-lactam 7a using proton sponge

To a solution of benzoylquinine **5a** (5.5 mg, 0.0129 mmol) and proton sponge **6** (31 mg, 0.142 mmol) in toluene (1 mL) at −78°C was added phenylacetyl chloride **1a** (20 mg, 0.129 mmol) in toluene (0.5 mL) immediately followed by α-imino ester **4** (33 mg, 0.129 mmol) in toluene (0.5 mL). The reaction was allowed to stir for 5 h as it slowly warmed to room temperature. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (15% EtOAc/hexanes) on a plug of silica gel to yield **7a** (65% yield, 33 mg).

4.1.1. *N*-(2*R*,3*R*-Diphenyl-2,5,6,7*S*-tetrahydro-3*H*-pyrrolo[1,2-*a*]imidazol-7-yl)-benzamide 11. To a pressure tube was added *S*-(+)-2-benzoylamine-4-bromobutanoic acid (674 mg, 2.36 mmol), (1*R*,2*R*)-(−)1,2-dipenylethylenediamine (500 mg, 2.36 mmol) and 0.5 mL of toluene and the mixture heated at 140°C for 3 h. The reaction was cooled and the solvent removed under reduced pressure. The resulting oil was chromatographed on silica gel using (20% EtOAc/EtOH) and the resulting product recrystallized from acetone to afforded 206 mg (23%) of the desired product as a white solid. Mp 142–145°C; ^{1}H NMR ($(CD_3)_2SO$) δ 8.58 (d, 1H), 7.87 (d, 2H), 7.54–7.40 (m, 4H), 7.32–7.14 (m, 8H), 4.92 (m, 1H), 4.55 (s, 2H), 3.58 (t, 2H), 2.20–2.11 (m, 1H), 2.08–1.97 (m, 1H) ppm; ^{13}C NMR ($(CD_3)_2SO$) 168.79, 167.99, 146.02, 135.97, 132.75, 129.98, 129.72, 128.98, 128.76, 127.75, 59.38, 47.64, 37.28; IR (KBr plate) 3360, 2984, 1680, 1657, 1520, 1420. Anal. calcd for $C_{25}H_{23}N_3O$, C, 78.71; H, 6.08; N, 11.02. Found C, 78.32; H, 6.20; N, 11.35.

Acknowledgements

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11. It is possible that acid chloride is deprotonated by BQ or PS (without the initial formation of an acylammonium salt) forming free ketene that can then react with the catalyst to form the zwitterionic intermediate (Scheme 1). IR experiments did not show the formation of free ketene, making this scenario seem unlikely, but not impossible. See Ref. 6a as well as: (a) Brady, W. T.; Scherubel, G. A. *J. Org. Chem.* **1974**, *39*, 3790–3791. (b) Brady, W. T.; Scherubel, G. A. *J. Am. Chem.*

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