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Communications

A Facially-Selective Protonation Controls the Stereochemistry of a Key Intermediate in the Synthesis of 1β-Methylcarbapenems

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Summary: Investigation into the selectivity observed in the synthesis of 1β-methylcarbapenems was carried out by examining (1) the rotational barrier between the two possible ketene acetal conformations A and B and (2) the protonation of ketene acetal **3** to the mono acid product **2**, using the MNDO Hamiltonian.

The discovery that a 1β-methyl substituent imparted enhanced chemical and metabolic stability to carbapenem antibiotics[1] catalyzed the search for efficient and stereoselective methods for their preparation.[2] Recently, Choi *et al.*[3] reported a novel synthesis of **2**, a key intermediate used in many approaches for preparing carbapenem antibiotics. In this approach malonate derivative **1** undergoes an acid catalyzed decarboxylation, resulting in the efficient formation of **2** in a 94:6 ratio of β:α isomers (see Scheme 1). ^{13}C-labeling studies[4] of the diacid **1** showed that only one of the carboxylic acid groups is lost, thus providing evidence for an unprecedented diastereoselective malonate decarboxylation reaction.

At the outset of this project the observed stereoselectivity was rationalized by postulating the following sequence of events: (a) a diastereoselective decarboxylation from conformation C1 (in which the CO_2 is lost from the less-hindered, back face of C1, away from the *N*-silyl group) resulting in the formation of ketene acetal **3** in conformation A and (b) a stereoselective protonation of **3** in conformation A from its less-hindered back face. Conformation A of **3** was thought to be preferred over the other likely alternative, conformation B, because the latter suffered unfavorable $A_{1,3}$-interactions between the ketene acetal hydroxyl group and the C3 methine proton. This postulate was corroborated using semiempirical molecular orbital calculations (MOPAC 5.0[5] employing the AM1 Hamiltonian[6]) which indicated that conformations A and B corresponded to the two lowest energy minima on the conformational surface (ΔH_f° for A and B

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(2) (a) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.* **1985**, *26*, 4739. (b) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2149. (c) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549. (d) Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143. (e) Martel, A.; Daris, J. P.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1537. (f) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675. (g) Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R. Reamer, R. A.; Schmidt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563. (h) Bender, D. R.; DeMarco, A. M.; Melillo, D. G.; Riseman, S. M.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2411. (i) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (j) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1987**, *28*, 1857. (k) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett.* **1988**, *44*, 2149. (l) Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801.

(3) Choi, W. B.; Churchill, H. R. O.; Lynch, J. E.; Thompson, A. S.; Humphrey, G. R.; Volante, R. P.; Reider, P. J.; Shinkai, I. *Tetrahedron Lett.*, in press.

(4) Personal communication with W. B. Choi.

(5) QCPE Program No. 455, Version 5.0.

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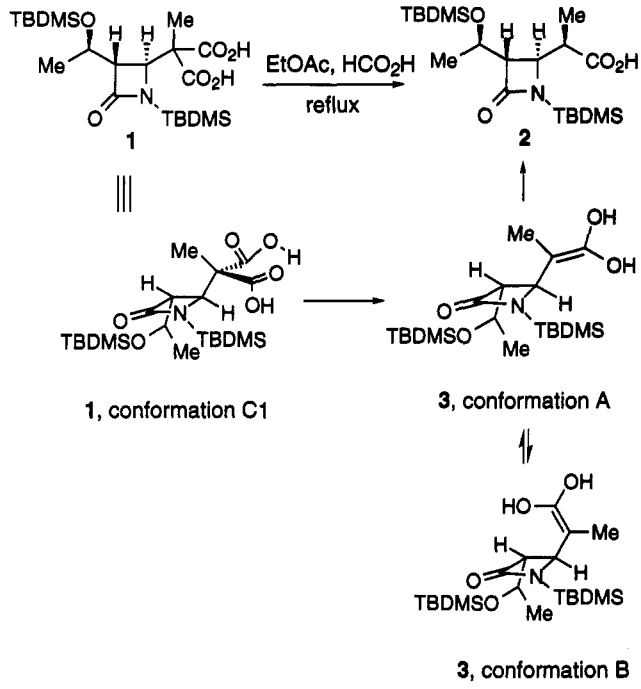
Scheme 1



are −253.31 and −252.87 kcal/mol, respectively).[7] Thus, the hypothesis that a diastereoselective decarboxylation produced ketene acetal **3** in its most favored conformation (*i.e.*, A) and that this intermediate was rapidly protonated from the face opposite to the bulky *N*-(trialkylsilyl) group appeared to be quite reasonable.

The objective of the present study was to continue to use semiempirical calculations to further investigate the proposed rationale.[3] In particular, we wished to examine (1) the rotational barrier between the two possible ketene acetal conformations A and B and (2) the protonation of ketene acetal **3** to the mono acid product **2**.

By means of a dihedral driver calculation, we were able to evaluate the rotational barrier between the two ketene acetal conformations A and B. The barrier to rotation between the two conformations was low (approximately 5 kcal/mol) implying that, at the reaction temperature of 80 °C, there should be facile interconversion among all the accessible conformations. Thus, unless decarboxylation and protonation occurred in a cage process, the conformation in which the ketene acetal **3** was initially formed should have no bearing on the ultimate product diastereoselectivity (the Curtin−Hammett principle).

In order to evaluate the protonation of the ketene acetal, we first examined a model system in which the β-lactam ring was replaced with a methyl group, thus allowing us to minimize the amount of CPU time needed to examine the viability of this approach. The protonation reaction surface for this model system was generated using a hydronium ion as a surrogate for the experimentally-used proton source, formic acid. Explicit location of the transition state was not achieved. Graphical examination of the saddle point region of the reaction surface indicated that the interactions which were occurring between the hydronium ion and the hydroxyl groups of the ketene acetal were probably an artifact resulting from the lack of solvent molecules in the system. Since these interactions were probably responsible for the problems experienced locating the protonation transition state, the hydronium ion was solvated with two molecules of water and generation of the model protonation reaction surface was repeated. Using this approach, the transition state was located with verification provided by the presence of one negative force constant (see Table 1).

Table 1. Results of the Model Protonation Study

	ΔH_f° starting material	ΔH_f° transition state[b]	E_a[b]
Intermolecular process[c]	−130.78	−124.07	6.71
Intramolecular process[d]	−130.78	−64.19	66.59

[a] β-Lactam ring replaced with Me group. [b] Units of kcal/mol. [c] H_3O^+ ion and $2H_2O$ molecules used as the proton source. [d] H_3O^+ ion and $2H_2O$ molecules included in the system for direct comparison with the intermolecular process.

Table 2. Results of a Study on the Protonation of 4[a,7]

conformation	ΔH_f° starting material	ΔH_f° transition state[b]	dipole moment[c]	E_a[b]
A (β-face protonation)	−198.80	−171.26	12.15	27.54
A (α-face protonation)	−198.80	−169.48	14.66	29.32
B (β-face protonation)	−198.43	−173.77	8.89	24.66
B (α-face protonation)	−198.43	−167.30	14.44	31.13

[a] To eliminate rotamer problems, the experimentally-used TBDMS protecting group was replaced with a TMS group. [b] In kcal/mol. [c] In D.

Although the *intermolecular* protonation transition state which was located appeared to be quite reasonable, we thought it was important to also evaluate the *intramolecular* protonation (*i.e.*, a 1,3-H-shift from one of the ketene acetal hydroxy groups to the carbon of the double bond being protonated) even though this process is symmetry forbidden in the suprafacial mode. Investigation of the 1,3-H-shift reaction surface for the model system and explicit transition-state location made comparison of these inter- and intramolecular protonation processes possible (see Table 1). With the intramolecular process activation energy approximately 60 kcal/mol higher than its intermolecular counterpart, the energetically unfavorable 1,3-H-shift could be eliminated from further consideration.

The knowledge gained from the hydrated protonation study of the model system enabled us to easily locate the four possible protonation transition states for **4**, a simplified analogue of **3** in which the side chain was removed (see Table 2).[7] The theoretical rate constants for protonation of each of the located transition states were determined by evaluating calculated partition functions in accord with transition-state theory.[8] The theoretical β:α ratio (93.4:6.6 at 80 °C) calculated using these rate constants was in excellent agreement with the experimental result (β:α = 94:6).

To our surprise, the most energetically favorable transition state proved to be the one which involved protonation of conformation B from the β-face (see Figure 1), a result which was at variance with our original postulate. Graphical examination showed that the $A_{1,3}$ strain, predicted from analysis of the conformational

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(7) The β-lactam side chain was removed from **2** to avoid the complications associated with side chain rotamers. However, since the side chain is quite remote from the site of reaction, this simplification appeared to us to be quite reasonable.

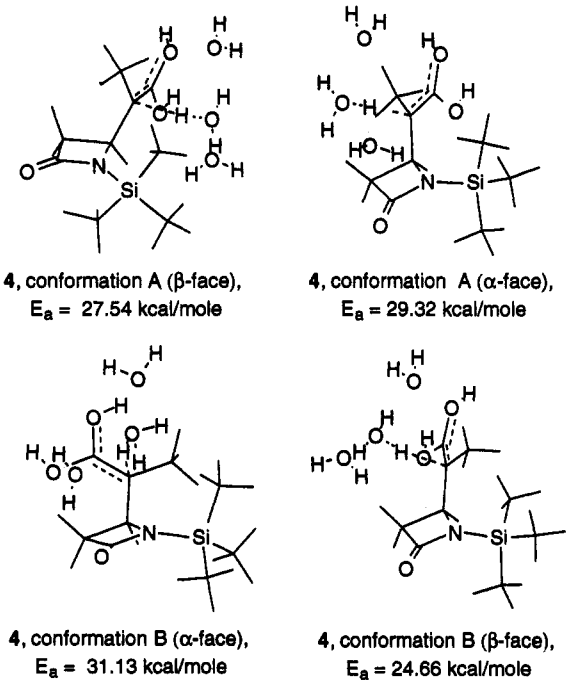

Figure 1.

surface of the starting ketene acetal **3**, had been substantially relieved in the actual transition state **4** by a combination of subtle geometric changes including the pyramidilization of the methyl-substituted carbon of the ketene acetal, as well as changes in various bond and dihedral angles. Indeed, in each of the four alternative transition states we have been unable to identify any obvious energetically-unfavorable interactions which can adequately account for the differences observed. However, an interesting correlation does exist between the magnitude of the dipole moment of the transition state in question and its activation energy (see Table 2), suggesting that the minimization of dipolar interactions in the transition state plays an important role in determining the observed diastereoselectivity.

Thus, we conclude that, due to the lack of any significant rotational barrier among the accessible ketene acetal conformations, it is the facially-selective protonation of the intermediate ketene acetal **3** that controls the final β:α product ratio observed. The diastereoselectivity of the decarboxylation step, while intriguing, actually plays no role in determining the ultimate reaction selectivity.

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Supplementary Material Available: Details on using transition-state theory to determine theoretical product distributions (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Rate constants calculated using $k = (RT/h)\ \exp\ (-V_o/RT)\cdot(Q^{\ddagger}_{vib}Q^{\ddagger}_{rot}/Q_{vib}Q_{rot})$ where R = gas constant (cal K^{-1} mol^{-1}); T = temperature (K); V_o = activation energy (cal); $Q^{\ddagger}_{vib}$ = transition-state vibrational partition function; Q_{vib} = ground-state vibrational partition function; $Q^{\ddagger}_{rot}$ = transition-state rotational partition function; Q_{rot} = ground-state rotational partition function. Translational partition functions were assumed to be negligible compared to the contribution of the rotational and vibrational partition function.