An Unusual Stereoselective Decarboxylation: A Key Reaction to an Important Intermediate for Carbapenem Antibiotics

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The dramatic difference in reactivity of the two diastereomeric acid esters **4A** and **4B** during decarboxylation has been thoroughly investigated. The (*R*) isomer **4A** underwent decarboxylation to provide a 94:6 mixture of **5A** and **5B** at 80 °C in 5–6 h. Under the same conditions the (S) isomer **4B** did not undergo decarboxylation and with further heating to 120 °C gave mainly the ring-opened decomposition product **6** along with unidentified decomposition products. A mechanistic rationale for this unusual reactivity profile is provided.

Introduction

In a recent communication,[1] we reported a stereoselective synthesis of the carbapenem intermediate **3** *via* decarboxylation of diacid **1**. From extensive computational studies,[2] we concluded that the selectivity was derived from a kinetically controlled protonation of the ketene acetal **2** (Scheme 1).

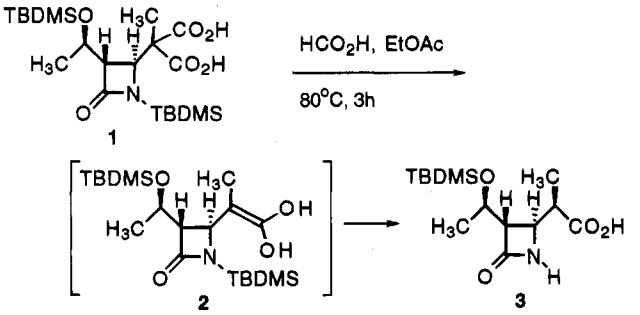
A dramatic difference in reactivity of the two diastereomeric acid esters **4A** and **4B** during decarboxylation was also reported.[1] The (*R*) isomer **4A**[3] underwent decarboxylation to provide a 94:6 mixture of **5A** and **5B** at 80 °C in 5–6 h. Under the same conditions the (*S*) isomer **4B** did not undergo decarboxylation and with further heating to 120 °C gave mainly the ring-opened decomposition product **6** along with unidentified decomposition products as shown in Scheme 2. Herein, more detailed results regarding the diastereospecific decarboxylation of diacid **1** are reported.

Results and Discussion

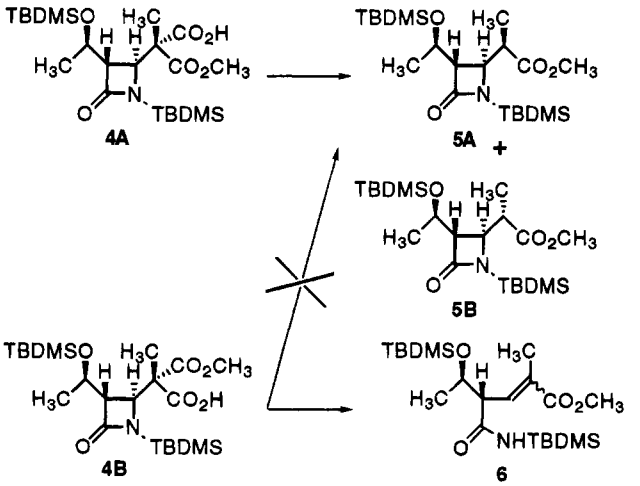
Labeling Study.[4] Our observations on the mixed acid esters **4A** and **4B** raised the question of the diastereospecificity of the decarboxylation of diacid **1**. In order to determine the different reactivities of the diastereotopic acid functionalities at the C-1 center, we prepared each of the C-13-labeled diacids **11A,B** as shown in Scheme 3 and 4. Treatment of methyl ester **7**[5] with 2 equiv of LDA and then C-13-labeled CO_2 gas at −50 °C followed by acidification and silica gel chromatographic separation provided **8A** and **8B** in 33% and 23% yields, respectively. Each isomer was then hydrolyzed to the corresponding diacid **9**, and the diacid was silylated with excess TBDMSTf/triethylamine. The bis-silyl diester **10** was selectively hydrolyzed to diacid **11** under carefully controlled acidic conditions (acetic acid in aqueous THF).

With *N*-TBDMS-protected diacids **11A** and **11B** in hand, each isomer was subjected to the decarboxylation conditions (3 equiv of formic acid in ethyl acetate at 80 °C). The resulting product was treated with an aqueous NaOH solution to selectively remove the silyl group on the lactam nitrogen. Subsequent acidification with aqueous HCl provided the corresponding decarboxylated products **3** and **13**, respectively (Scheme 5).

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1995.

(1) 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.* **1994**, *35*, 2275.

(2) Jones, D. K.; Liotta, D. C.; Choi, W.-B.; Volante, R. P.; Reider, P. J.; Shinkai, I.; Churchill, H. R. O.; Lynch, J. E. *J. Org. Chem.* **1994**, *59*, 3749.

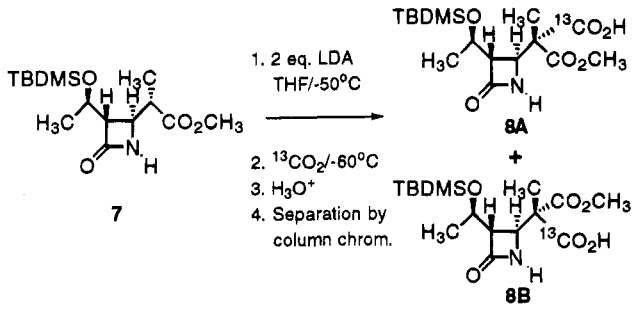
(3) The configuration of C1 was assigned by X-ray crystallography of the isotopically unlabeled acid ester **7A**.

(4) Enzyme-catalyzed decarboxylation of a C-13-labeled diacid has been studied. See: Miyamoto, K.; Tsuchiya, S.; Ohta, H. *J. Am. Chem. Soc.* **1992**, *114*, 6256.

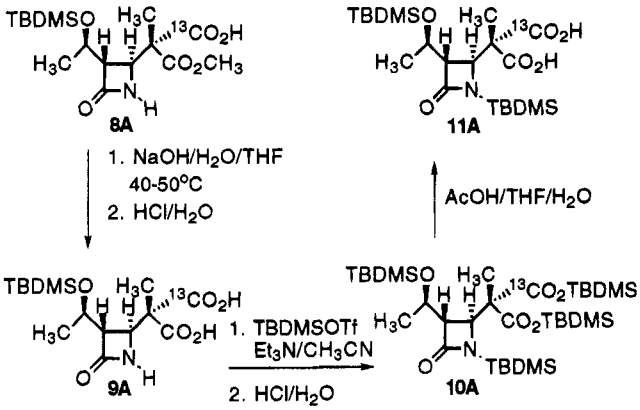
(5) Bender, D. R.; DeMarco, A. M.; Melillo, D. G.; Riseman, S. M.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2411.

0022-3263/95/1960-8367$09.00/0

Scheme 3



Scheme 4



Analysis of the crude products by GC-MS clearly showed that the mass of acid **13**, obtained from **11B**, was 1 mass unit higher than that of acid **3**, obtained from **11A**. Furthermore, no unlabeled acid **3** was detectable in the product derived from **11B**. We conservatively estimate the limit of detection in the mass spectrometer at less than 1%. Thus, the selectivity of the decarboxylation is at least 99:1 with the pro-*S* CO_2H being lost.

Computational Results. A survey of the literature revealed that the majority of computational decarboxylation studies have been carried out on small monoacid molecules at the *ab initio* level[6] with none of these studies providing a viable mechanistic pathway for the 1,3-diacid **1**. But in *ab initio* studies by Siegel *et al.* on model systems of polyether antibiotics containing a β-hemiketal carboxylic acid group,[7] loss of CO_2 and H_2O *via* a six-membered transition state was investigated. The obvious similarities between Siegel's system and the diacid **1** suggested that a similar approach to reaction surface generation be adopted to enable the relevant decarboxylation transition states to be located, i.e., systematic variation of (1) the C−C bond breaking to form CO_2 and (2) the O−H bond being formed during intramolecular proton transfer.

A model system was initially investigated, replacing the β-lactam ring with a methyl group, thus minimizing utilization of CPU time while the theoretical approach was being tested. The model system reaction surface for decarboxylation *via* a six-membered transition state was examined semiempirically (MOPAC 5.0,[8] AM1 Hamiltonian[9]), and location of the transition state[10] was verified by the presence of one negative force constant and normal mode analysis.[11]

Table 1. MOPAC Results for Decarboxylation of 14−16

conformation[a]	ΔH_f^o(s.m.)[b]	ΔH_f^o(t.s.)[b]	ΔH_f^o(product)[b]	E_a[b]
14A	−344.4	−298.7	−331.6	45.7
14B	−344.4	−297.2	−334.8	47.2
15A	−343.4	−299.5	−334.9	43.9
15B	−343.4	−299.9	−333.3	43.5
16A	−344.1	−304.0	−332.8	40.1
16B	−344.1	−296.4	−334.2	47.7

[a] The dihedral driver calculation of the C−C bond joining the diacid to the β-lactam showed the barriers to rotation between **14A**, **15A**, and **16A** or **14B**, **15B**, and **16B** to be relatively small, i.e., approximately 5, 6, and 7 kcal/mol, respectively. [b] Units of kcal/mol.

The six possible decarboxylation transition states for the β-lactam substituted system[12] are shown in Figure 1. Three separate rotamers about the C−C bond joining the diacid and the β-lactam ring were considered (**14**−**16**), and within each of these rotamers there exists two distinct conformations corresponding to which of the two carboxylic acid groups is transferring the proton and being eliminated as CO_2 (designated **A** and **B**). Knowing the values of the six key bond lengths from the model decarboxylation transition state, it was relatively easy to explicitly locate the six relevant transition states for the diacid (see Table 1).

The theoretical rate constants for decarboxylation *via* each transition state were determined by evaluating calculated partition functions in accord with transition state theory.[13] Subsequent determination of the theoretical amount of each carboxylic acid group lost (98:2 at 80 °C) showed good agreement with the experimental result. (**14A**, **15A**, and **16A** represent conformations from which loss of the ^{13}C-bearing carboxylic acid was experimentally observed.)

We initially anticipated that the transition state depicted by rotamer **14A** with proton transfer and loss of CO_2 coming from the carboxyl oriented α as illustrated and positioned opposite to the silyl group would provide the lowest energy decarboxylation pathway. However, **16A** rather than **14A** proved to be more stable; thus decarboxylation *via* this transition state was calculated as having a lower activation energy. Careful examina-

(6) (a) Goddard, J. D.; Yamaguchi, Y.; Schaefer, H. F., III. *J. Chem. Phys.* **1992**, *96*, 1158. (b) Francisco, J. S. *J. Chem. Phys.* **1992**, *96*, 1167. (c) Nguyen, M. T.; Ruelle, P. *Chem Phys Lett.* **1987**, *138*, 486. (d) Murto, J.; Raaska, T.; Kunttu, H.; Rasanen, M. *J. Mol. Struct. (Theochem)* **1989**, *200*, 93. (e) Bock, C. W.; Redington, R. L. *J. Chem. Phys.* **1986**, *85*, 5391. (f) Bock, C. W.; Redington, R. L. *J. Phys. Chem.* **1988**, *92*, 1178.

(7) Siegel, M. M.; Colthup, N. B. *Appl. Spectrosc.* **1987**, *41*, 1227.

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

(9) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Jie, C. *Organometallics* **1987**, *6*, 1486. A semiempirical approach was adopted to make this a more computationally tractable problem considering the computational resources available and the number of heavy atoms in the experimentally studied β-lactam system.

(10) Key bond lengths in the model six-membered decarboxylation transition state: C−C(O), 1.70 Å; C(O)−O, 1.25 Å; O−H, 1.88 Å; H−O(C), 1.00 Å; O(C)−C(O), 1.33 Å; C(O)−C, 1.45 Å.

(11) An alternative to the six-membered transition state decarboxylation mechanism is reaction of the diacid to form the corresponding cyclic anhydride, which could undergo acid-catalyzed thermolysis to give the intermediate ketene and CO_2. Study of a methyl-substituted model system including explicit transition state location for this alternative mechanism showed that it was less energetically viable than the original six-membered transition state studied, thus precluding this alternate pathway from further studies.

(12) To eliminate rotamer problems the TBDMS protecting group in **2** was calculated as a TMS group (see Figure 1, **13**−**15**).

(13) Rate constants calculated using $k = (RT/h)\ \exp(-V_0/RT)\cdot(Q^{\ddagger}_{vib}Q^{\ddagger}_{rot}/Q_{vib}Q_{rot})$ where R = gas constant (cal K^{-1} mol^{-1}), T = temperature (K), V_0 = 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, and 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.

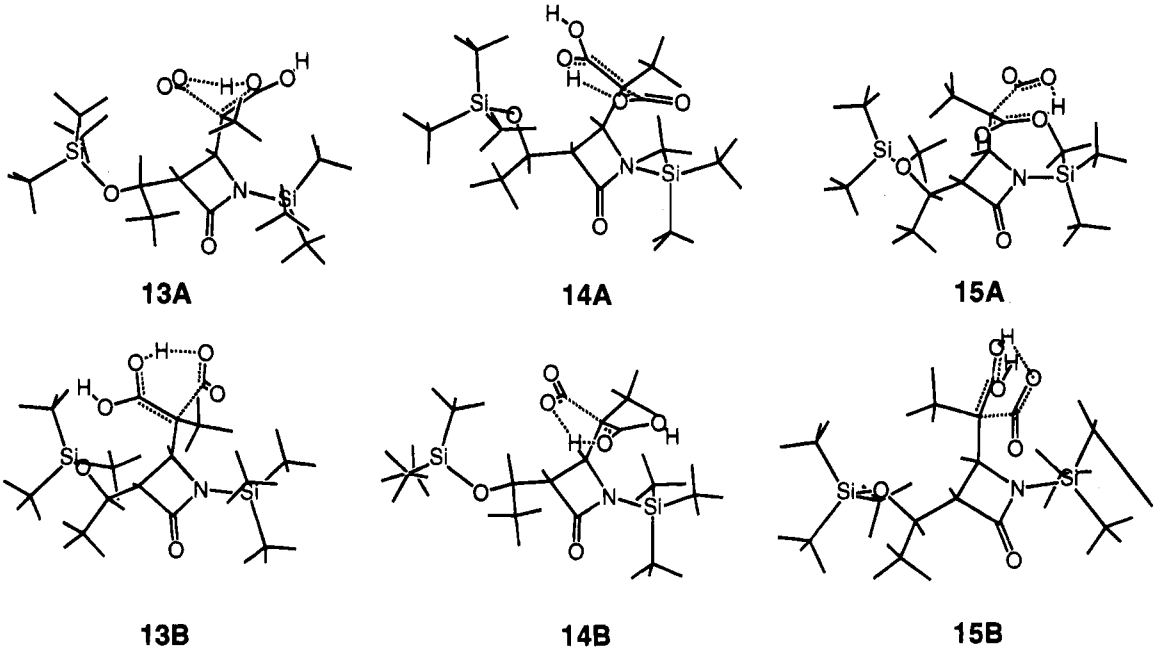
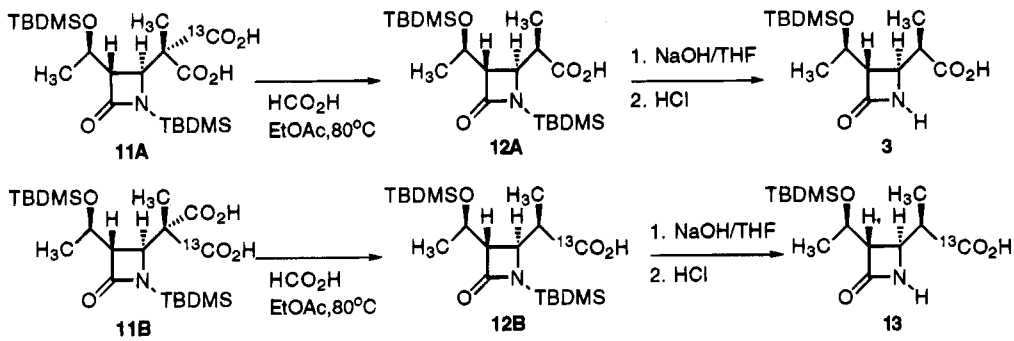


Figure 1. Six decarboxylation transition states located.

Scheme 5



tion of the transition state geometries suggested that steric factors govern the relative stabilities of the six transition states.

Conclusion

Both the modeling results and the labeling experiments clearly support the stereospecific decarboxylation of compound **2**; a rationale for this phenomenon was proposed that CO_2 should be lost through the energetically favored rotamer **16A**.

Experimental Section

NMR spectra were recorded at 300.1 MHz for proton and 75.5 MHz for carbon-13 NMR. Elemental analyses were performed at Robertson Microlit Laboratories, Madison, NJ. All reagents were used as purchased unless otherwise described. The isolated crude products **3** and **13** were silylated with *N,O*-bis-TMS acetamide prior to the analysis by GC-MS.

Preparation of 8A and 8B. LDA solution was prepared with diisopropylamine (4.3 mL, 30.7 mmol) and *n*-butyllithium (11.7 mL, 2.5 M in hexane, 29.3 mmol) in THF (40 mL) at 0 °C. The LDA solution was cooled to −70 °C. Methyl ester **7** (4.0 g, 12.7 mmol) was dissolved in 20 mL of THF, and the solution was added to the LDA solution at −70 °C. The mixture was aged at −50 °C for 1 h and was then cooled to −60 °C, and C-13-labeled CO_2 gas was bubbled through the solution for 20 min. The mixture was then warmed to −10 °C, and the reaction was quenched with acetic acid (4 mL) followed by water (20 mL). The mixture was then extracted with ethyl acetate (30 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography (0.5% acetic acid in ethyl acetate as eluent) to give **8A** (R_f = 0.40, 1.55 g, 35%) and **8B** (R_f = 0.21, 1.06 g, 23%). **8A**: ^{1}H NMR (CD_3OD) δ 4.27 (1H, dd, J = 2.6, 3.5 Hz), 4.24 (1H, dq, J = 2.6, 6.4 Hz), 3.75 (3H, s), 3.02 (1H, t, J = 3.5 Hz), 1.42 (3H, d, J = 4.6 Hz), 1.18 (3H, d, J = 6.4 Hz), 0.91 (9H, s), 0.10 and 0.08 (6H, 2s); ^{13}C NMR (CD_3OD) δ: 173.6, 171.7, 171.6, 65.9, 60.4, 53.6, 53.1, 48.8, 26.4, 22.7, 18.9, 16.6, −4.1, −4.8; MS (FAB) 141, 186, 226, 303, 345, 361; high-resolution MS M^+ calcd 361.1877, found 361.1809. **8B**: ^{1}H NMR (CD_3OD) δ 4.24 (1H, dq, J = 2.7, 6.3 Hz), 4.20 (1H, dd, J = 2.0, 4.0 Hz), 3.75 (3H, s), 3.09 (1H, t, J = 2.4 Hz), 1.45 (3H, d, J = 2.4 Hz), 1.15 (3H, d, J = 6.3 Hz), 0.91 (9H, s), 0.10 and 0.08 (6H, 2s); ^{13}C NMR (CD_3OD) δ 173.9, 171.5, 171.1, 65.9, 60.6, 53.6, 53.2, 48.8, 26.4, 22.8, 18.9, 17.3, −4.1, −4.8; MS (FAB) 141, 182, 226, 303, 345, 361; high-resolution MS M^+ calcd 361.1877, found 361.1856.

Hydrolysis of 8. The acid ester **8A** (400 mg, 1.1 mmol) was dissolved in THF (2 mL), and aqueous NaOH solution (4 mL, 1 N) was added. The mixture was aged at 40 °C for 5 h. The mixture was cooled to room temperature, the reaction was quenched with aqueous HCl (4.5 mL, 1 N), and the mixture was extracted with ethyl acetate (15 mL). The organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated to dryness to give a white solid (**9A**, 380 mg, 1.1 mmol). **9A**: ^{1}H NMR (CD_3OD) δ 4.25 (2H, m), 3.06 (1H, t, J = 2.2 Hz), 1.43 (3H, d, J = 4.7 Hz), 1.18 (3H, d, J = 6.4 Hz), 0.91 (9H, s), 0.10 and 0.08 (6H, 2s); ^{13}C NMR (CD_3OD) δ 173.9,

171.7, 65.9, 60.4, 53.8, 26.4, 22.8, 18.9, 16.9, −4.0, −4.7. Similarly **8B** (400 mg, 1.1 mmol) was hydrolyzed to **9B** (370 mg, 1.1 mmol). ^1H and ^{13}C NMR spectra were identical to those of **9A**.

Silylation/Decarboxylation to 13. Diacid (190 mg) **9B** was dissolved in acetonitrile (10 mL), and triethylamine (0.62 mL, 4.4 mmol) was added. The mixture was cooled to 0 °C, and TBDMSOTf (0.9 mL, 3.5 mmol) was added dropwise. The mixture was aged for 30 min at 0 °C, and the reaction was quenched with water (5 mL). The aqueous layer was acidified with 1 N aqueous HCl solution to pH 3, and the mixture was extracted with ethyl acetate (15 mL × 2). The combined organic layer was washed with brine solution (5 mL) and concentrated to dryness. The resulting oil was dissolved in a water/THF/acetic acid mixture (2 mL/2 mL/6 mL) and aged for 30 min at rt. The solution was then diluted with 10 mL water and extracted with ethyl acetate (10 mL × 2). The combined organic layer was washed with water (5 mL) and concentrated to give a white foam. The foam was dissolved in ethyl acetate (10 mL), formic acid (0.125 mL) was added, and the mixture was refluxed for 3.5 h. The mixture was concentrated to dryness, and the residue was taken up in THF (1 mL). Then a 1 N NaOH aqueous solution (2 mL) was added at room temperature, and the mixture was stirred for 1 h. The solution was acidified with 1 N HCl (2.5 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over $MgSO_4$ and concentrated to an off-white solid (100 mg). **13**: ^1H NMR (CD_3OD) δ 4.23 (1H, dq, J = 4.6 and 6.4 Hz), 3.82 (1H, dd, J = 2.1 and 4.6 Hz), 3.01 (1H, t, J = 2.1 Hz), 2.55 (1H, m), 1.27 (3H, dd, J = 4.8 and 6.7 Hz), 1.19 (3H, d, J = 6.3 Hz), 0.88 (9H, s), 0.09 and 0.08 (6H, 2s); ^{13}C NMR (CD_3OD) δ 178.6, 171.6, 66.0, 62.9, 53.4, 46.3, 45.6, 26.3, 22.7, 14.4, −4.0, −4.9; MS (FAB) 150, 169, 245, 185, 303; high-resolution MS M^+ calcd 303.1822, found 303.1831.

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