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 4A³ 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 diastereosepecific 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 7⁵ with 2 equiv of LDA and then C-13-labeled CO₂ 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 TBDMS/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).

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³ The configuration of C1 was assigned by X-ray crystallography of the isotopically unlabeled acid ester 7A.
Eylation studies have been carried out on small monoacid members of 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 CO₂ (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. 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 13C-bearing carboxylic acid was experimentally observed.)

We initially anticipated that the transition state depicted by rotamer 14A with proton transfer and loss of CO₂ coming from the carbonyl 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 examination

Table 1. MOPAC Results for Decarboxylation of 14–16

| Conformation | ΔH(s.m.)b | ΔH(t.s.)b | ΔH(product)b | Ekb.  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>14A</td>
<td>-344.4</td>
<td>-298.7</td>
<td>-331.6</td>
<td>45.7</td>
</tr>
<tr>
<td>14B</td>
<td>-344.4</td>
<td>-297.2</td>
<td>-334.8</td>
<td>47.2</td>
</tr>
<tr>
<td>15A</td>
<td>-343.4</td>
<td>-299.5</td>
<td>-334.8</td>
<td>43.9</td>
</tr>
<tr>
<td>15B</td>
<td>-343.4</td>
<td>-299.9</td>
<td>-333.3</td>
<td>43.5</td>
</tr>
<tr>
<td>16A</td>
<td>-304.0</td>
<td>-332.8</td>
<td>-341.1</td>
<td>40.1</td>
</tr>
<tr>
<td>16B</td>
<td>-344.1</td>
<td>-296.4</td>
<td>-332.2</td>
<td>47.7</td>
</tr>
</tbody>
</table>

* 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.

Analysis of the crude products by GC-MS clearly showed that the mass of acid 18, 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 transition states to be located, i.e., systematic variation of (1) the C–C bond breaking to form CO₂ and 1 mass unit higher than that of acid 11A.

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 level⁶ 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 CO₂ and H₂O 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 CO₂ 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 Hamilto-
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 CO₂ 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 then cooled to −60 °C, and C-13-labeled CO₂ 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 Na₂SO₄, and concentrated to dryness. The residue was purified by column chromatography (0.5% acetic acid in ethyl acetate as eluent) to give 8A (Rf = 0.40, 1.55 g, 35%) and 8B (Rf = 0.21, 1.06 g, 23%). 8A: ¹H NMR (CD₃OD) δ 4.27 (1H, dd, J = 2.6, 3.5 Hz), 4.24 (1H, dq, J = 2.0, 4.0 Hz), 3.75 (3H, s), 3.02 (1H, t, J = 3.5 Hz), 1.42 (3H, d, J = 6.4 Hz), 1.18 (3H, s), 0.91 (9H, s), 0.10 and 0.08 (6H, 2s); ¹³C NMR (CD₃OD) 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.

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 cooled 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 MgSO₄, and concentrated to dryness to give a white solid (8A, 380 mg, 1.1 mmol). 9A: ¹H NMR (CD₃OD) 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); ¹³C NMR (CD₃OD) δ 173.9,
Similarly 8B (400 mg, 1.1 mmol) was hydrolyzed to 9B (370 mg, 1.1 mmol). \(^1\)H 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 \(\times\) 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 \(\times\) 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 \(\times\) 2). The combined organic layers were dried over MgSO\(_4\) and concentrated to an off-white solid (100 mg). 13: \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 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, 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\(_3\)OD) \(\delta\) 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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