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Rapid cleavage of cyclic tertiary amides of Kemp's triacid: effects of ring structure

Michael L. Dougan,[†] Jonathan L. Chin,[‡] Ken Solt[§] and David E. Hansen*

Department of Chemistry, Amherst College, Amherst, MA 01002, USA

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Abstract—The piperidyl and prolyl amides of Kemp's triacid (**7** and **8**, respectively) have been prepared and their rates of intramolecular acylolysis measured as a function of pD. The piperidyl derivative **7** reacts approximately four-times faster (e.g., $t_{1/2} = 3$ min at 20 °C and pD 7.7) than the previously reported pyrrolidyl and methylphenethyl amide derivatives, while the prolyl derivative **8** reacts two-times more slowly (e.g., $t_{1/2} = 30$ min at 20 °C and pD 7.8). Molecular-mechanics calculations indicate that the nonbonded interactions in the piperidyl derivative **7** are distinct from those in the prolyl, pyrrolidyl, and methylphenethyl amide derivatives, a result that supports the suggestion that ground-state pseudoallylic strain contributes to the enormous reactivity of Kemp's triacid tertiary amides. In sum, the results reported indicate that the Kemp's triacid scaffolding provides a general means of activating tertiary amide derivatives.

In 1988, Menger and Ladika[1] reported that the pyrrolidyl amide of Kemp's triacid[2] (**1a**, Fig. 1) undergoes intramolecular acylolysis (k_1) with a half-life of 8 min at pD 7.05 and 21.5 °C. The anhydride formed (**2a**) then opens (k_2) to generate Kemp's triacid itself (**3a**), and the overall transformation is thus the hydrolysis of an unactivated amide. pH-rate studies revealed that just one of the carboxylic acid functionalities, in its conjugate acid form, participates in the reaction.

Menger and Ladika also determined that the pyrrolidyl amide, methyl ester derivative **1b** reacts with a half-life comparable to that observed for **1a**, confirming that only one of the carboxylic acid functionalities in **1a** is necessary for rapid reaction. Remarkably, the amide functionality in **1b** cleaves rather than the ester, due presumably to initial protonation of the more-basic amide by the adjacent carboxylic acid.

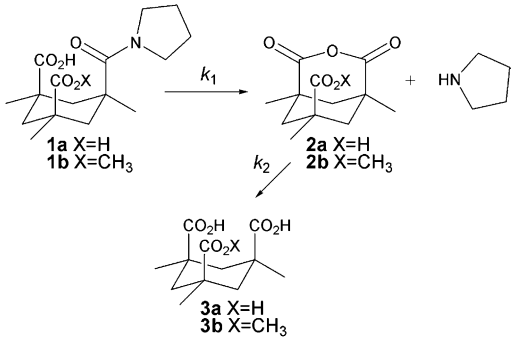

Figure 1. Reaction of pyrrolidyl amide derivatives of Kemp's triacid.

Under comparably mild conditions, an unactivated peptide bond hydrolyzes with a half-life of approximately 500 years, in a reaction independent of buffer catalysis and apparently involving direct attack of water.[3,4] In comparison to this rate, the cleavage of the amide bond in **1a** or **1b** occurs 3 million times faster, due, concluded Menger and Ladika, to the 'sustained proximity' of the amide and carboxylic acid functionalities. They noted as well that 'relief of internal compression' of these functionalities upon anhydride formation also contributes to the rate acceleration, but that this effect must be relatively small. In 1990, Menger and Ladika[5] showed that the pyrrolidyl amide monoacid

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* Corresponding author. Tel.: +1-413-542-2731; fax: +1-413-542-2735; e-mail: dehansen@amherst.edu
† Present address: Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA.
‡ Present address: Department of Urology, David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA.
§ Present address: Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, MA 02114, USA.

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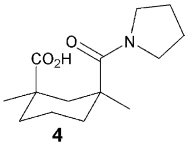

Figure 2. Pyrrolidyl amide monoacid derivative.

derivative **4** (Fig. 2) reacts at essentially the same rate as **1a** and **1b**, an observation that conclusively established that any reduction in activation barrier due to compression must be less than the 3.7 kcal/mol cost of placing two methyl groups in the 1,3-diaxial conformation (since, otherwise, the cyclohexane ring would simply undergo a chair flip).

In 1994, Curran et al.[6] demonstrated that while the methylphenethyl amide of Kemp's triacid (**5**, Fig. 3) undergoes intramolecular acylolysis at a rate almost identical to that of the derivative **1a**, the secondary phenethyl amides **6a** and **6b** react 10^2–10^4 times more slowly, depending on the pH. These workers proposed, therefore, that an important factor in the enormous reactivity of the tertiary amides is relief of 'pseudoallylic strain'[7] (Fig. 4) upon nucleophilic attack of the amide bond.

Regardless of the underlying reasons, tertiary amide derivatives of Kemp's triacid cleave extremely rapidly, and we have been interested in exploiting this fact in the development of catalysts for the hydrolysis of simple amides. In particular, we hope to create 'artificial' enzymes for the hydrolysis of piperidyl and L-prolyl peptide derivatives. We thus wished to establish whether the corresponding Kemp's triacid derivatives **7** and **8** (Fig. 5) react with a rate similar to that of **1a** and **5**.

To measure these rates, we employed the approach Menger and Ladika had described in their 1988 paper. First, the corresponding Kemp's anhydride amides **10** and **11** were synthesized from the anhydride acid chloride **9**[2] (Fig. 6).[8,9]

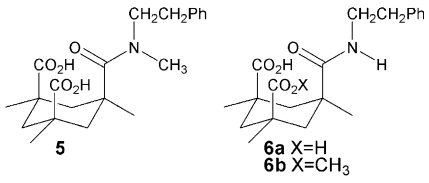

Figure 3. Tertiary (**5**) and secondary (**6a**,**b**) amide derivatives.

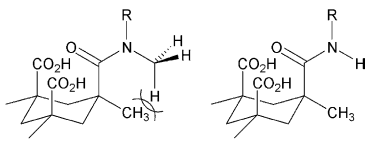

Figure 4. Pseudoallylic strain in tertiary amide derivatives relative to secondary. For the tertiary amide, a steric clash (one is shown explicitly) is unavoidable.

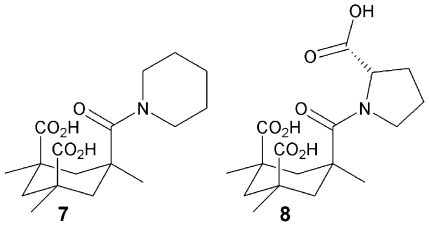

Figure 5. The piperidyl (**7**) and prolyl (**8**) amides of Kemp's triacid.

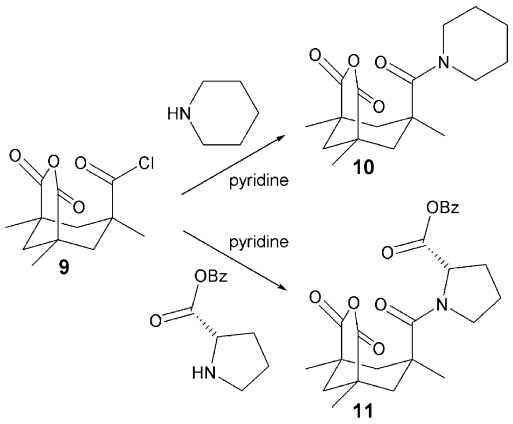

Figure 6. Synthesis of Kemp's anhydride amide derivatives **10** and **11**.

The derivatives **7** and **8** were then generated from **10** and **11** by in situ hydrolysis of the anhydride functionality (and for **11**, also the benzyl ester protecting group) in KOD, followed by acidification with DCl to the desired pD.[10,11] The cleavage reaction was then immediately monitored at 20(±1) °C via ^{1}H NMR.[12] As a point of reference, we also repeated the original work of Menger and Ladika with pyrrolidyl amide **1a**. The kinetic results we obtained for the intramolecular acylolysis of derivatives **1a**, **7**, and **8** are summarized in the pD-rate profile shown in Figure 7.

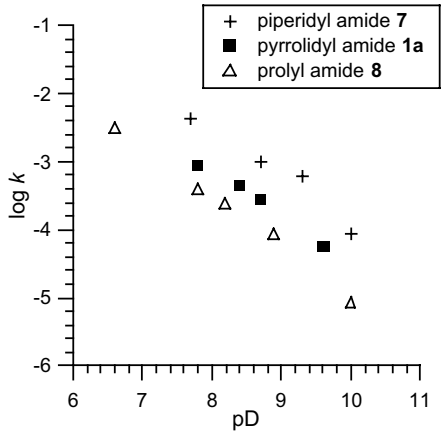

Figure 7. Plot of log k (s^{-1}) versus pD at 20(±1) °C for the acylolysis of the Kemp's triacid amide derivatives **1a**, **7**, and **8**. To convert pD to pH, subtract 0.5.[11] The measurement of accurate rates at lower pDs proved impossible since the reactions were essentially over before the first NMR spectrum could be recorded.

Theoretical fits for the data in Figure 7 are not given, since, as noted in the earlier reports,[1,6] the rate dependence on pD for cleavage of Kemp's diacid amide derivatives is not readily modeled.

In our hands, pyrrolidyl amide **1a** shows the same reactivity as previously reported.[1] Across the pD range studied, piperidyl amide **7** cleaves approximately four-times more quickly than **1a**, whereas prolyl amide **8** cleaves approximately two-times more slowly (to yield the acid anhydride **2a** and proline—thus the prolyl carboxylic acid functionality does not directly participate in the reaction). At pD 7.7, for example, piperidyl amide **7** has a half-life of 3 min; at pD 7.8, prolyl amide **8** has half-life of 30 min, and the half-life for pyrrolidyl amide **1a** is 13 min. These results indicate that the Kemp's triacid scaffolding provides a general means of activating tertiary amide derivatives.

We used molecular mechanics to explore whether, following the suggestion of Curran et al.,[6] greater pseudoallylic strain in piperidyl derivative **7** might be the reason for its enhanced reactivity relative to the previously reported tertiary amide derivatives **1a** and **5**. The minimized structures[13] of the three species are shown in Figure 8. The nonbonded interactions in the pyrrolidyl and methylphenethyl amide derivatives **1a** and **5** are remarkably similar, each having three almost identical hydrogen–hydrogen close contacts. However, due to the pseudo-chair conformation of the piperidyl ring, derivative **7** uniquely has two nonbonded interactions with a hydrogen–hydrogen distance of only 2 Å.

While it is not possible to quantify accurately the relief of strain upon formation of the rate-determining transition state(s), the above modeling results do support the notion that ground-state pseudoallylic strain contributes to the enhanced reactivity of tertiary amide derivatives. Since the nonbonded interactions in the minimized structure of prolyl derivative **8** (not shown) are identical to those in **1a**, its slower rate of cleavage likely arises from a perturbation of the carboxylic acid group directly participating in the reaction by the nearby prolyl carboxylic acid functionality.

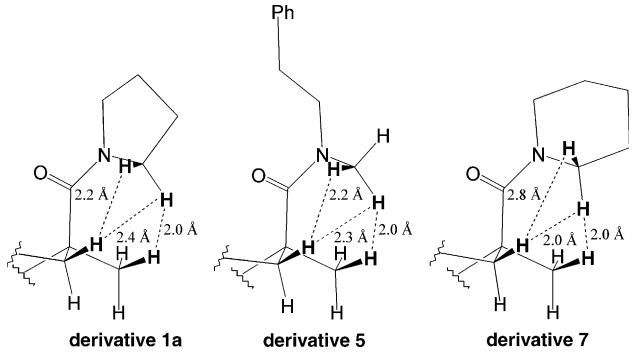

Figure 8. Pseudoallylic strain in energy-minimized conformations of derivatives **1a**, **5**, and **7**. The distances of all hydrogen–hydrogen close contacts are shown. The structures are truncated to emphasize the nonbonded interactions.

In summary, we have demonstrated that the Kemp's triacid piperidyl amide derivative **7** and prolyl amide derivative **8** undergo intramolecular acylolysis at rates comparable to that of the previously reported pyrrolidyl and methylphenethyl amide derivatives **1a** and **5**. Molecular mechanics calculations suggest that relief of pseudoallylic strain in these tertiary amide derivatives does contribute to the rapid rate of reaction.

Acknowledgements

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8. To a stirred suspension of anhydride, acid chloride **9**[2] (889 mg, 3.44 mmol) in 120 mL of dry acetonitrile under argon was added dry pyridine (8.7 mL). The mixture was cooled to −40 °C (CO_2/acetonitrile), and piperidine (305 μL) was then added. A yellow color quickly developed. The mixture was allowed to warm to room temperature and was stirred for 12 h. The solvent was removed by evaporation under reduced pressure to yield a bright yellow solid, which was purified by column chromatography (1:1 hexanes–ethyl acetate, $R_f = 0.36$) to give anhydride amide **10** as a white solid (116 mg, 11%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (m, 4H), 2.80 (d, $J = 12.8$ Hz, 2H), 2.01 (dt, $J = 13.5$, 1.8 Hz, 1H), 1.55–1.65 (m, 6H), 1.35 (d, $J = 13.5$ Hz, 1H), 1.35 (s, 6H), 1.31 (s, 3H), 1.23 (d, $J = 13.9$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.55, 171.51, 46.8, 43.1, 42.4, 40.5, 40.1, 28.64, 28.62, 25.76, 25.74, 25.1, 24.5. IR ($CHCl_3$, cm^{-1}) 1801, 1764, 1621, 1015. HRMS (TOF ES+) calculated for $C_{17}H_{26}NO_4$ $(M+H)^+$ 308.1862. Found 308.1859.
9. To a stirred suspension of anhydride, acid chloride **9** (404 mg, 1.56 mmol) in 50 mL dry acetonitrile under argon

was added dry pyridine (4.0 mL). The mixture was cooled to −40 °C (CO_2/acetonitrile), and a solution of proline benzyl ester (400 mg, 1.95 mmol) in 10 mL of dry acetonitrile was added. (Proline benzyl ester was prepared by dissolving the hydrochloride in 5% sodium bicarbonate and extracting three times with ethyl acetate; the combined organic layers dried, and the solvent removed.) A yellow color quickly developed. The mixture was allowed to warm to room temperature and was stirred for 12 h. The solvent was removed by evaporation under reduced pressure to yield a bright yellow solid, which was purified by column chromatography (2:1 dichloromethane–ethyl acetate, $R_f = 0.80$) to yield anhydride amide **11** as a white solid (476 mg, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (m, 5H), 5.17 (d, $J = 12.5$ Hz, 1H), 4.99 (d, $J = 12.5$ Hz, 1H), 4.53 (app. d, $J = 6.6$ Hz, 1H), 3.71 (m, 1H), 3.47 (m, 1H), 2.93 (d, $J = 13.6$ Hz, 1H), 2.77 (d, $J = 14.6$ Hz, 1H), 2.04–1.82 (m, 5H), 1.40 (d, $J = 13.6$ Hz, 2H), 1.32 (s, 6H), 1.21 (s, 3H), 1.06 (d, $J = 13.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 171.5, 171.4, 170.4, 135.5, 128.0, 127.7, 127.6, 65.9, 61.0, 48.3, 46.1, 42.4, 42.3, 42.2, 39.92, 39.89, 27.0, 26.8, 25.3, 24.9, 24.7. IR ($CHCl_3$, cm^{-1}) 1801, 1762, 1740, 1622, 1012. HRMS (TOF ES+) calculated for $C_{24}H_{30}NO_{16}$ $(M+H)^+$ 428.2073. Found 428.2067.

10. In a typical kinetic run, 1 mg of anhydride amide and 10 μL CD_3CN were added to a 5 mm NMR tube, followed by 0.5 mL of 50 mM sodium tetraborate decahydrate (Borax) solution in D_2O. The pD was raised to >12 by addition of 7 μL of 40% KOD for the piperidyl anhydride amide derivative **10** and for the corresponding pyrrolidyl derivative; for the prolyl benzyl ester anhydride amide derivative **11**, 20 μL of 40% KOD was added. The resultant solution was vigorously shaken. A ^{1}H NMR spectrum was recorded to ensure that the anhydride (and in the case of prolyl derivative **11**, the benzyl ester) had completely hydrolyzed. An aliquot of DCl solution was then added (from between 7 and 20 μL depending on the final pD for the pyrrolidyl and piperidyl amide derivatives, or from between 33 and 40 μL for prolyl amide derivative). The NMR tube was rapidly inverted many times to mix the solution.
11. Narrow-range Baker-pHIX® or EM Science colorpHast® pH strips were used to measure the pD of each solution. The pD was taken as the 'pH' indicated plus 0.5, the correction factor for borate buffer (Schowen, K. B.; Schowen, R. L. *Methods Enzymol.* **1982**, *87*, 551–606).
12. H NMR spectra were recorded at 20(±1) °C, the temperature of the (unthermostatted) internal probe, for, typically, at least two half-lives. For each data point, either 8 or 16 transients were collected; the time for each point was taken to be when the collection was half completed. Spectra were integrated, and the relative intensities of reactant amide and product amine –N–CH_2–, and/or –N–C*H*– for the prolyl derivative, signals were used to determine the extent of reaction. Rate constants were then calculated using the integrated first-order rate equation.
13. Molecular mechanics calculations were performed using HyperChem™ RELEASE 5.11 Pro for Windows (Hypercube, Inc.). The MM+ force field with the block-diagonal Newton–Raphson algorithm was employed.