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Intramolecular Nucleophilic Displacement Reactions at Carboxyl Oxygen

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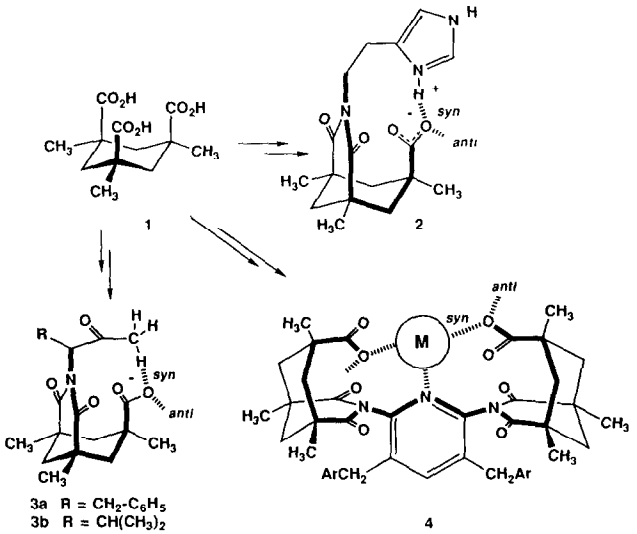
Summary: Lactonization reactions of Kemp triacid derivatives show no kinetic advantage of *syn* vs *anti* lone pairs at carboxyl oxygen.

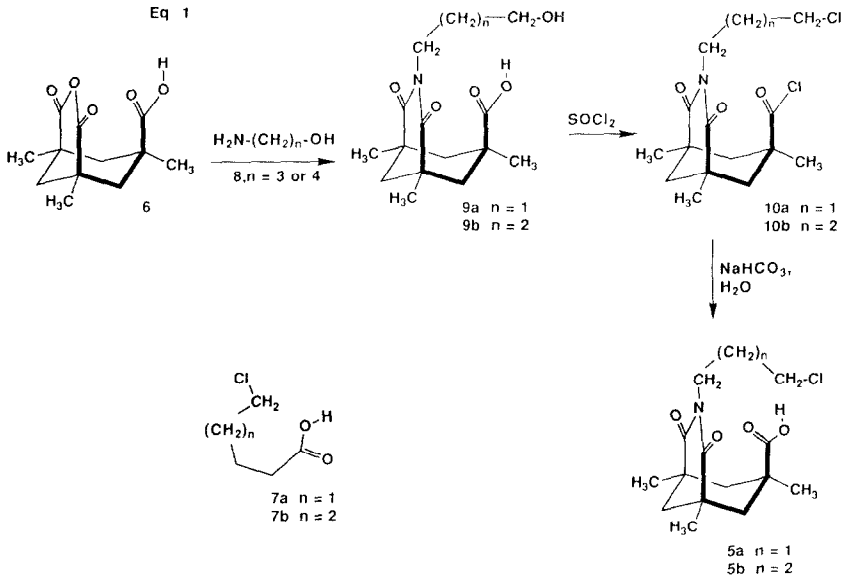
Derivatives of the Kemp triacid **1** provide a means by which stereoelectronic effects at carboxyl oxygen[1] can be assesed. For example, in model compounds for the serine proteases **2** and in cases **3** involving intramolecular general base catalysis, the *syn* lone pairs were 1-2 kcal/mol more effective than the *anti* lone pairs of comparable structures[2-4]. Earlier studies of the effect as it pertains to metal ion chelation[5] are harder to evaluate; fair comparisons for **4** are lacking, since it is practically impossible to change only the one variable (*syn* vs. *anti*) using small molecules[6].



In the cases cited above, there are large electrostatic components[4], and *distance* rather than orientation is the dominant factor. It was hoped that the displacement reactions of carboxylate at carbon electrophiles would

show larger stereoelectronic preferences. The transition states for such processes would involve more covalent character, and the product esters show very large differences in stability of *syn* vs. *anti* conformations.[7-9]

Accordingly, we set out to examine the cyclization behavior of Kemp triacid derivatives **5**, in which the electrophile is placed "above" the carboxyl function. These were prepared from the ω-amino alcohols with 3- and 4-carbon chains through condensation with the anhydride **6** followed by routine functional group manipulations. (Eq. 1) For suitable comparisons, the cyclizations of ω-halo acids **7** were examined. The latter compounds, which lead to small rings, are required to involve the *anti* lone pairs as nucleophiles.



Lactonization of the acids **5** and **7** were studied in DMSO-d_6 at 50 °C.(Eq. 2) Deprotonation of the carboxylic acids was carried out through the use of excess diisopropylethylamine, and the ionic strength was maintained at 0.10 M with lithium triflate. The progress of the reaction was followed by ^{1}H NMR spectroscopy The products were shown to be exclusively the lactones **11**. The latter were also prepared for comparsion by Mitsunobu reactions[10] of the hydroxy acids. The results are reported in the Table.

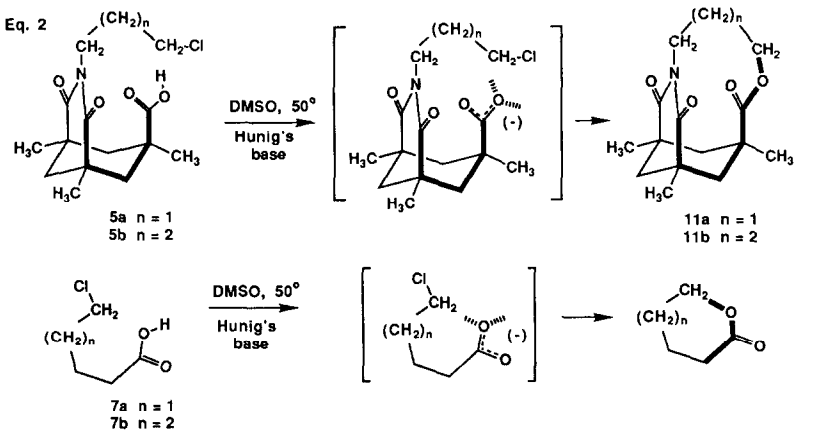


Table 1. Kinetic data for cyclizations of Eq. 2 ; DMSO-d_6; 50 °C; μ = 0.1.

Acid	k_{obs}, sec^{-1}
5a	11 x 10^{-5}
5b	11 x 10^{-5}
7a	11 x 10^{-5}
7b	5.8 x 10^{-7}

Cyclization of **5a** and **5b** occured at the same rate. This is surprising, since in the chemistry of unstrained, open chain compounds a 200-fold reduction in cyclization rates has been observed[11] upon the addition of one methylene unit (cf. **7a** and **7b**). This is generally attributed to entropic effects. In the current case, it is likely that the cyclization rate of **5a** is suppressed for reasons of strain. There is already a good deal of strain in the ground state, and this can be relaxed by divergence of the carboxylate from the imide plane. However, in the lactone product **11a**, the carboxylate carbon is pulled back toward the center of the structure and experiences steric compression with the imide function. Such distortions were observed in simple energy minimized structures obtained from calculations using MacroModel[12]. In the lactone **11b**, the 4-carbon bridge spans the two functions easily and less of this transannular strain is present. Thus, the cyclization of **5a** is retarded, whereas that of **5b** is probably normal.

At first glance, the cyclization rate for **5b** (an 11-membered transition state) could be considered quite rapid. Because of the rigidity of the skeleton however, free rotations about only 4 single bonds are possible, and its comparsion with the cyclization rate of **7a** (a 6-membered transition state) is appropriate. Since the rates are comparable, the effect of the more basic *syn* lone pair does not appear to be expressed in these reactions. A recent study by Zimmerman[13], involving a carboxylate-imidazolium pair, concludes that no special stabilization is provided in nucleophilic and general base catalyzed processes of *imidazole* when a nearby carboxylate is oriented with its *syn* lone pair in contact with the heterocyclic nucleus. Our most recent experiments[14] also suggest that stereoelectronic effects at carboxyl oxygen are more subtle than previously supposed.

Acknowledgements

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