

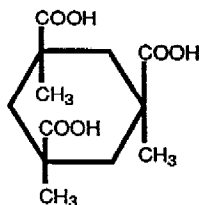
ION-INDUCED CONFORMATIONAL CHANGES IN KEMP'S TRIACID

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Summary: NMR and MACROMODEL/molecular dynamics calculations show that Mg^{++} can convert Kemp's triacid (trianionic form) from a chair into a half-chair conformation.

Owing to current research activity with Kemp's triacid (**1**)^{1,2,3}, and to its recent commercial availability,⁴ we decided to explore the conformational behavior of the compound. Proton NMR and MACROMODEL/molecular dynamics⁵ provided information on conformational changes within the triacid when the pH and ion content of aqueous solutions were systematically varied.



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Kemp and Petrakis¹ have already reported that the nonequivalent methylene protons of **1** have widely divergent chemical shifts (1.2 and 2.6 ppm). The NMR spectrum was best accommodated by a triaxial orientation of the carboxyl groups, a conclusion later confirmed by X-ray analysis.⁶ When **1** was converted into the trianionic state, the methylene resonances moved much closer together (i.e. to a separation similar to that of 1,3,5-cyclohexanetricarboxylate), indicating that **1** flips into a triequatorial-CO₂⁻/triaxial-CH₃ configuration. Electrostatic repulsion obviously predominates here over the usual preference for a carbonyl to assume an axial position relative to a methyl group.

Figure 1 gives the chemical shift separation (Δ) as a function of pH.⁷ The plot is consistent with the Kemp and Petrakis data showing that full ionization of **1** (pK_a 's = 3.3, 5.9, and 7.3)¹ is required for the conformational flip. We next added metal salts to **1** (D₂O, pD \geq 9.5) in order to determine if metal association can stabilize 1,3,5-triaxial carboxylates and, consequently, drive **1** back into the "low pH" configuration. Our results are summarized below.

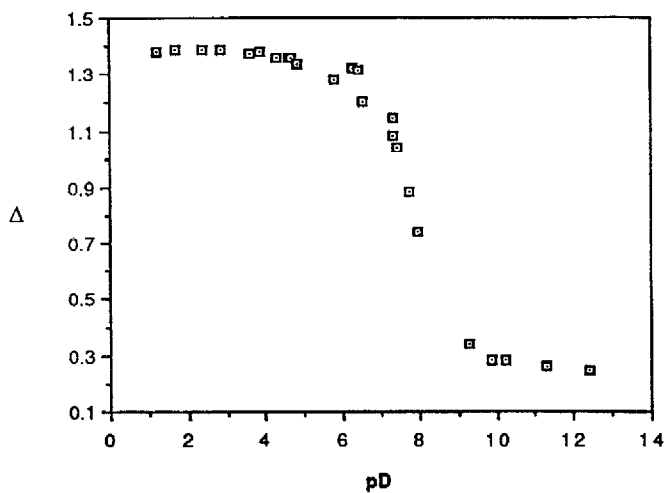


Figure 1. Difference in chemical shifts (Δ) between methylene protons of Kemp's triacid as a function of pD. Runs were carried out with 0.01 M triacid in D_2O on a GE QE-300 NMR spectrometer.

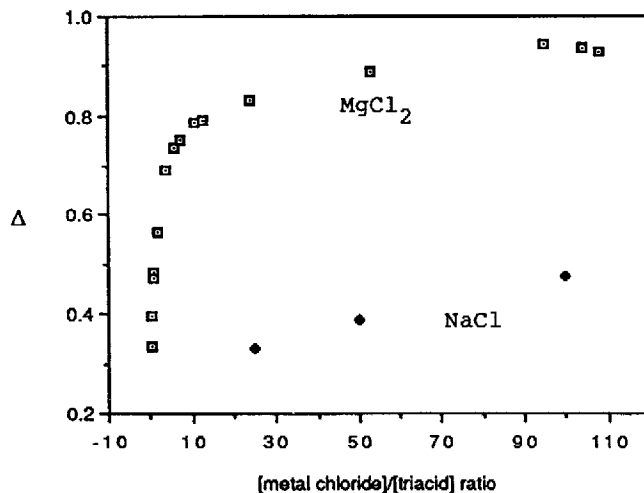


Figure 2. Difference in chemical shifts (Δ) between geminal methylene protons of 0.01 M Kemp's triacid in D_2O vs. molar excess of added $MgCl_2$ or $NaCl$. The pD was adjusted to 9.9 ± 0.3 without the use of an inorganic buffer.

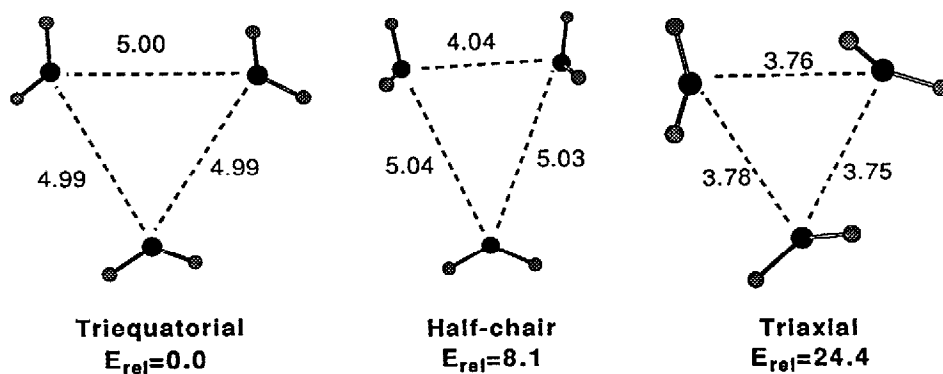


Figure 3. Geometries and relative steric energies of the three conformational minima of Kemp's triacid trianion as found by MACROMODEL. Distances are in angstroms.

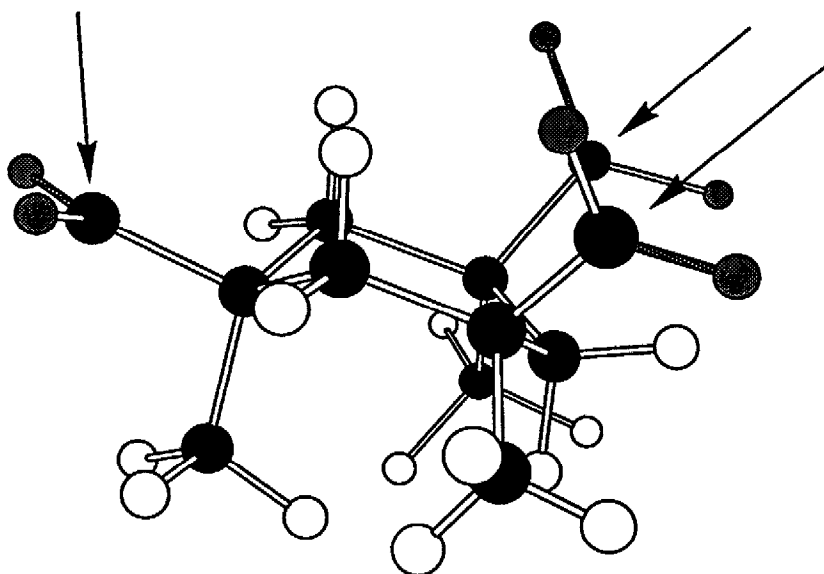


Figure 4. Half-chair conformation as found by MACROMODEL. Arrows point to carboxylate carbons.

(A) Figure 2 proves that the trianion of **1** experiences a major conformational change in the presence of a >10-fold molar excess of MgCl₂. (B) In contrast, no change in Δ was observed when 1,3,5-cyclohexanetricarboxylate acid trianion was mixed with a 100-fold excess of MgCl₂. Thus, relief of strain among axial methyls of **1** is necessary for the carboxylates to move out of their equatorial positions in the presence of MgCl₂. (C) As seen in Figure 2, NaCl has a much smaller effect than does MgCl₂. At an extremely high [NaCl] of 3.4 M, Δ does increase from 0.33 to 0.71 ppm, indicating an enhanced axial-CO₂⁻ population. It is unclear whether this represents sodium complexation or a nonspecific "ion atmosphere" effect. (D) Related studies with CaCl₂ were unsuccessful owing to precipitate formation. In one spectrum with a 100-fold excess CaCl₂ (taken before solid fell from solution) we found that Δ = 1.8 ppm, a value even greater than that for **1** at low pH. (E) Diacid corresponding to **1** (i.e. lacking the third CH₃/COOH at carbon-5) was shown to have an identical Δ /MgCl₂ profile as does **1**. Hence, two axial carboxylate units suffice for Mg⁺⁺ interactions. Since it was surprising to us that a third carboxylate does not enhance association with Mg⁺⁺, we carried out MACROMODEL calculations to explore theoretically the conformations of trianionic **1**.

MACROMODEL readily disclosed two energy minima (Figure 3), namely a triequatorial-CO₂⁻ (E_{rel} = 0.00 kcal/mol) and a triaxial-CO₂⁻ (E_{rel} = 24.4 kcal/mol). Molecular dynamics, however, was able to dislodge the structure from the triaxial-CO₂⁻ local minimum, resulting in the discovery of a third conformation: a half-chair (E_{rel} = 8.1 kcal/mol) depicted in Figure 4. We surmise that in solution the trianion of **1** exists as the equatorial-CO₂⁻, but when MgCl₂ is added the molecule transforms into the half-chair where two axial carboxylates associate with the metal. A third carboxylate remains equatorial and contributes little to the ionic interactions (in agreement with the NMR experiments). Owing to methyl group equivalence in the NMR, the half-chair must pseudo-rotate freely at 25°C with the Mg⁺⁺ ion hopping rapidly among the carboxylates.

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References.

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7. Solutions (with added HCl or NaOH) were buffered only by the solute to minimize the counterion concentration.

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