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Molecular recognition involving Kemp's triacid: selectivity towards the 8-substituted quinoline system as seen in the cocrystalline adducts with 8-aminoquinoline and 8-hydroxyquinoline

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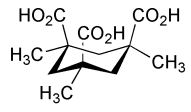
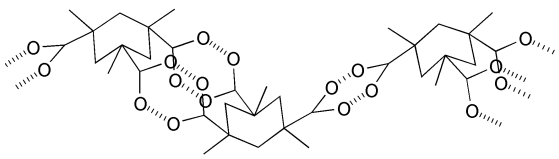
The crystal structure determinations of two molecular adducts of Kemp's triacid (*r*-1,*c*-3,*c*-5-trimethylcyclohexane-1,3,5-tricarboxylic acid = KTA), [$(KTA)_2$(8-aminoquinoline)] (1) and [$(KTA^-)_2$ (8-hydroxyquinoline$^+$)$_2$] (2) have revealed an interactive selectivity towards the 8-substituted quinoline system.

Kemp's triacid (*r*-1,*c*-3,*c*-5-trimethylcyclohexane-1,3,5-tricarboxylic acid) was synthesized in 1981[1] and its unique all-equatorial carboxylic acid configuration demonstrated, and later confirmed in crystal structure analyses.[2,3] Most significantly, the molecules showed no intramolecular hydrogen bonding associations involving the carboxylic acid groups as might have been expected but instead formed an unusual chain structure made up of head-to-tail cyclic hydrogen bonded units, with two at the head and one at the tail. This association is not only unique to Kemp's triacid but the polymeric or 'catemer' mode[4] is itself rare among carboxylic acids where the discrete cyclic hydrogen-bonded dimeric association [graph set $R^2_2(8)$[5]] predominates. The structure also indicates the possible reason for both the high melting point (241–243 °C) and the amomalously small p$K_{a2,3}$ value for the acid (1.5)[1] where the unusually high value for pK_{a3} (for an aliphatic tricarboxylic acid) makes the trianion one of the most basic carboxylate anions known.



Kemp's triacid (KTA)


KTA Framework structure

Previous work has indicated that Kemp's triacid and its derivatives, such as the 2 : 1 condensation products with various aromatic diamines (*e.g. m*-xylidenediamine and acridine yellow), possess potential for molecular recognition.[2] These diacid products have discrete encapsulating environments with dimensions which vary with the nature of the parent aromatic diamine used. However, no actual structures of adducts of this type are known. The trianionic form of Kemp's acid has exhibited enhanced affinity compared to the trianions of the *cis-trans*-isomer and other tricarboxylic acids, for the tetraprotonated [21]ane N_7 macromolecule.[6,7] It is proposed that interaction proceeds *via* hydrogen bonding between the favourably oriented carboxylate groups and all or most of the four protonated sites of the macromolecule. These studies in fact involve recognition of Kemp's triacid rather than using it to recognize other simple molecular species. Work in our laboratories has primarily been directed towards both the homogeneous and heterogeneous self-assembly of carboxylic acids as well as co-crystallization of carboxylic acids with Lewis bases, particularly in those cases where proton transfer does not occur.[8] Kemp's triacid was therefore interacted with a series of bifunctional carboxylic acids and Lewis bases with a view to examining the structures of the adducts formed, using single crystal X-ray diffraction. These included compounds having particular associative utility in structure making, including the isomeric monoaminobenzoic acids, 2-aminopyrimidine, 2,6-diaminopyridine, adenine, melamine, xanthine, hypoxanthine, and urea. The very limited success we achieved is reflected in the paucity of structural data on KTA and its compounds in the CSD. However, with 8-aminoquinoline (8-AQ),† large crystals of an adduct were obtained which was confirmed by elemental analysis as having the unexpected stoichiometry [$(KTA)_2$(8-AQ)] (**1**). The crystal structure of **1**‡ indicated that Kemp's triacid has particular affinity for the 8-amino-substituted quinoline system. This structure retains the basic hydrogen-bonded backbone polymer, based upon the KTA repeating unit, as found in the parent acid,[2,3] with the 8-aminoquinoline molecules linking the chains laterally by hydrogen bonds between the 8-amino substituent group [N(2)] and the CO_2H groups in the polymer chains (Fig. 1). Another feature of the structure is the 50% disorder of the 8-AQ molecules across inversion centres in the cell, meaning that half of the molecules lie with the amino group directed towards one carboxylic acid in the first chain [N(2)···O(1), 2.97 Å (x, 1 + y, z)] while the other half are directed towards another acid group in the second chain [N(2)···O(5), 3.14 Å (−1 + x, 1 + y, z)]. The hetero-nitrogen is not involved in intermolecular hydrogen bonding but does form an intramolecular hydrogen bond with the amino group (2.62 Å). Furthermore, this nitrogen is not protonated as might be

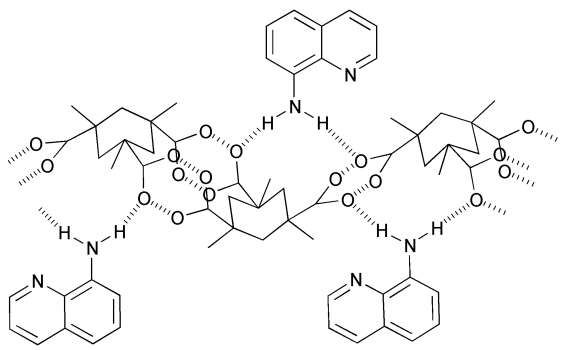


Fig. 1 Molecular associations in the KTA chain polymer structure and the laterally linking 8-aminoquinoline molecules in **1**, shown in the schematic. The 8-AQ molecules are 50% disordered across inversion centres in the unit cell. Hydrogen-bonding distances (Å) in the structure (shown as broken lines) are: intra-chain: O(1)···O(2), 2.68; O(4)···O(6), 2.60; O(3)···O(5), 2.68. Inter-chain: N(2)···O(1), 2.97; N(2)···O(5), 3.14.

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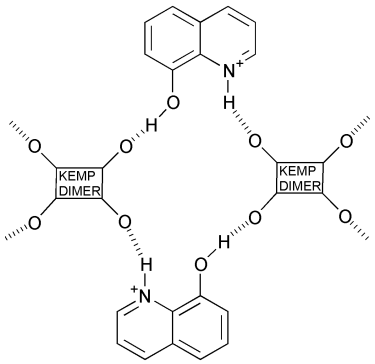

Fig. 2 The centrosymmetric dimeric KTA anion units and the cross-linking 8-hydroxyquinolinium cations in **2**. Schematic shows the hydrogen-bonding associations in the ribbon polymer. Hydrogen-bonding distances (Å) in the structure are: intra-dimer: O(1)···O(6),[a] 2.53; O(3)···O(5), 2.57; inter-dimer: N(1)···O(2), 2.68; O(7)···O(5),[b] 2.66. Unless otherwise indicated, atoms are carbon. [a] $-x$, $1-y$, $1+z$. [b] $-1+x$, y, z.

expected {comparative pK_a values of the acid (pK_{a1} = 3.3) and base [pK_{a2} (hetero-N) = 4.0}.

The apparent size specificity for KTA towards 8-AQ prompted a trial involving another available 8-substituted quinoline, quinolin-8-ol (8-HQ) with Kemp's acid using similar preparative conditions.† This also resulted in the production of good crystals but these had an analysis consistent with a 1:1 complex rather than 2:1 as found in **1**. The crystal structure of [(KTA)(8-HQ)] (**2**)‡ (Fig. 2) unexpectedly showed the presence of a chain polymer based on unusual centrosymmetric hydrogen-bonded KTA dimer repeating units, in contrast to the KTA backbone structure as found in **1** and in the parent acid. These dimer interactions differ from conventional hydrogen-bonded cyclic dimers in that they involve the *cis*-related acid groups [O(1)···O(6), 2.53 Å]. The oxygen of one of these acid groups [O(6)] is devoid of a proton which is located on the hetero-N of the 8-HQ molecule. This protonated group subsequently forms a strong hydrogen bond with the other oxygen of the second CO_2H group [N(1)···O(2), 2.68 Å]. The HO groups of the two bridging 8-HQ molecules provide the links between the dimer units *via* O(5) [O(7)···O(5), 2.66 Å] in a three-centre relationship which involves the third CO_2H group in an intramolecular hydrogen bond [O(3)···O(5), 2.57 Å]. There is a labile partial molecule of 8-HQ in the lattice which appears to be lost during collection of X-ray diffraction data while maintaining crystal stability and further work on this phenomenon is proceeding. The formula for the adduct **2** after removing the effect of the disordered partial molecule of lattice 8-HQ is therefore $[(KTA^-)_2(HQ^+)_2]$.

The presence or absence of proton transfer with examples of this type may be predictable on the basis of pK_a differences between the interacting species. For the pyridine system, this ΔpK_a minimum is found to be 3.5.[10] However, with Kemp's triacid and the 8-substituted quinoline system, the difference would appear to be considerably less than this [for 8-HQ: pK_a = 5.0 (hetero-N); ΔpK_a = 1.7 (proton transfer) while for 8-AQ: pK_a = 4.0; ΔpK_a = 0.7 (no proton transfer)]. The hetero-N in both 8-AQ and 8-HQ is readily protonated by relatively strong nitro-substituted aromatic carboxylic acids [*e.g.* 3,5-dinitrobenzoic acid (pK_a = 2.8), 5-nitrosalicylic acid (pK_a = 2.2) and 3,5-dinitrosalicylic acid (pK_a = 2.1)] giving 1:1 adducts,[10] based on cyclic hydrogen-bonded A–B heterodimers.[11] These form in preference to the B–B homodimer found in the parent structure of 8-HQ[12] and in its adducts with the neutral compounds chloranil[13] and 1,3,5-trinitrobenzene.[14] Adducts **1** and **2** therefore differ significantly in many respects: adduct **1** has 2:1 stoichiometry, involves no proton transfer, is based on a hydrogen bonded polymeric backbone structure and interacts with 8-AQ in a parallel cross-linking mode. Adduct **2** has effectively a 1:1 interactive stoichiometry but involves proton transfer and is based on hydrogen-bonded dimers which interact with two cross-linking 8-HQ molecules in a perpendicular mode. However, these two examples provide chemical evidence of the particular molecular specificity of Kemp's triacid for at least the 8-(interactive group)-substituted quinoline system. This basic proposal is currently being pursued using other similar Lewis bases.

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Notes and references

† *Preparation*. Adducts were prepared by refluxing 0.10 g (0.194 mmol) of KTA with respectively 0.056 g of 8-aminoquinoline or 0.057 g of quinolin-8-ol (0.388 mmol) in 20 cm^3 of 50% aqueous EtOH (compound **1**) or 80% aqueous EtOH (compound **2**) for *ca*. 15 min. The solutions were allowed to evaporate at rt yielding after 1 week, pale brown prisms of **1**, mp 292.5–296.8 °C [Found: C, 60.1; H, 6.9; N, 4.3%. Calc. for $C_{33}H_{44}N_2O_{12}$: C, 60.0; H, 6.7; N, 4.2%], and after 3 weeks, pale yellow prisms of **2**, mp 189.9–192.2 °C [Found: C, 62.5; H, 6.0; N, 3.9%. Calc. for $C_{21}H_{25}NO_7$: C, 62.5; H, 6.3; N, 3.5%]. Variation of the stoichiometric ratio of Kemp's acid to Lewis base gave the same products.

‡ *Crystal analysis* Compound **1**: $C_{33}H_{44}N_2O_{12}$, M = 660.7, triclinic, space group $P\bar{1}$, a = 8.3968(9), b = 8.7615(8), c = 12.3337(9) Å, α = 76.161(6)°, β = 74.331(8)° γ= 70.17(1)°, U = 810.9(1) Å^3, Z = 1, D_c = 1.349 g cm^{-3}, Mo-Kα radiation (λ 0.71073 Å); 3063 reflections measured (2851 unique: R_{int} = 0.0143); R_1 = 0.041 (F) [for 2254 reflections with $I > 2\sigma(I)$], wR_2 = 0.106 (F^2); T = 293(2) K. Compound **2**: $C_{42}H_{50}N_2O_{14}$, M = 806.8, triclinic, space group $P\bar{1}$, a = 8.662(1), b = 10.413(2), c = 14.153(2) Å, α = 99.06(2), β = 103.64(1)°, γ= 102.91(1)°, U = 1179.1(3) Å^3, Z = 1 (dimer repeat), D_c = 1.208 g cm^{-3}; Cu-Kα radiation (μ = 1.5418 Å); 5164 reflections measured (4832 unique: R_{int} = 0.0113); R_1 = 0.053 (F) [4304 reflections with $I > 2\sigma(I)$], wR_2 = 0.159 (F^2); T = 293(2) K. * $R1 = \Sigma[1F_o| - |F_c|]/\Sigma|F_o|$, $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o)^2]\}^{\frac{1}{2}}$. Intensity data were collected on Enraf-Nonius four-circle diffractometers using either Mo-Kα for **1** or Cu-Kα radiation for **2**. Structures were solved and refined using SHELXL97.[15] The 8-AQ molecules in **1** are disordered across inversion centres in the respective cell, indicating that in each the 8-amino groups occupy 50% sites in one orientation and 50% in the inverted orientation. With **2**, as mentioned in the discussion, the disordered partial 8-HQ molecules of crystallization were initially modelled crystallographically with partial occupancy but this did not achieve a completely satisfactory result (*R ca*. 0.08) although the basic hydrogen-bonded polymer framework is quite stable and devoid of any disorder. Subsequently, the use of the programme Squeeze within Platon[16] (which removed the effect of the electron density due to the partial lattice molecule), resolved the problem giving R = 0.054. CCDC 182/1827.

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