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Salts of hexamethylenetetramine with organic acids: Enhanced anomeric interactions with a lowering of molecular symmetry revealed by crystal structures

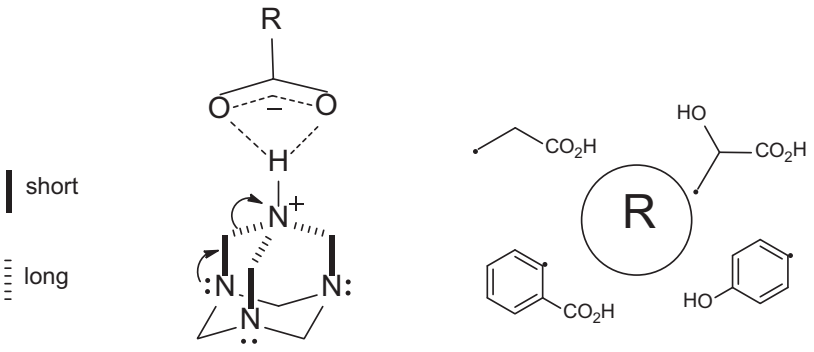
Sosale Chandrasekhar *, Somnath Mukherjee

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

HIGHLIGHTS

- Crystal structures of 4 salts of hexamethylenetetramine with organic acids.
- Structures analyzed in terms of the antiperiplanar lone pair hypothesis (ALPH).
- A major anomeric interaction involving the protonated nitrogen centre dominates.
- Strength of anomeric interaction proportional to the extent of proton transfer.
- Secondary hydrogen bonding in two cases leads to competing anomeric effect.

GRAPHICAL ABSTRACT



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ABSTRACT

The hexamethylenetetramine (HMT) framework displays interesting stereoelectronic interactions of the anomeric type. In the highly symmetrical parent system, the nitrogen centres act as both donors and acceptors. Protonation lowers symmetry and also leads to an enhancement of the anomeric interaction around the protonated centre. X-ray diffraction crystal structures of four derivatives of HMT – with succinic, (DL)-malic, phthalic and 4-hydroxybenzoic acids – reveal significant trends. (The first three form well-defined salts, 4-hydroxybenzoic acid forming a co-crystalline compound.) Each molecular structure is essentially characterised by a major anomeric interaction involving the protonated centre as acceptor. In two cases (succinic and 4-hydroxybenzoic), secondary protonation leads to a weaker anomeric interaction site that apparently competes with the dominant one. Bond length changes indicate that the anomeric interaction decreases as malic > phthalic > succinic > 4-hydroxybenzoic, which correlates with the degree of proton transfer to the nitrogen centre. Along with other bond length and angle changes, the results offer insight into the applicability of the antiperiplanar lone pair hypothesis (ALPH) in a rigid system.

Introduction

The classical anomeric effect is now firmly established and theoretically based in the antiperiplanar lone pair hypothesis (ALPH) [1–6]. Whilst the effect originated in carbohydrate chemistry – determining both ground state conformational behaviour and reactivity – it has now been generalised to include a range of compounds which possess a carbon atom geminally disubstituted with heteroatoms (X and Y in **1,** Scheme 1). The resulting 'generalised anomeric effect' applies to a wide variety of acetals, orthoesters and their nitrogen and sulphur analogues. The effect essentially

* Corresponding author.
E-mail address: sosale@orgchem.iisc.ernet.in (S. Chandrasekhar).

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involves the overlap of a lone pair of electrons on a heteroatom (X) with the antibonding orbital of the adjacent carbon-heteroatom (C–Y) σ-bond (**2**). [The antibonding orbital is also the lowest unoccupied molecular orbital (LUMO), designated as σ*.]

Early work by Kirby and co-workers established the utility and importance of crystal structures in revealing structure–reactivity trends in anomeric systems (summed up in [4]). Also, the vast majority of these – many designed to isolate and mimic the prototypical effect in the sugars – were necessarily unsymmetrical. In these, the dominant anomeric interaction was determined by the natural electron flow towards a nucleofugic group. Thus, in tetrahydropyranyl systems the 'endo-anomeric effect' was dominant, relative to the exo-anomeric effect involving the electron-withdrawing nucleofugic group.

Interestingly, certain symmetrical heterocyclic systems would only display a single anomeric effect, e.g. hexahydropyrimidine and imidazolidine. An intriguing system is the highly symmetrical tricyclic compound, hexamethylenetetramine (**3,** also 'urotropine', henceforth 'HMT'). In this the four nitrogen atoms are equivalent and take part in anomeric interactions as both donors and acceptors. Also, the absence of conformational flexibility implies that the nitrogen lone pairs are rigidly antiperiplanar to the corresponding vicinal C–N bond. Intriguingly, however, each lone pair is antiperiplanar to three different (but equivalent) C–N bonds, although each σ* orbital may overlap with just one (synperiplanar) lone pair.

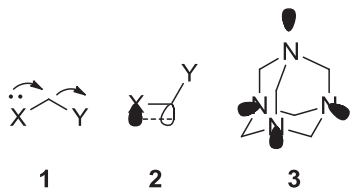
This raises interesting questions about how the electron density on a lone pair is distributed between the various available σ* orbitals of the adjacent C–N bonds: clearly of general and fundamental import. Also, although the parent HMT is symmetrical, it is unclear how it would react to an electronic perturbation.

As an approach to the above apparent conundrums, we embarked on a study of the structures of salts of HMT (**4,** Scheme 2). In these, a nitrogen centre is protonated, with two consequences. Firstly, the symmetry of the parent HMT molecule is substantially lowered; secondly, the energies of the adjacent C–N σ* orbitals are also lowered. Thus, the protonated nitrogen atom becomes the acceptor centre of the dominant anomeric interaction, which can be studied in isolation from the rest of the molecule.

Interestingly, in **4,** the protonated acceptor centre can draw upon the electron density of 3 adjacent lone pairs: how are these 'triaged'? Also, although several crystallographic studies of HMT and its derivatives have been reported [7–12], they do not, apparently, deal with anomeric interactions within the HMT framework.

Results and discussion

Four derivatives (**4**) of HMT (**3**) with succinic, DL-malic, phthalic and 4-hydroxybenzoic acids (resulting in **4a-4d** respectively), were obtained via slow evaporation of MeOH-EtOAc solutions of the components. This led to the isolation of single crystals suitable for X-ray diffraction analysis, the results being discussed below



Scheme 1. The anomeric effect represented as movement of electrons in **1** and **2** (the shaded orbital is a lone pair, the unshaded orbital the σ* of the C–Y bond and the dotted line the overlap between them); **3** shows hexamethylenetetramine (HMT) with the nitrogen lone pairs.

[13,14]. The crystallographic data are collected in Table 1, and the structural data in Tables 2–4; the ORTEP diagrams are shown in Figs. 1–4.

The bond identification scheme shown in Scheme 2 is employed in the discussion (α, β and γ are relative to the protonated nitrogen centre). It is noteworthy that, whilst the parent HMT (**3**) possesses a single C–N bond length by virtue of symmetry, in **4** the bonds designated as α, β and γ are distinct in principle. Furthermore, these do not vary uniformly, as discussed below. (The numerical subscripts are clearly arbitrary, and relative to the viewer.)

General trends

There is an apparent inverse relationship between each α bond length and the corresponding β bond length (three pairs in all), around the protonated nitrogen centre in **4** (Table 2). Relative to the parent HMT (**3**) in which the C–N bond length is reportedly 1.462 Å [7], the α bonds in **4** are longer (1.472–1.510 Å) and the β bonds are generally shorter (1.441–1.472 Å). The six γ bond lengths of the hexahydrotriazine base moiety in **4** also show considerable variation (1.452–1.480 Å), but within a slightly narrower range than the α and β bonds.

Two exceptional departures from the above trends involve unusually long β bond lengths in **4a** (β_1 = 1.472 Å) and **4d** (β_2 = 1.471 Å). Also, the β_1 and β_3 lengths (1.461 Å) in **4d** are practically identical to the reported bond length in **3.** Apart from these, all β bonds are short, relative to both the corresponding α bonds and the bond in HMT.

The bond angles vary in a narrow range (Table 3), averaging ~108.5° at the nitrogen centres (12 in all) and ~111.5° at the carbon centres (N–C–N, 6 in all). The torsions around C-N again vary in a narrow range, averaging ~59.0°, apparently showing a marginal negative deviation from the *gauche* ideal of 60.0° (e.g. the cyclohexane chair conformer). These are similar to those reported for HMT itself [7].

Each of the derivatives **4a-4d** displays several intermolecular hydrogen bonds involving the nitrogen centres of the HMT moiety (Table 4, Figs. 1–4, Scheme 3). These presumably stabilise the lattice as a whole and, importantly, affect the stereoelectronics at the molecular level (*vide infra*). Thus, in all the four derivatives the protonated nitrogen centre engages in (N–H–O) hydrogen bonding with the carboxylate group of the counterion. In **4a-4c** this involves both the oxygen atoms of the same carboxylate group (bifurcated hydrogen bonds) [15]. Additionally, in **4a** and **4d,** another nitrogen centre is involved in (N-H-O) hydrogen bonding with a second counterion moiety. This is between N_1 and an unreacted CO_2H (in the case of **4a**), and between N_3 and a phenolic OH group (in the case of **4d**). Also, the presence of N-H-C hydrogen bonds in **4b** and **4d** is noteworthy.

Also, intriguingly, the hydrogen bonds to donor (D—H) and acceptor (H···A) show considerable variation in length. These apparently indicate variable proton transfer, and apparently 'map' the extent of the transfer in the four derivatives. There is indeed a rough inverse relationship between the (D—H) and (H···A) lengths, although it is apparently complicated by competing effects (e.g. the 'bifurcated' hydrogen bonds, *vide supra*).

Also, in the case of **4d,** the extent of protonation of the nitrogen centre is negligible, judging from the relatively long N–H and short O–H bonds. This is most likely due to the relatively low acidity of the donor (4-hydroxybenzoic acid, pK_a 4.57) [16], and implies that a hydrogen bonded complex, rather than a salt, has been formed.

Among **4a-4c,** interestingly, the extent of proton transfer (Scheme 3) decreases in the order **4a** > **4c** > **4b.** (This represents the inverse order of the extent of protonation of the N centre.) Since the pK_a order of the corresponding acids is phthalic (2.94) < malic (3.40) < succinic (4.21) [16], this possibly indicates