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Hydrogen-bonded frameworks for conformational analysis of reactive substrates

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Guanidinium organosulfonate (GS) hydrogen-bonded host frameworks were used to trap α-halopropiophenones and α-halocyclooctanones to determine their molecular structure by single crystal X-ray diffraction. The majority of encapsulated guest molecules adopted conformations expected from computational analysis and stereochemical outcomes of Grignard reactions.

Guanidinium organosulfonate (GS) hydrogen-bonded frameworks have been deployed for a variety of applications,[1,2] owing their utility to a persistent hydrogen-bonded network of charge-assisted hydrogen bonds between complementary guanidinium cations (**G**, $C(NH_2)_3^+$) and organosulfonate anions (**S**) (Figure 1A).[3] These frameworks readily form stoichiometric inclusion compounds with a wide range of guests.[4,5] Puckering of the GS sheet and conformational flexibility of some organosulfonates allow the framework to "shrink wrap" around guests and achieve optimal packing density. Moreover, a given GS framework can adopt various architectures that adapt to the size and shape of guest molecules.

Our laboratories previously reported the encapsulation of 2-chloropropiophenone as a guest within a GS host framework. The conformation of this ketone guest corroborated the stereochemical outcome of the nucleophilic addition of allylmagnesium halide to 2-chloropropiophenone (Figure 2A).[6] Moreover, the conformation of the 2-chloropropiophenone guest closely resembled that predicted by the polar Felkin–Anh stereochemical model, in which the carbon–chlorine bond is oriented to maximize hyperconjugative interactions ($\sigma_{C\text{-}Cl} \rightarrow \pi^*_{C\text{-}O}$) with the carbon–oxygen bond (Figure 2B). Nucleophilic attack on this conformational isomer occurred on the diastereoface opposite the chlorine atom (Figure 2C),[6] resulting in high diastereoselectivity for the 1,2-*anti* alcohol product. Encapsulation within the framework enables analysis of the substrate conformations associated with these reactions.

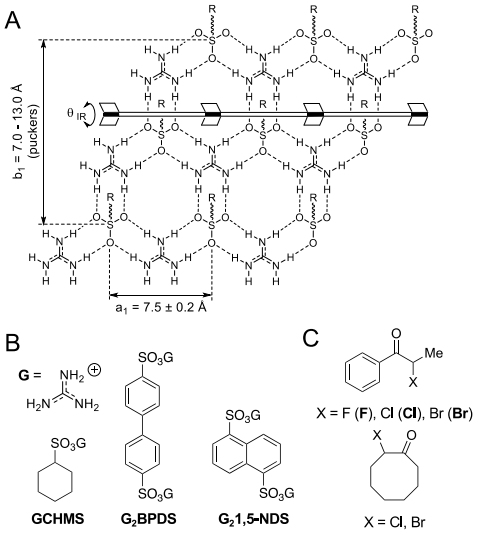

Figure 1. (A) Hydrogen-bonded sheet formed by guanidinium and organosulfonate ions. The sheet consists of one-dimensional GS "ribbons" joined by hydrogen bonds along their edges, serving as "hinges" that permit puckering, denoted as the inter-ribbon angle (θ_{IR}). (B, C) Molecular structures of GS hosts and guest molecules.

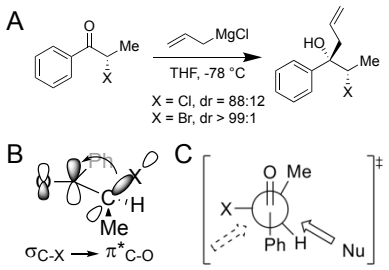

Figure 2. (A) Reaction of 2-chloro- and 2-bromopropiophenone with allylmagnesium chloride (B) Hyperconjugative interactions of $\sigma_{C\text{-}X} \rightarrow \pi^*_{C\text{-}O}$. (C) Newman projection showing the polar Felkin–Anh transition state in nucleophilic attack to α-halopropiophenones.

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A series of α-halopropiophenones were encapsulated in GS host frameworks. Three different GS hosts were employed to ascertain their influence (or absence thereof) on the preferred conformations of these guest molecules and whether the conformations corroborate the stereochemical outcomes of their Grignard reactions. This approach was extended to other α-halogenated ketones.

α-Halopropiophenones. Three α-halopropiophenones, which exist as liquids at room temperature, were encapsulated separately in guanidinium cyclohexanemonosulfonate (GCHMS), guanidinium 4,4'-biphenyldisulfonate (G_2BPDS), and guanidinium 1,5-naphthalenedisulfonate ($G_2$1,5-NDS) host frameworks by single-step crystallization in methanol and ethanol (Figure 1B). These frameworks were selected because they exhibit varying degrees of freedom with respect to achieving dense packing, permitting exploration of the influence of the host on the conformation of the guest. GCHMS inclusion compounds are not constrained by covalent connections between opposing GS sheets,[7] unlike G_2BPDS and $G_2$1,5-NDS hosts. Rotation of the phenyl rings in G_2BPDS can facilitate packing of guest molecules between the GS sheets, but the rigid core of the naphthalene moiety in $G_2$1,5-NDS can frustrate dense packing.

Single crystal X-ray diffraction was used to characterize the structure of nine inclusion compounds derived from racemic mixtures of 2-fluoropropiophenone (**F**), 2-chloropropiophenone (**Cl**), and 2-bromopropiophenone (**Br**) (Figure 1C) in GCHMS, G_2BPDS, and $G_2$1,5-NDS. The various architectures formed by these inclusion compounds can be described by the projection topologies of their organic residues from either side of the GS sheet (Figure S1).[7] $(GCHMS)_4$⊃**Cl** and $(GCHMS)_4$⊃**Br** adopted the recently reported "tetrad II" architecture (Figure 3).[7] GCHMS⊃**F** formed the "s-CLIC" host architecture, but refinement of the guest was not possible owing to disorder of the guest along channels. G_2BPDS⊃**F** adopted a "bilayer" architecture, while G_2BPDS⊃**Br** and G_2BPDS⊃**Cl**[6] formed a unique "bilayer" architecture with water molecules bridging adjacent bilayers. The $G_2$1,5-NDS inclusion compounds assembled in the simple brick architecture, although the hydrogen-bonding motif in the GS sheet of $G_2$1,5-NDS⊃**Br** departs slightly from the typical quasi-hexagonal motif, with one fewer hydrogen bond than the customary six (Figure S3).[3] All crystallization experiments were performed with a racemic mixture of guests. $G_2$1,5-NDS⊂**Br** crystallized as a conglomerate in the enantiomorphic $P2_1$ space group. All other structures contain both enantiomers in equal amounts.

The conformations of the α-halopropiophenone guests in all the inclusion compounds can be classified, according to their O–C–C–X dihedral angles ($\phi_{O\text{-}C\text{-}C\text{-}X}$), as "*anticlinal*," "*gauche*," and "*synperiplanar*," with $\phi_{O\text{-}C\text{-}C\text{-}X}$ = 135° – -135°, |45° – 135°|, and -45° – 45°, respectively (Figure 4, Figure S2). The *synperiplanar* conformation of **F** was confirmed in $G_2$1,5-NDS. The *gauche* conformation of **Cl** was confirmed in G_2BPDS. The *gauche* conformation of **Br** was confirmed in all three host frameworks (Figure 4). Conformation assignments of **Cl** in GCHMS and $G_2$1,5-NDS, and **F** in G_2BPDS were ambiguous due to positional disorder of the guests that made it difficult to localize the halogen during refinement and distinguish the halogen from the methyl group. The anticlinal conformation could be ruled out in each case, however.

The experimentally determined conformations can be understood by comparison to the calculated conformational preferences. Computational studies (at the M06-2X/6-311+G(d,p) level) have suggested a favored *gauche* conformation for **Br** and **Cl**, with a stronger preference in the case of **Br**.[8] The *gauche* conformation maximizes $\sigma_{C-X} \rightarrow \pi^*_{C-O}$ hyperconjugation (Figure 2B), which is particularly favored for **Br** over **Cl** because the carbon–bromine bond is the stronger electron donor.[6,8] In contrast, the lowest energy conformer calculated for **F** was *anticlinal*, with $\phi_{O-C-C-X}$ = -149°, consistent with σ_{C-F} being a weaker electron donor relative to the other carbon–halogen bonding orbitals, as indicated by $\sigma_{C-X} \rightarrow \pi^*_{C-O}$ stabilization energies: σ_{C-F} (1.68 kcal/mol) < σ_{C-Cl} (5.33 kcal/mol) < σ_{C-Br} (7.65 kcal/mol).[8] The *synperiplanar* conformation of **F** was favored in polar solvents, however (ca. 70% in methanol).[8] This result suggests that the *synperiplanar* **F** conformer in $G_2$1,5NDS⊃**F** reflects the dominant conformer in methanol, the crystallization solvent. Despite the effectively identical number of electrons in the fluoro and methyl group, which can make it difficult to distinguish their positions, the refinement was sufficient to ascertain bond lengths and confirm the *synperiplanar* conformer in $G_2$1,5NDS⊃**F**, unlike G_2BPDS⊃**F**.

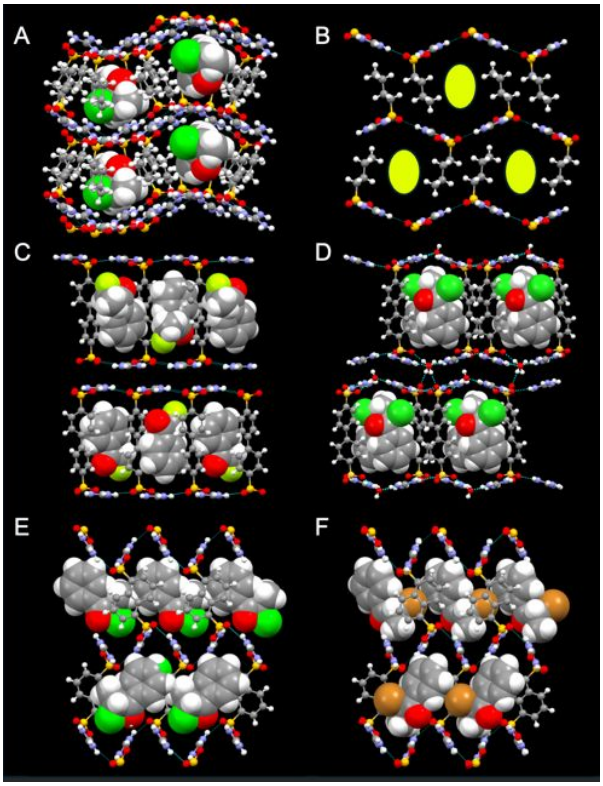


Figure 3. (A) $(GCHMS)_4$⊃**Cl**. (B) GCHMS⊃**F**. The lime-colored ovals represent disordered guests that could not be refined. (C) G_2BPDS⊃**Cl**. (D) G_2BPDS⊃**Cl**. (E) $G_2$1,5-NDS⊃**Cl**. (F) $G_2$1,5-NDS⊃**Br**. The GS frameworks are depicted as ball-and-stick and the guest molecules as space-filling.

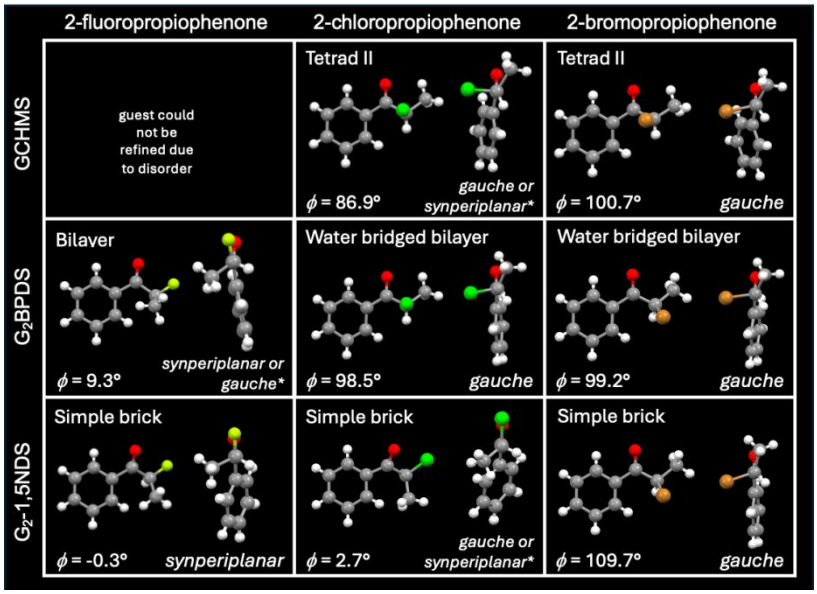


Figure 4. Summary of the structural features for the host frameworks (rows) and their **F**, **Cl**, and **Br** guest molecules (columns). Each guest is portrayed in two orientations: (left) perpendicular to the plane of the phenyl ring, (right) along the C–C bond of the O–C–C– X dihedral angle. *The positions of the halogen and methyl group in these cases is ambiguous (see text), such that two conformations are possible in unspecified ratios. The anticlinal conformation can be ruled out in all cases, however.

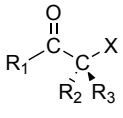
The crystal structures based on the $G_2$1,5NDS host reveal a competition between sustaining hydrogen bonds in the GS sheet and the conformational preference of the guest. The simple brick architecture in the $G_2$1,5NDS inclusion compounds affords channels perpendicular to the puckering axis with widths that increase in the order $G_2$1,5NDS⊃**F** (7.483 Å) < $G_2$1,5NDS⊃**Cl** (7.659 Å) < $G_2$1,5NDS⊃**Br** (7.760 Å). The channel widths of the first two in the series fall within the typical range of 7.5 ± 0.2 Å for GS hosts (a_1, Figure 1). The void volume (with guests removed) increases in the same order, reflecting the compliance of the host framework that accommodates the steric requirements of the different guests. The larger channel width and void volume for $G_2$1,5NDS⊃**Br** can be attributed to the perturbed GS sheet, wherein a subtle change in the alignment of adjacent ribbons is accompanied by a loss of one hydrogen bond (Figure S3). This observation illustrates that the GS sheet can sustain a reduction in hydrogen bonding to accommodate the larger guest while permitting its inclusion as its preferred gauche conformer, which accounts for about 80% of the population in methanol.[8]

Computations indicate that **Cl** prefers the *gauche* conformer (ca. 70:30 *gauche:synperiplanar* in methanol).[8] The assignment of these two conformers in $G_2$1,5NDS⊃**Cl** and GCHMS⊃**Cl**, proved ambiguous owing to positional disorder of the guest and low occupancy of the halogen, which clouded the location of these chloro and methyl substituents. It is likely that some distribution of the synperiplanar and gauche conformations may exist within the framework, reflecting the presence of both in methanol as expected from computations.

The observed conformers in the GS frameworks are consistent with the stabilization energies calculated for the *gauche* conformation ($\sigma_{C-X} \rightarrow \pi^*_{C-O}$), which increase in the order **F** < **Cl** < **Br**, whereas the synperiplanar conformation ($\sigma_{C-Me} \rightarrow \pi^*_{C-O}$) decreases in the order **F** > **Cl** > **Br**.[8] **F** gains more hyperconjugative stabilization through $\sigma_{C-Me} \rightarrow \pi^*_{C-O}$ in the *synperiplanar* conformation than it would for $\sigma_{C-X} \rightarrow \pi^*_{C-O}$ in the *gauche* conformation (Δ = 3.13 kcal/mol), while the opposite is true in the case of **Br** (Δ= -2.43 kcal/mol). Meanwhile, the difference in stabilization energy between $\sigma_{C-Me} \rightarrow \pi^*_{C-O}$ and $\sigma_{C-X} \rightarrow \pi^*_{C-O}$ for **Cl** is minor (Δ = -0.34 kcal/mol).

The observed conformational preferences of the encapsulated α-halopropiophenones reflect statistical distributions of the O–C–C–X dihedral angles in crystal structures reported for acyclic α-halo-substituted ketones found in the Cambridge Structural Database (CSD).[9] Surveys of the CSD were performed for four fragments intended to mimic the α-halogenated ketones (Figure 5). The conformational preferences observed in the GS inclusion compounds of **F**, **Cl**, and **Br** agree with the trends observed for crystal structures of analogous crystalline α-halo ketones in the CSD (details are provided as SI).

α-Halocyclooctanones. 2-Chlorocyclooctanone and 2-bromocyclooctanone (Figure 1C), which exist as liquids at room temperature, were encapsulated in the GCHMS host. Analysis of the crystal structure of the guest revealed one conformer in $(GCHMS)_3$⊃2-bromocyclooctanone, classified as *gauche* (resembling the chloro-analogue in Figure 5A), with $\phi_{O-C-C-Br}$ = 99.4°. In contrast, two conformers of 2-chlorocyclooctanone were observed in the $(GCHMS)_3$⊃2-chlorocyclooctanone inclusion compound. These conformers resemble the *gauche* and *synperiplanar* conformations (Figure 6), with occupancies of 39% and 23%, respectively (the remaining 38% of the electron density was too disordered to refine).



(i) R_1 = any atom; R_2, R_3 = any non-halogen atom
(ii) R_1 = phenyl; R_2, R_3 = any non-halogen atom
(iii) R_1 = any atom; R_2 = H; R_3 = any non-halogen atom
(iv) R_1 = phenyl; R_2 = H; R_3 = any non-halogen atom

X = F, Cl, Br

Figure 5. Four fragments used for the Cambridge Structural Database (CSD) surveys (i-iv) of acyclic α-halo-substituted ketones.

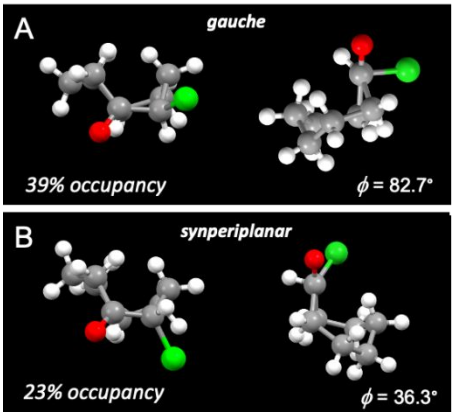


Figure 6. The crystal structure of 2-chlorocyclooctanone guest encapsulated in GCHMS reveals two conformers (A) *gauche* (39% occupancy), and (B) *synperiplanar* (23% occupancy), and their respective O−C−C−Cl dihedral angles (ϕ). The remainder of the guests were disordered and could not be refined. The structures on the right correspond to their respective Newman projections.

The conformations of 2-chlorocyclooctanone and 2-bromocyclooctanone observed in the GCHMS host were consistent with the computed lowest energy conformers. Calculations revealed that chair-boat conformations were lowest in energy, and the lowest energy conformer is described by a *gauche* conformation wherein the halogen atom is oriented equatorially on the boat side of the carbonyl group.[10] The next lowest energy conformer is described by a *synperiplanar* conformation wherein the halogen atom is oriented axially on the boat side of the carbonyl group (Figure S5).[10] These calculations revealed that the energy difference between these two conformers, for both compounds, decreased with increasing solvent polarity. The observation of both *gauche* and *synperiplanar* conformers of 2-chlorocyclooctanone in the GCHMS framework aligns with the small energy differences (ca. 0.5 kcal/mol calculated in CH_3CN) and the sensitivity of their energy ranking to the computational method used.[10] For example, the energy difference calculated at the B3LYP level corresponds to K_{eq} = 0.47 (at 273 K) for the equilibrium *gauche* ⇌ *synperiplanar*, compared with K_{eq} = 0.59 (at 100 K) obtained from the crystal structure, demonstrating reasonable agreement between the occupancy distribution and computations.

This investigation has revealed that the preferred conformers of α-halopropiophenones were confirmed in most of the inclusion compounds here. Conformational assignment in three examples was ambiguous, although consistent with the two most preferred conformations. Furthermore, two halocyclooctanones were included in the adaptable GCHMS host, and the lowest energy conformer was observed for 2-bromocyclooctanone. In contrast, multiple conformers of 2-chlorocyclooctanone were observed, consistent with the very small energy differences between the conformers. These results demonstrate that in most cases the GS hosts allowed the guests to adopt their lowest-energy conformation. The ambiguity in in the aforementioned three examples can be attributed to positional disorder of the guest owing to a "loose fit" of the guest in the host cavities, which prevented localization of the halogen atoms. These findings suggest that the use of GS frameworks for elucidating conformations of guests is promising, with implications for understanding stereochemical outcomes of their reactions. [6] The results, however, reveal the importance of judicious selection of "Goldilocks" host frameworks that allow the guest to adopt its lowest energy conformation without undue influence by packing forces exerted by the host, while immobilizing the guest sufficiently to reduce positional disorder.

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Data Availability statement

Crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif with numbers 2123655, 2307222-2307223, and 2364251-2364258. Electronic Supplementary Information (ESI) available: Experimental methods, crystal data and crystallographic information files, supporting figures and CCDC conformation survey results.

Conflicts of interest

There are no conflicts to declare.

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Data Availability Statement

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