

Hydrogen-bonded frameworks for conformational analysis of reactive substrates

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Materials

Cyclohexane sulfonic acid, 4,4'-biphenyldisulfonic acid and 1,5-naphthalene sulfonic acid were purchased from Sigma-Aldrich (St. Louis, MO). Guest 2-bromopropiophenone was purchased from Oakwood Chemical (West Columbia, SC). Guests 2-fluoropropiophenone¹ and 2-chloropropiophenone² were synthesized according to previously reported procedures. Guests 2-bromocyclooctanone and 2-chlorocyclooctanone were also synthesized according to previously reported procedures.³

The apo-host salts, guanidium cyclohexanesulfonate, guanidinium 4,4'-biphenyldisulfonate, and guanidinium 1,5-naphthalenedisulfonate, were prepared by combining acetone solutions of approximately 1.10 molar equivalents of guanidinium tetrafluoroborate and 1.0 molar equivalent of the organosulfonic acid to produce a precipitate of the corresponding guest-free apo-host. The precipitate was filtered, and the resulting solid was washed with acetone several times and dried in vacuo, affording the apo-host salt of the corresponding guanidium organosulfonate.

Methods

Crystallization. Single crystals of inclusion compounds were obtained by evaporation of a 1:1 solution of methanol:ethanol containing the target guest molecule (10 mg) and the guanidinium organosulfonate (GS) apohost (10 mg in 500 μ L of methanol). Single crystals of the inclusion compounds were grown by slow evaporation of the solvent under ambient temperature over a period of several days.

Single crystal X-ray diffraction. Crystals were mounted on MiTeGen MicroMount loops with Type B immersion oil (Cargille Labs) and X-ray diffraction data was obtained using several instruments. Data for G₂BPDS \supset 2-fluoropropiophenone (**4**), G₂BPDS \supset 2-chloropropiophenone (**5**), G₂BPDS \supset 2-bromopropiophenone (**6**), G₂1,5NDS \supset 2-fluoropropiophenone (**7**), G₂1,5NDS \supset 2-chloropropiophenone (**8**), and G₂1,5NDS \supset 2-bromopropiophenone (**9**) were collected at 100 K on a Bruker SMART APEX II diffractometer equipped with a PHOTON-II-C14 detector. The X-ray beam generated from an INCOATEC micro-focused source was monochromated and collimated by a Montel multilayer optics (Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å). Full data sets were collected with omega and phi scan methods. X-ray diffraction data for compounds (GCHMS)₄ \supset 2-chloropropiophenone (**2**) and (GCHMS)₄ \supset 2-bromopropiophenone (**3**) were collected at 130 K on a Bruker D8 VENTURE diffractometer using Cu $K\alpha$ radiation ($\lambda = 1.5406$ Å). For both Bruker instruments, the data sets were processed with the INTEGRATE program of the APEX4 software for reduction and cell refinement.⁴ Multi-scan absorption corrections were applied by the SCALE program for the area detector. X-ray diffraction data for compounds GCHMS \supset 2-fluoropropiophenone (**1**), (GCHMS)₃ \supset 2-chlorocyclooctanone (**10**), and (GCHMS)₃ \supset 2-bromocyclooctanone (**11**) were collected at 100 K using a Rigaku XtaLAB Synergy instrument equipped with a graphite monochromator (Cu $K\alpha$ radiation, $\lambda = 1.5406$ Å) and a HyPix-6000HE detector. Data was processed using CrysAlisPro V 1.171.42.54A, and absorption corrections were applied using spherical harmonics or through face indexing using SCALE3 ABSPACK. The structures were solved by intrinsic phasing methods (SHELXT or SHELXS) and the structure models were completed and refined using the full-matrix least-square methods on F^2 (SHELXL).^{5,6} Non-hydrogen atoms in the structures were refined with anisotropic displacement parameters, and hydrogen atoms on carbons were placed in idealized positions (C-H = 0.95-1.00 Å) and included as riding with $U_{\text{iso}}(\text{H}) = 1.2$ or $1.5U_{\text{eq}}(\text{non-H})$. PLATON/SQUEEZE was used to remove disordered guest/solvent molecules that could not be refined in **1**.⁷ Restraints for interatomic distances and thermal displacement parameters were used for disordered host molecules in **2**, **6**, **7**, **8**. Benzene rings in **2**, **3**, **4**, **6**, **7**, **8** were constrained to have idealized geometry. The geometry of the rest of the molecule and

thermal displacement parameters for the whole guest molecule were restrained to different extent depending on the severity of disorder for all crystal structures determined here. Crystal structures of **6** and **9** were refined as inverse twins. The constraints and restraints applied to the structures in refinement did not affect their conformer classification. Graphical representation of crystallographic data was done using Mercury (Version 4.3.1).⁸ Crystallographic data of these structures, including cif, res, fcf, and hkl files, have been deposited with the Cambridge Crystallographic Data Centre with Numbers 2123655, 2307222-2307223, and 2364251-2364258. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Table S1. Detailed crystallographic data of GCHMS inclusion compounds with 2-fluoro, 2-chloro-, and 2-bromopropiophenone guests.

Compound name	GCHMS \supset 2-fluoropropiophenone	(GCHMS) $_4\supset$ 2-chloropropiophenone	(GCHMS) $_4\supset$ 2-bromopropiophenone
Structure file name	1	2	3
X-ray lab code	mds189_auto_sq	147d_Hunter	23mdw94d
CCDC no.	2364251	2364253	2364252
Formula by X-ray	C ₇ H ₁₇ N ₃ O ₃ S	C _{17.5} H _{37.5} Cl _{0.39} N ₆ O _{6.39} S ₂	C _{18.5} H _{38.5} Br _{0.5} N ₆ O _{6.5} S ₂
Formula weight	223.29	512.20	553.13
Crystal habit	colorless plate	colorless plate	colorless plate
Crystal size (mm)	0.550 × 0.180 × 0.070	0.35 × 0.27 × 0.01	0.29 × 0.18 × 0.02
Crystal system	orthorhombic	monoclinic	monoclinic
Space group (no.)	<i>Pnma</i> (62)	<i>Pn</i> (7)	<i>Pn</i> (7)
a (Å)	17.2223(4)	17.5076(8)	17.4620(7)
b (Å)	7.28010(10)	8.6683(4)	8.6851(3)
c (Å)	12.1354(2)	19.0441(8)	19.0810(7)
α (°)	90	90	90
β (°)	90	99.021(3)	99.365(2)
γ (°)	90	90	90
V (Å³)	1521.54(5)	2854.4(2)	2855.24(18)
Z	4	4	4
D_c (g cm⁻³)	0.975	1.192	1.287
F(000)	480.0	1097.0	1172.0
μ (mm⁻¹)	1.851	2.375	2.878
Total reflections	8001	144528	64513
Unique reflections	1576	11470	11250
R_{int}	0.0430	0.0707	0.0868
R₁^a [<i>I</i> > 2 σ(<i>I</i>)]	0.0388	0.0826	0.1263
wR₂^b (all data)	0.1161	0.2360	0.3666
GOF (all data)	1.097	1.043	1.588
Flack parameter^c	n/a	-0.021(19)	-0.11(4)

^aR₁ = $\sum||F_o| - |F_c|| / \sum|F_o|$; ^bwR₂ = $\{\sum[w(F_o^2 - F_c^2)^2] / \sum[w(F_o^2)^2]\}^{1/2}$; ^cn/a – not applicable.

Table S2. Detailed crystallographic data of G₂BPDS inclusion compounds with 2-fluoro, 2-chloro-, and 2-bromopropiophenone guests. The crystal structure of G₂BPDS⊃2-chloropropiophenone (**5**) was published previously.⁹

Compound name	G ₂ BPDS⊃2-fluoropropiophenone	G ₂ BPDS⊃2-chloropropiophenone	G ₂ BPDS⊃2-bromopropiophenone
Structure file name	4	5	6
X-ray lab code	23mdw65d	21mdw1d	23mdw67d
CCDC no.	2364258	2123655	2364257
Formula by X-ray	C ₂₃ H ₂₉ FN ₆ O ₇ S ₂	C ₂₃ H ₃₃ ClN ₆ O ₉ S ₂	C ₂₃ H ₃₃ BrN ₆ O ₉ S ₂
Formula weight	584.64	637.12	681.58
Crystal habit	colorless plate	colorless plate	colorless needle
Crystal size (mm)	0.360 × 0.190 × 0.030	0.030 × 0.130 × 0.325	0.250 × 0.050 × 0.020
Crystal system	triclinic	monoclinic	monoclinic
Space group (no.)	<i>P</i> -1 (2)	<i>Cc</i> (9)	<i>Cc</i> (9)
<i>a</i> (Å)	7.3252(5)	31.790(3)	31.674(3)
<i>b</i> (Å)	12.7523(9)	11.6317(10)	11.6225(12)
<i>c</i> (Å)	30.161(2)	8.2943(7)	8.2592(8)
<i>α</i> (°)	96.337(4)	90	90
<i>β</i> (°)	94.485(4)	101.394(3)	101.032(6)
<i>γ</i> (°)	93.536(4)	90	90
<i>V</i> (Å³)	2784.6(3)	3006.6(4)	2984.3(5)
<i>Z</i>	4	4	4
<i>D_c</i> (g cm⁻³)	1.395	1.408	1.517
<i>F</i>(000)	1224.0	1336	1408.0
<i>μ</i> (mm⁻¹)	0.250	0.324	1.576
Total reflections	50789	25319	21396
Unique reflections	13848	7432	7077
<i>R</i>_{int}	0.0624	0.0452	0.1091
<i>R</i>₁^a [<i>I</i> > 2 <i>σ</i>(<i>I</i>)]	0.1468	0.0589	0.0831
<i>wR</i>₂^b (all data)	0.3125	0.1649	0.1996
GOF (all data)	1.131	1.066	1.053
Flack parameter^c	n/a	0.34(15)	0.33(3)

^a*R*₁ = $\sum ||F_o| - |F_c|| / \sum |F_o|$; ^b*wR*₂ = $\{\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]\}^{1/2}$; ^cn/a – not applicable.

Table S3. Detailed crystallographic data of G₂1,5NDS inclusion compounds with 2-fluoro-, 2-chloro-, and 2-bromopropiophenone guests.

Compound name	G ₂ 1,5NDS⊃2-fluoropropiophenone	G ₂ 1,5NDS⊃2-chloropropiophenone	G ₂ 1,5NDS⊃2-bromopropiophenone
Structure file name	7	8	9
X-ray lab code	23mdw6d	24mdw38d	23mdw66d
CCDC no.	2364254	2364256	2364255
Formula by X-ray	C ₂₁ H ₂₇ FN ₆ O ₇ S ₂	C ₂₁ H ₂₇ ClN ₆ O ₇ S ₂	C ₂₁ H ₂₇ BrN ₆ O ₇ S ₂
Formula weight	558.60	575.05	619.51
Crystal habit	colorless needle	colorless plate	colorless needle
Crystal size (mm)	0.200 × 0.050 × 0.030	0.910 × 0.270 × 0.110	0.370 × 0.180 × 0.050
Crystal system	orthorhombic	monoclinic	monoclinic
Space group (no.)	<i>Pn</i> nm (58)	<i>P</i> 2 ₁ / <i>n</i> (14)	<i>P</i> 2 ₁ (4)
a (Å)	7.9767(8)	7.6588(5)	7.7603(6)
b (Å)	21.0642(19)	20.9928(11)	21.0415(17)
c (Å)	7.4827(7)	8.0310(5)	7.9327(6)
α (°)	90	90	90
β (°)	90	90.117(4)	99.550(4)
γ (°)	90	90	90
V (Å³)	1257.3(2)	1291.22(13)	1277.37(17)
Z	2	2	2
D_c (g cm⁻³)	1.476	1.479	1.611
F(000)	584.0	600.0	636.0
μ (mm⁻¹)	0.273	0.363	1.827
Total reflections	12389	12933	22477
Unique reflections	1206	3239	5651
R_{int}	0.0939	0.0541	0.0774
R₁^a [I > 2 σ(I)]	0.0843	0.1588	0.0669
wR₂^b (all data)	0.2150	0.4046	0.1832
GOF (all data)	1.059	1.120	1.110
Flack parameter^c	n/a	n/a	0.13(2)

^aR₁ = Σ||F_o| - |F_c|| / Σ|F_o|; ^bwR₂ = {Σ[w(F_o² - F_c²)²] / Σ[w(F_o²)²]}^{1/2}; ^cn/a – not applicable.

Table S4. Detailed crystallographic data of GCHMS inclusion compounds with 2-chlorocyclooctanone and 2-bromocyclooctanone guests. These two inclusion compounds were reported previously.¹⁰

Compound name	(GCHMS) ₃ ⊃2-chlorocyclooctanone	(GCHMS) ₃ ⊃2-bromocyclooctanone
Structure file name	10	11
X-ray lab code	mdr054	mds056
CCDC no.	2307222	2307223
Formula by X-ray	C _{25.97} H _{59.07} Cl _{0.62} N ₉ O _{9.62} S ₃	C ₂₉ H ₆₄ BrN ₉ O ₁₀ S ₃
Formula weight	833.54	875.0
Crystal habit	colorless plate	colorless plate
Crystal size (mm)	0.490 x 0.090 x 0.040	0.230 x 0.150 x 0.020
Crystal system	monoclinic	orthorhombic
Space group (no.)	<i>P</i> 2 ₁ / <i>c</i> (14)	<i>Pmn</i> 2 ₁ (31)
a (Å)	12.4187(2)	20.6941(5)
b (Å)	31.3315(4)	8.4766(3)
c (Å)	12.52302(19)	12.3109(3)
α (°)	90	90
β (°)	119.397(4)	90
γ (°)	90	90
V (Å³)	4245.27(14)	2159.52(11)
Z	4	2
D_c (g cm⁻³)	1.204	1.346
F(000)	1654	928.0
μ (mm⁻¹)	2.415	3.145
Total reflections	52511	10457
Unique reflections	8183	3394
R_{int}	0.0428	0.0374
R₁^a [I > 2 σ(I)]	0.0747	0.0628
wR₂^b (all data)	0.2400	0.1765
GOF (all data)	1.038	1.044
Flack parameter^c	n/a	-0.006(19)

^aR₁ = Σ||F_o| - |F_c||/Σ|F_o|; ^bwR₂ = {Σ[w(F_o² - F_c²)²]/Σ[w(F_o²)²]}^{1/2}; ^cn/a – not applicable.

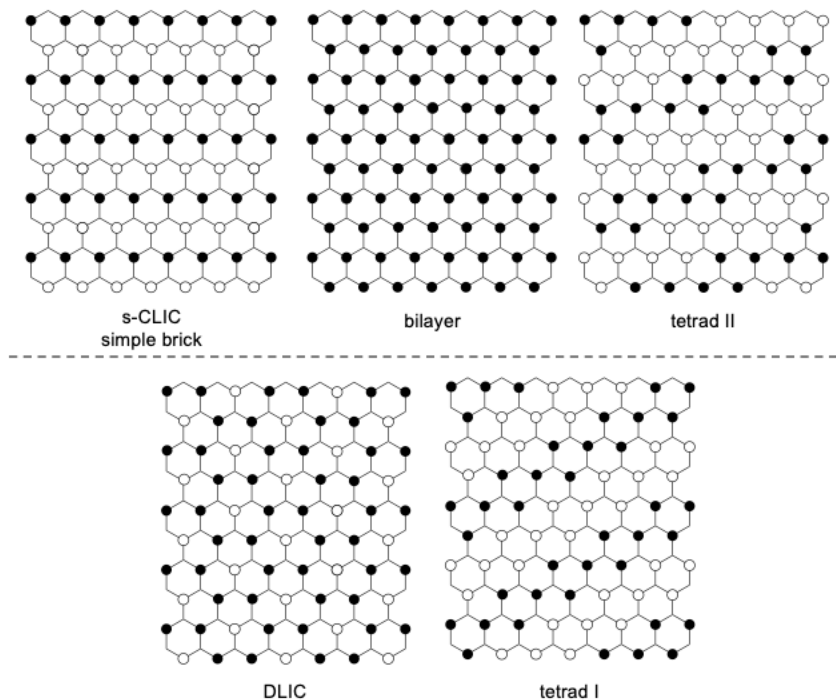


Figure S1. Projection topologies of the architectures observed in the inclusion compounds with (top) α -halopropiophenone guests and (bottom) with α -halocyclooctanone guests. Filled and open circles depict organic groups projecting from the sulfonate nodes above and below the sheet, respectively. The guanidinium ions sit on the undecorated nodes of the hexagonal tiling.

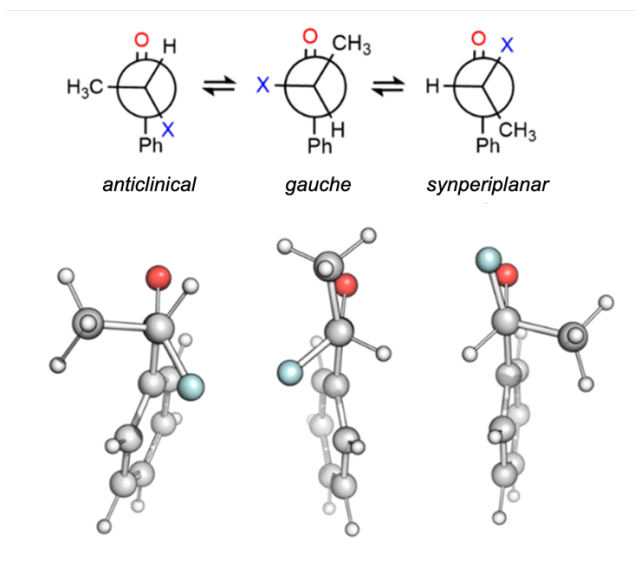


Figure S2. The three low energy minima conformers of the α -halopropiophenones studied by Francisco et al.¹¹ The labels for each conformer, *anticlinal*, *gauche*, and *synperiplanar*, are referred to throughout the manuscript and indicative of O-C-C-X dihedral angles (ϕ) of $135^\circ - -135^\circ$, $|45^\circ - 135^\circ|$, and $-45^\circ - 45^\circ$, respectively. Adapted with permission from *J. Phys. Chem. A* 2024, 128, 9, 1566–1575. Copyright 2024 American Chemical Society.¹¹

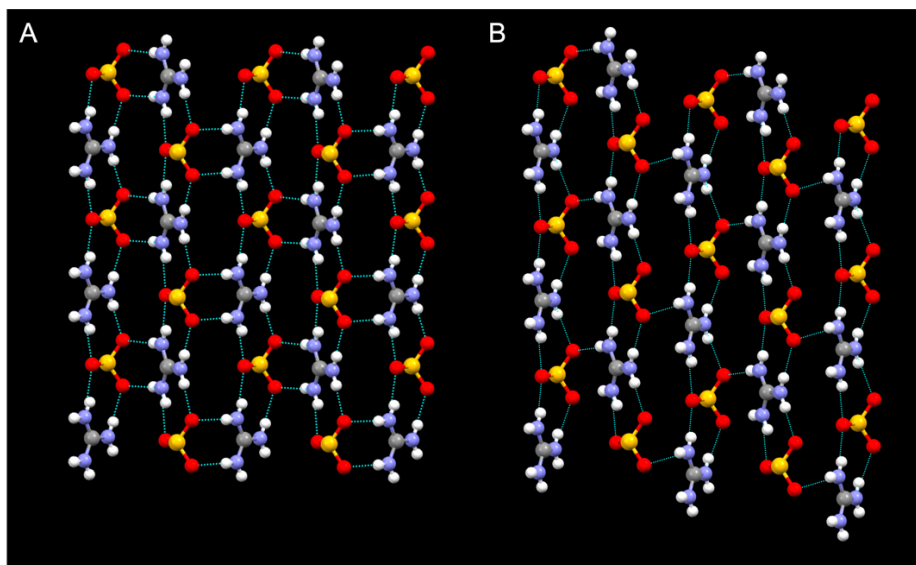
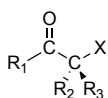
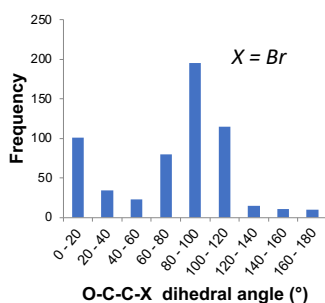


Figure S3. GS sheets in $G_{21,5NDS=2}$ -chloropropiophenone and $G_{21,5NDS=2}$ -bromopropiophenone.

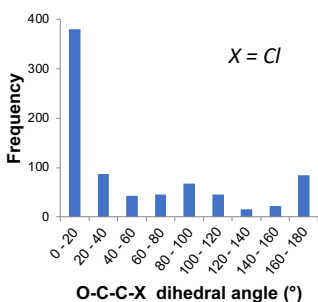
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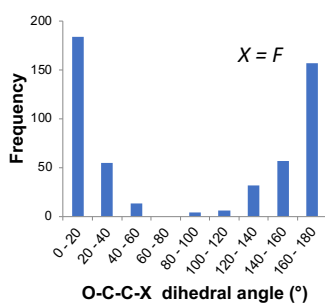
R_1 = any atom
 $R_2; R_3$ = any non-halogen atom



O-C-C-X dihedral angle (°)	Number of entries
0 - 20	101
20 - 40	34
40 - 60	23
60 - 80	80
80 - 100	195
100 - 120	115
120 - 140	15
140 - 160	11
160 - 180	10
total	584

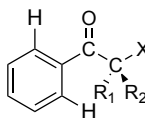


O-C-C-X dihedral angle (°)	Number of entries
0 - 20	381
20 - 40	87
40 - 60	43
60 - 80	46
80 - 100	68
100 - 120	45
120 - 140	15
140 - 160	22
160 - 180	85
total	792

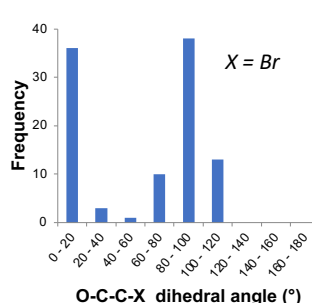


O-C-C-X dihedral angle (°)	Number of entries
0 - 20	184
20 - 40	55
40 - 60	13
60 - 80	0
80 - 100	4
100 - 120	6
120 - 140	32
140 - 160	57
160 - 180	157
total	508

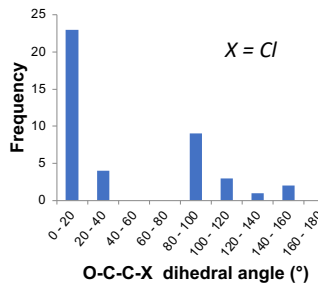
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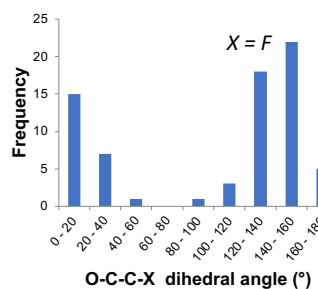
$R_1; R_2$ = any non-halogen atom



O-C-C-X dihedral angle (°)	Number of entries
0 - 20	36
20 - 40	3
40 - 60	1
60 - 80	10
80 - 100	38
100 - 120	13
120 - 140	0
140 - 160	0
160 - 180	0
total	101



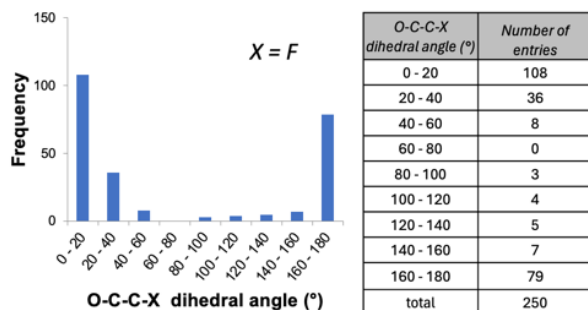
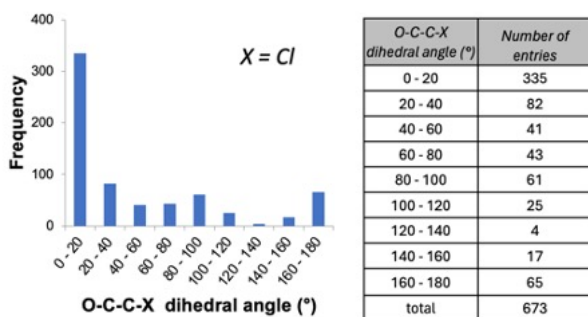
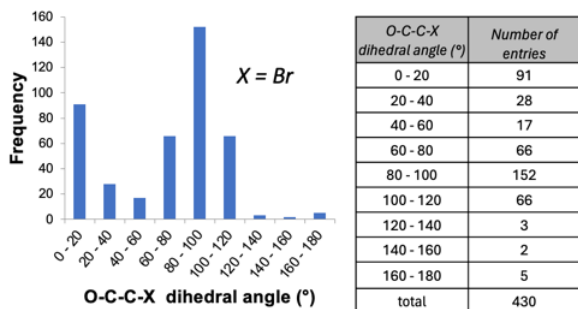
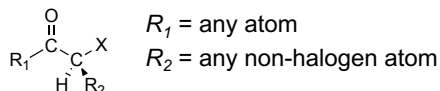
O-C-C-X dihedral angle (°)	Number of entries
0 - 20	23
20 - 40	4
40 - 60	0
60 - 80	0
80 - 100	9
100 - 120	3
120 - 140	1
140 - 160	2
160 - 180	0
total	42



O-C-C-X dihedral angle (°)	Number of entries
0 - 20	15
20 - 40	7
40 - 60	1
60 - 80	0
80 - 100	1
100 - 120	3
120 - 140	18
140 - 160	22
160 - 180	5
total	72

Figure S4. Histograms of surveys from the Cambridge Structural Database¹² of α -halogenated ketones. The details of the surveys include organic compounds only with acyclic carbon atoms bonded to oxygen and the halogen. The survey was performed for four fragments intended to mimic the composition of the α -halogenated ketones wherein (A) the ketone contained only a single halogen atom at the α position (i.e. excluding di- and tri-halogenated compounds) and any other substituents; (B) the ketone contained only a single halogen atom at the α position and a phenyl group with ortho hydrogen atoms. The fragments can be seen above the histograms and tables.

C



D

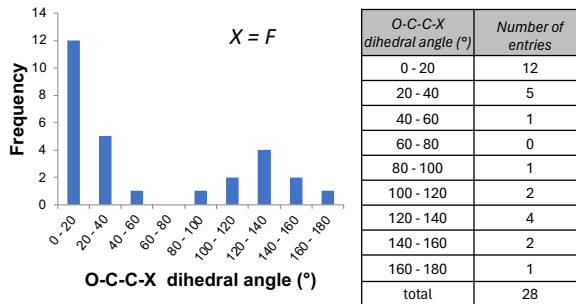
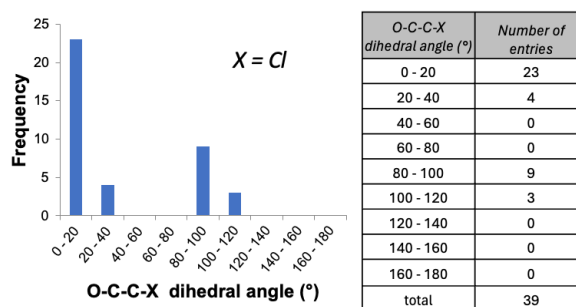
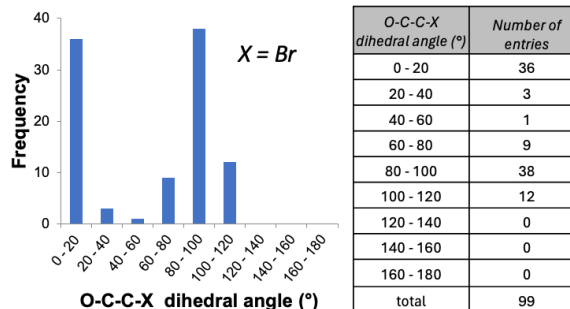
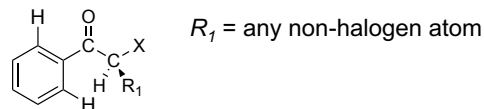


Figure S4 (continued). Histograms of surveys from the Cambridge Structural Database¹² of α -halogenated ketones. The details of the surveys include organic compounds only with acyclic carbon atoms bonded to oxygen and the halogen. The survey was performed for four fragments intended to mimic the composition of the α -halogenated ketones wherein (C) the ketone contained only a single halogen atom and one hydrogen atom at the α position and any other substituents and (D) the ketone contained only a single halogen atom and a hydrogen atom at the α position and a phenyl group with ortho-substituted hydrogen atoms. The fragments can be seen above the histograms and tables.

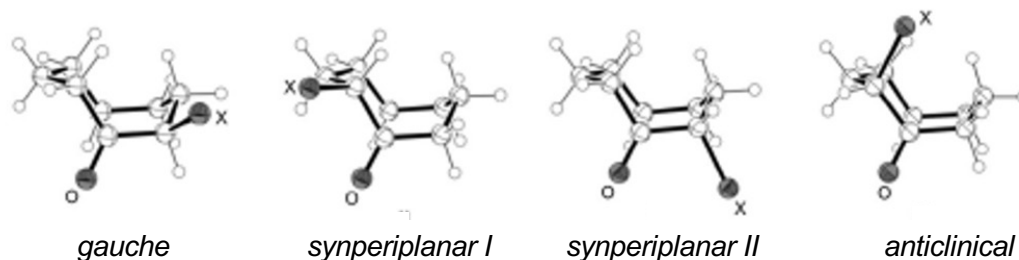


Figure S5. The four low energy conformers of α -halocyclooctanones as determined by Rozada et al.¹³ where X = F, Cl, Br, and I. There are two *synperiplanar* conformations identified as low energy conformers, differentiated by the location of the halogen on the chair-boat conformation wherein (I) the halogen is oriented axially on the chair side of the carbonyl and (II) the halogen is oriented axially on the boat side of the carbonyl. Adapted from *Spectrochim. Acta A Mol. Biomol. Spectrosc.*, 2015, **137**, 176–184, Copyright (2015), with permission from Elsevier.¹³

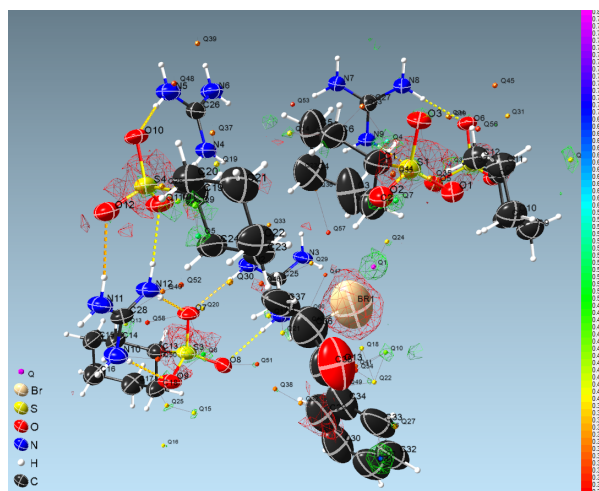


Figure S6. The residual density plot for GCHMS-2-bromopropiophenone (compound **3**; 23mdw94d). The bromine atom could not be refined with full occupancy. The red gridlines surrounding the bromine atom represent a deficit of electrons compared to that expected for bromine at that position. Nonetheless, the electron density at this position is sufficient for an unambiguous assignment of the *gauche* conformation for 2-bromopropiophenone.

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