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ORIGINAL PAPER

Analysis of Small Molecule X-Ray Crystal Structures: Chemical Crystallography with Undergraduate Students in a Teaching Laboratory

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Abstract The molecular structures of six small molecule organic compounds have been studied by X-ray diffraction in collaboration with undergraduate students enrolled in an advanced integrated laboratory course. The structures of 3-chloro-2-fluorobenzonitrile (**1**) [orthorhombic, $P2_12_12_1$, $a = 3.7679(13)$ Å, $b = 12.546(4)$ Å, $c = 13.780(5)$ Å], 5-chloro-2-fluorobenzonitrile (**2**) [monoclinic, $P2_1/c$, $a = 3.7909(7)$ Å, $b = 14.265(3)$ Å, $c = 12.171(2)$ Å, $\beta = 92.314(3)°$], 2-bromo-3′-hydroxyacetophenone (**3**) [triclinic, P-1, $a = 7.7081(3)$ Å, $b = 9.8840(3)$ Å, $c = 10.7320(4)$ Å, $\alpha = 98.4345(4)°$, $\beta = 90.6184(4)°$, $\gamma = 105.9259(4)°$], 3-chlorobenzoylacetonitrile (**4**) [monoclinic, Cc, $a = 4.8086(6)$ Å, $b = 32.929(4)$ Å, $c = 10.5855(13)$ Å, $\beta = 97.665(1)°$], 4-bromo-1-indanone (**5**) [triclinic, P-1, $a = 7.3731(4)$ Å, $b = 7.5419(4)$ Å, $c = 8.2370(4)$ Å, $\alpha = 62.927(1)°$, $\beta = 71.160(1)°$, $\gamma = 71.521(1)°$], and 4-bromo-1-indanol (**6**) [monoclinic, $P2_1/c$, $a = 12.7914(9)$ Å, $b = 4.6949(4)$ Å, $c = 27.864(2)$ Å, $\beta = 94.707(1)°$] reveal several different types of intermolecular interactions, such as hydrogen bonding, π-stacking, halogen–halogen interactions, and C–H···X (X = O, N, halogen) interactions.

Keywords Small molecule crystal structures · Molecular structure · Intermolecular interactions · π-Stacking · Crystallography education

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Experimental Section

General Considerations

3-Chloro-2-fluorobenzonitrile (**1**), 5-chloro-2-fluorobenzonitrile (**2**), 2-bromo-3′-hydroxyacetophenone (**3**), 3-chlorobenzoylacetonitrile (**4**), 4-bromo-1-indanone (**5**), and 4-bromo-1-indanol (**6**), all 97 %, were obtained from Sigma-Aldrich. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at room temperature using a Bruker Avance DPX 300 MHz spectrometer. ^{1}H chemical shifts are reported in ppm referenced to TMS (δ 0 ppm) for chloroform-*d*, the residual protio solvent for acetone-d_6, and ^{13}C chemical shifts are reported in ppm referenced to the solvent resonances of δ 77.0 ppm for chloroform-*d* and δ 29.8 ppm for acetone-d_6. Infrared (IR) spectra were recorded neat by ATR (Thunderdome) or as a KBr pellet on a Thermo Nicolet Nexus 670 FT-IR spectrometer and are reported in cm^{-1}. GC–MS data were obtained with an Agilent 7890 GC/5975 MS.

Spectroscopic Data

*NMR, IR and GC–MS Data for 3-Chloro-2-fluorobenzonitrile (**1**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.29 (m, 1H, $C_{aryl}H$), 7.53–7.60 (m, 1H, $C_{aryl}H$), 7.65–7.72 (m, 1H, $C_{aryl}H$). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, $CDCl_3$): δ 103.16 (d, C_{aryl}, $J_{C–F}$ 15.9 Hz), 113.05 ($C\equiv N$), 122.72 (d, C_{aryl}, $J_{C–F}$ 15.9 Hz), 125.50 (d, $C_{aryl}H$, $J_{C–F}$ 5.3 Hz), 131.79 ($C_{aryl}H$), 135.75 ($C_{aryl}H$), 158.94 (d, C_{aryl}, $J_{C–F}$ 261 Hz). IR (neat, cm^{-1}): 3085.1 (m, C_{aryl}–H *str*), 2239.2 (m, C≡N *str*), 1602.4 (w, C=C *str*), 1459.5 (s, C=C *str*), 1256.7 (m), 1180.7 (w), 1151.0 (w), 1076.0 (w), 861.3 (m), 827.2 (m), 784.8 (m), 714.0 (m). GC/MS: M+ 155 (calc. exact mass 154.99).

*NMR, IR and GC–MS Data for 5-Chloro-2-fluorobenzonitrile (**2**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (t, 1H, *J* 8.5 Hz, $C_{aryl}H$), 7.54–7.64 (m, 2H, $C_{aryl}H$). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, $CDCl_3$): δ 103.09 (d, C_{aryl}, J_{C-F} 17.1 Hz), 112.76 ($C\equiv N$), 118.06 (d, $C_{aryl}H$, J_{C-F} 21.1 Hz), 130.30 (d, C_{aryl}, J_{C-F} 3.6 Hz), 132.98 ($C_{aryl}H$), 135.31 (d, $C_{aryl}H$, J_{C-F} 8.3 Hz), 161.81 (d, C_{aryl}, J_{C-F} 258 Hz). IR (neat, cm^{-1}): 3108.0 (w, C_{aryl}–H *str*), 3064.7 (w, C_{aryl}–H *str*), 2236.0 (m, C≡N *str*), 1604.0 (w, C=C *str*), 1487.1 (s, C=C *str*), 1473.4 (m, C=C *str*), 1394.9 (m), 1263.8 (m), 1243.3 (m), 1200.8 (m), 1177.8 (m), 1116.4 (m), 1086.2 (w), 889.0 (m), 829.2 (m), 757.2 (m), 708.9 (w). GC/MS: M+ 155 (calc. exact mass 154.99).

*NMR, IR and GC–MS Data for 2-Bromo-3′-hydroxyacetophenone (**3**)*

^{1}H NMR (300 MHz, acetone-d_6): δ 4.71 (s, 2H, CH_2), 7.13 (d, 1H, $C_{aryl}H$, *J* 8.0 Hz), 7.37 (t, 1H, $C_{aryl}H$, *J* 7.8 Hz), 7.47 (s, 1H, $C_{aryl}H$), 7.53 (d, 1H, $C_{aryl}H$, *J* 7.7 Hz), 8.83 (br s, 1H, O*H*). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, acetone-d_6): δ 33.02 (CH_2), 115.76 ($C_{aryl}H$), 121.01 ($C_{aryl}H$), 121.66 ($C_{aryl}H$), 130.74 ($C_{aryl}H$), 136.46 (C_{aryl}), 158.59 (C_{aryl}), 191.78 (*C*=O). IR (neat, cm^{-1}): 3445.9 (s, O–H *str*), 3429.6 (s, O–H *str*), 3078.5 (w, C_{aryl}–H *str*), 3046.7 (w, C_{aryl}–H *str*), 2989.7 (w, C–H *str*), 2938.3 (w, C–H *str*), 1683.4 (s, C=O *str*), 1672.8 (s, C=O *str*), 1594.0 (s, C=C *str*), 1446.3 (s, C=C *str*), 1387.2 (w), 1352.7 (w), 1322.7 (w), 1287.8 (s), 1222.5 (m), 1165.2 (m), 1101.4 (w), 1043.1 (w), 997.2 (w), 903.0 (w), 889.6 (w), 881.7 (w), 866.5 (w), 800.7 (w), 783.0 (w), 748.7 (w), 704.2 (w). GC/MS: M+ 214 (calc. exact mass 213.96).

*NMR, IR and GC–MS Data for 3-Chlorobenzoylacetonitrile (**4**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.09 (s, 2H, CH_2), 7.49 (t, 1H, *J* 7.9 Hz, $C_{aryl}H$), 7.64 (d, 1H, *J* 8.0 Hz, $C_{aryl}H$), 7.80 (d, 1H, *J* 7.8 Hz, $C_{aryl}H$), 7.90 (t, 1H, *J* 1.9 Hz, $C_{aryl}H$). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, $CDCl_3$): δ 29.66 (CH_2), 113.46 ($C\equiv N$), 126.63 ($C_{aryl}H$), 128.60 ($C_{aryl}H$), 130.61 ($C_{aryl}H$), 134.81 ($C_{aryl}H$), 135.73 (C_{aryl}), 135.78 (C_{aryl}), 186.15 (*C*=O). IR (KBr pellet, cm^{-1}): 3075.6 (m, C_{aryl}–H *str*), 2941.1 (m, C_{alkyl}–H *str*), 2914.5 (m, C_{alkyl}–H *str*), 2256.1 (m, C≡N *str*), 1702.8 (vs, C=O *str*), 1639.5 (w, C=C *str*), 1590.4 (m, C=C *str*), 1573.6 (m, C=C *str*), 1472.8 (m), 1425.9 (s), 1396.4 (m), 1331.2 (s), 1215.1 (s), 1076.2 (w), 1028.8 (w), 998.4 (w), 945.3 (m), 893.3 (m), 791.1 (s), 724.2 (s), 679.2 (s). GC/MS: M+ 179 (calc. exact mass 179.01).

*NMR, IR and GC–MS Data for 4-Bromo-1-indanone (**5**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.74 (t, 2H, *J* 5.9 Hz, CH_2), 3.09 (t, 2H, *J* 5.9 Hz, CH_2), 7.28 (t, 1H, $C_{aryl}H$, *J* 7.6 Hz), 7.71 (d, 1H, $C_{aryl}H$, *J* 7.6 Hz), 7.76 (d, 1H, $C_{aryl}H$, *J* 7.7 Hz). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, $CDCl_3$): δ 26.91 (CH_2), 36.08 (CH_2), 122.21 (C_{aryl}), 122.54 ($C_{aryl}H$), 129.08 ($C_{aryl}H$), 137.30 ($C_{aryl}H$), 139.05 (C_{aryl}), 154.66 (C_{aryl}), 206.0 (*C*=O). IR (neat, cm^{-1}): 3072.4 (w, C_{aryl}–H *str*), 2914.4 (w, C–H *str*), 1704.3 (vs, C=O *str*), 1652.7 (w), 1591.9 (s), 1571.3 (m), 1435.6 (w), 1412.9 (w), 1318.2 (m), 1286.3 (w), 1267.3 (m), 1196.9 (m), 1168.4 (w), 1119.0 (w), 1052.1 (m), 1031.9 (w), 857.8 (w), 836.5 (m), 811.5 (w), 742.8 (w), 692.3 (w). GC/MS: M+ 210 (calc. exact mass 209.97).

*NMR, IR and GC–MS Data for 4-Bromo-1-indanol (**6**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88–2.01 (m, 1H, CH_2 and O*H*), 2.45–2.57 (m, 1H, CH_2), 2.74–2.88 (m, 1H, CH_2), 3.00–3.12 (m, 1H, CH_2), 5.29 (m, 1H, C*H*), 7.12 (t, 1H, $C_{aryl}H$, *J* 7.7 Hz), 7.33 (d, 1H, $C_{aryl}H$, *J* 7.4 Hz), 7.42 (d, 1H, $C_{aryl}H$, *J* 7.9 Hz). Assignment of overlapping OH and diastereotopic methylene CH at δ 1.88–2.01 ppm, as well as the methine CH at δ 5.29, in the ^{1}H NMR was made by obtaining the spectrum of the deuterated alcohol prepared by shaking a sample of 4-bromo-1-indanol (**6**) in D_2O and extracting it with $CDCl_3$. ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, $CDCl_3$): δ 31.16 (CH_2), 34.96 (CH_2), 77.16 (COH), 120.26 (C_{aryl}), 123.08 ($C_{aryl}H$), 128.62 ($C_{aryl}H$), 131.33 ($C_{aryl}H$), 143.56 (C_{aryl}), 146.80 (C_{aryl}). IR (neat, cm^{-1}): 3281.9 (br, s, O–H *str*), 3168.3 (br, s, O–H *str*), 2953.4 (s, C–H *str*), 2926.2 (m, C–H *str*), 2853.4 (m, C–H *str*), 1569.4 (m), 1456.6 (m), 1445.6 (m), 1425.4 (m), 1336.9 (m), 1315.3 (m), 1289.0 (m), 1203.3 (w), 1115.9 (vs, C–O *str*), 1063.6 (s), 837.2 (m), 796.3 (m), 781.9 (s), 773.3 (s), 702.0 (m). GC/MS: M+ 212 (calc. exact mass 211.98).

X-Ray Structure Determinations

X-ray diffraction data were collected on a Bruker APEX DUO CCD platform diffractometer [Mo Kα (λ = 0.71073 Å)] at 125 K. Recrystallizations were conducted by slow evaporation with several common solvents. 3-Chloro-2-fluorobenzonitrile (**1**) was recrystallized from hexanes, 5-chloro-2-fluorobenzonitrile (**2**) from ethyl acetate, 3-chlorobenzoylacetonitrile (**4**) from hexanes, 4-bromo-1-indanone (**5**) from acetone, 4-bromo-1-indanol (**6**) from 100 % ethanol, and 2-bromo-3′-hydroxyacetophenone (**3**) was best used as received. Suitable crystals were mounted in a nylon loop with Paratone N cryoprotectant oil. The structures were solved using direct methods and standard difference map techniques, and were refined by full-matrix

Table 1 Crystal, intensity collection and refinement data for **1–6**

	(1)	(2)	(3)	(4)	(5)	(6)
Formula	C_7H_3ClFN	C_7H_3ClFN	$C_8H_7BrO_2$	C_9H_6ClNO	C_9H_7BrO	C_9H_9BrO
Formula weight	155.55	155.55	215.05	639.21	211.06	213.07
Lattice	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_1/c$	P-1	Cc	P-1	$P2_1/c$
a (Å)	3.7679(13)	3.7909(7)	7.7081(3)	4.8086(6)	7.3731(4)	12.7914(9)
b (Å)	12.546(4)	14.265(3)	9.8840(3)	32.929(4)	7.5419(4)	4.6949(4)
c (Å)	13.780(5)	12.171(2)	10.7320(4)	10.5855(13)	8.2370(4)	27.864(2)
α (°)	90	90	98.4345(4)	90	62.927(1)	90
β (°)	90	92.314(3)	90.6184(4)	97.6650(10)	71.160(1)	94.707(1)
γ (°)	90	90	105.9259(4)	90	71.521(1)	90
V (Å^3)	651.4(4)	657.7(2)	776.63(5)	1,661.2(4)	378.06(3)	1,667.7(2)
Z, Z'	4, 1	4, 1	4, 2	8, 2	2, 1	8, 2
Temperature (K)	125(2)	125(2)	125(2)	125(2)	125(2)	125(2)
Radiation (λ, Å)	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
Crystal size (mm)	0.30 × 0.28 × 0.07	0.15 × 0.05 × 0.03	0.25 × 0.17 × 0.10	0.34 × 0.18 × 0.03	0.33 × 0.20 × 0.10	0.20 × 0.05 × 0.02
Color, habit	Colorless, plate	Colorless, needle	Colorless, block	Colorless, plate	Colorless, block	Colorless, needle
$\rho_{Calcd.}$ (g cm^{-3})	1.586	1.571	1.839	1.436	1.845	1.697
μ (Mo Kα), (mm^{-1})	0.511	0.506	5.234	0.403	5.364	4.865
Max., min. trans.	0.9651, 0.8619	0.9850, 0.9280	0.6227, 0.3545	0.9880, 0.8751	0.6160, 0.2705	0.9090, 0.4429
θ range (°)	2.20–30.60	2.20–30.46	1.92–30.50	2.30–30.47	2.84–30.54	2.08–30.54
Completeness to $\theta_{max.}$ (%)	30.60°, 99.1	30.46°, 97.3	30.50°, 99.3	30.47°, 98.7	30.54°, 99.1	30.54°, 99.4
Reflections collected	9,198	9,388	12,615	12,518	6,164	25,313
Unique reflections	1,981	1,953	4,686	4,916	2,297	5,094
R_{int}, R_σ	0.0579, 0.0438	0.0412, 0.0337	0.0186, 0.0219	0.0631, 0.0833	0.0170, 0.0180	0.0969, 0.0818
Data, restraints, parameters	1,981/0/92	1,953/0/91	4,686/2/205	4,916/2/218	2,297/0/100	5,094/2/205
R_1, wR_2 [F^2, $I > 2\sigma(I)$][a, b]	0.0639, 0.1691	0.0419, 0.0876	0.0243, 0.0600	0.0506, 0.0963	0.0179, 0.0458	0.0583, 0.1214
R_1, wR_2 (F^2, all data)[a, b]	0.0711, 0.1735	0.0608, 0.0942	0.0307, 0.0624	0.0798, 0.1061	0.0193, 0.0464	0.1227, 0.1441
GOF[c]	1.149	1.066	1.040	1.010	1.059	1.023
Largest difference peak, hole (e/Å^{-3})	0.974, −0.613	0.396, −0.248	0.717, −0.943	0.448, −0.297	0.420, −0.259	2.359, −0.724
Flack x, Hooft y	0.10(14), 0.08(5)	–	–	0.03(6), 0.02(5)	–	–

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

[b] $w = 1/[\sigma^2(F_o)^2 + (aP)^2 + bP]$, where $P = [1/3]\ \max(0, F_o^2) + [2/3]F_c^2$

[c] GOF $= S = [\Sigma w(F_o^2 - F_c^2)^2/(N_R - N_P)]^{1/2}$, where N_R is the number of reflections and N_P is the number of parameters

least-squares procedures on F^2 with SHELXTL (Version 2008; [1]). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on carbon were included in calculated positions and were refined using a riding model. The hydrogen atoms on oxygen in 2-bromo-3′-hydroxyacetophenone (**3**) and 4-bromo-1-indanol (**6**) were located in the difference Fourier map and refined semi-freely with the help of a distance restraint. Crystal data and refinement details are presented in Table 1. The structures were investigated with SHELX XP [1], Mercury 3.0 [2], and OLEX2 1.2.2. [3]. Supplementary crystallographic data for the structures reported in this paper, 3-chloro-2-fluorobenzonitrile (**1**; Cambridge Crystallographic Data Centre, CCDC number 926148), 5-chloro-2-fluorobenzonitrile (**2**; CCDC number 925541), 2-bromo-3′-hydroxyacetophenone (**3**; CCDC number 925483), 3-chlorobenzoylacetonitrile (**4**; CCDC number 926369), 4-bromo-1-indanone (**5**; CCDC number 925786), and 4-bromo-1-indanol (**6**; CCDC number 926556) can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

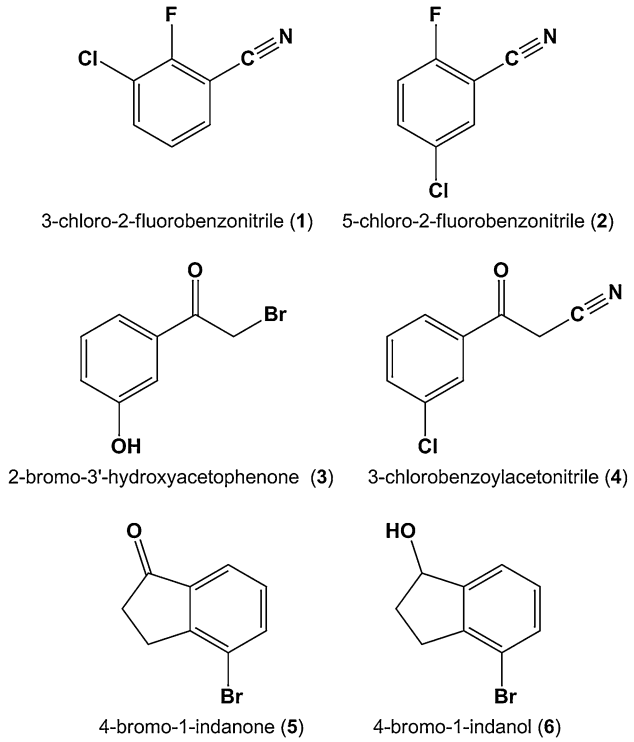

Fig. 1 Six compounds analyzed by X-ray diffraction

Introduction

X-ray crystallography is an essential analytical technique used extensively in the physical and biological sciences for the determination of molecular structure with atomic scale resolution. For several decades, therefore, it has been recognized that fundamental aspects of chemical crystallography should be taught to students studying science [4], including during secondary education [5]. With increases in the speed and reliability of commercially available X-ray diffraction systems equipped with area detectors, the effort and time necessary to collect and analyze data has decreased from days to hours, allowing for the incorporation of X-ray crystallographic methods into undergraduate research training and education on a larger scale [6]. In recent years, less expensive and more reliable "desktop" X-ray diffractometers have made it even easier for institutions to install in-house instrumentation. Even in the absence of in-house instrumentation, it has been recognized that other means and methods of crystallography education have taken hold that make use of short courses and resources found online [7]. In addition, there are now a good number of published examples of exercises designed to teach students about crystallographic methods, about the nature of the results that can be obtained, and about the fundamental structural concepts in science that are informed by crystallographic results [8–11]. While still growing, training in crystallographic methods for undergraduate science students has seen modest gains.

In this paper, we report the spectroscopic characterization and X-ray structures of six small molecule organic compounds completed as part of an advanced undergraduate teaching laboratory at Vassar College (Fig. 1). Students enrolled in the laboratory course, which is required for chemistry majors, are each given an unknown solid organic compound to determine the identity of by ^{1}H, ^{13}C and DEPT NMR spectroscopy, IR spectroscopy, and GC/MS. After completing a laboratory report detailing the identity of the organic compound, the students then perform recrystallizations and determine the X-ray crystal and molecular structure of the compound, and finally write up the results in the format of an *Acta Crystallographica* Structure Report. For each instrumental technique, the students are guided in the hands-on use of the instrumentation and acquire and analyze the data individually. The compounds were selected in part because their structures have not been reported, such that students could have the opportunity to be part of the publication of the results of their work. After appropriate editing, this provides one possible mechanism for future publication of the results, integrating teaching with discovery based research and the communication of new scientific knowledge.

Besides the molecular structures themselves, which enhance understanding of the three-dimensional arrangement of atoms in molecules, the structures reported here highlight several different types of intermolecular interactions. These interactions include hydrogen bonding, π-stacking,

halogen–halogen interactions, and C–H···X (X = O, N, halogen) interactions. Intermolecular interactions are important for students to learn about as they come to understand the ways in which atoms and molecules may pack together in the solid state. A high impact way to teach students about the different types of intermolecular interactions is as part of the process of carrying out the actual experiment of a crystal structure determination.

Results and Discussion

Six small molecule organic compounds were obtained from commercial sources and their structures have been determined by X-ray diffraction at 125 K. Crystal, intensity and refinement data is provided in Table 1 for 3-chloro-2-fluorobenzonitrile (**1**), 5-chloro-2-fluorobenzonitrile (**2**), 2-bromo-3′-hydroxyacetophenone (**3**), 3-chlorobenzoylacetonitrile (**4**), 4-bromo-1-indanone (**5**), and 4-bromo-1-indanol (**6**).

3-Chloro-2-fluorobenzonitrile (**1**)

3-Chloro-2-fluorobenzonitrile (**1**) may be synthesized by selective fluorination of the chloride group *ortho* to the nitrile group of 2,3-dichlorobenzonitrile with anhydrous tetrabutylammonium fluoride [12]. It has found use in the synthesis of biologically active imidazole compounds [13]. Crystallization of commercially obtained 3-chloro-2-fluorobenzonitrile (**1**) by slow evaporation of a hexane solution yields thin colorless plates suitable for X-ray diffraction analysis. The crystal structure (Fig. 2) reveals that the molecule is flat, with an rms deviation from the plane of all non-hydrogen atoms of 0.0158. The nitrile C–C–N bond angle is nearly linear at 178.6(4)°, and the nitrile C≡N bond length of 1.138(4) Å is comparable to that found in the structure of benzonitrile itself [14], with C≡N length 1.14(1) Å. The molecules pack together via an offset face-to-face π-stacking parallel to the crystallographic *a* axis, with intermolecular Cl···F interactions at a distance of 3.154(2) Å forming a one-dimensional spiral chain linking two of the π-stacked columns together, as shown in Fig. 3. In π-stacking structures, the ring centroid-to-centroid distance, *d*, gives an indication of the closeness of the interaction, while comparison of the centroid-to-centroid distance and centroid-to-plane distance gives an indication of how slipped, or offset, the face-to-face overlap is. This offset π-stacking motif has been referred to as parallel displacement, with displacement distance *r* [15, 16]. In 3-chloro-2-fluorobenzonitrile (**1**) the centroid-to-centroid distance, *d*, of 3.768(1) Å and centroid-to-plane distance of 3.435(2) Å yields a ring offset, slippage parameters, *r*, of 1.548(5) Å.

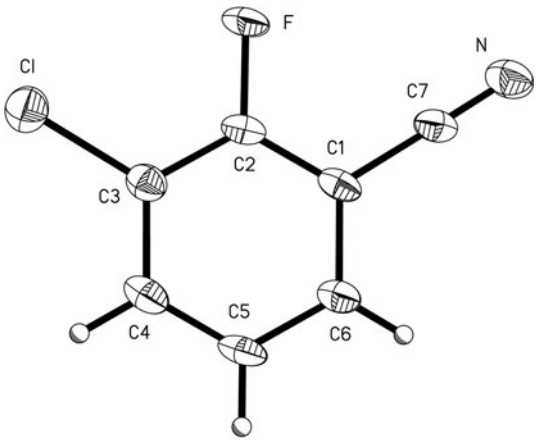

Fig. 2 Molecular structure of 3-chloro-2-fluorobenzonitrile (**1**) with thermal *ellipsoids* at the 50 % probability level. Selected bond lengths (Å) and angles (°): C2–F 1.346(3), C3–Cl 1.722(3), C7–N 1.138(4), C1–C7–N 178.6(4)

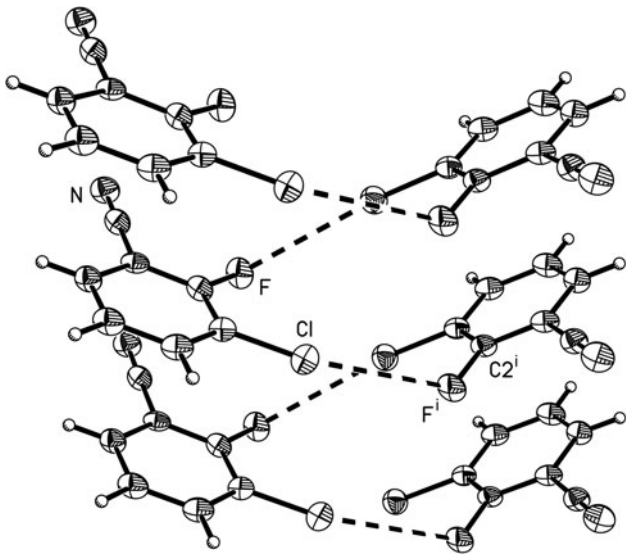

Fig. 3 Molecular packing of 3-chloro-2-fluorobenzonitrile (**1**) with thermal *ellipsoids* at the 50 % probability level. π-Stacking centroid-to-centroid distance 3.768(1) Å, centroid-to-plane 3.435(2) Å, ring offset 1.548(5) Å. Intermolecular Cl···F distance 3.154(2) Å. Symmetry code *i* $x - 1/2, -y - 1/2, -z + 1$

It is interesting to note that the compound crystallizes in the non-centrosymmetric chiral space group $P2_12_12_1$; whereas the molecule is not chiral, the intermolecular π-stacking and Cl···F interaction create a handed spiral about the twofold screw axis in $P2_12_12_1$ with direction [1, 0, 0] at *x*, 1/4, 0. Intermolecular Cl···F interactions have been discussed by Desiraju and colleagues [17]. In 3-chloro-2-fluorobenzonitrile (**1**), the Cl···F interaction at a distance of 3.154(2) Å is less the sum of the van der Waals radii of chlorine and fluorine, 3.30 Å [17]. The geometry of halogen···halogen interactions may be categorized as types I or II, depending on the values of the two C–X–X angles

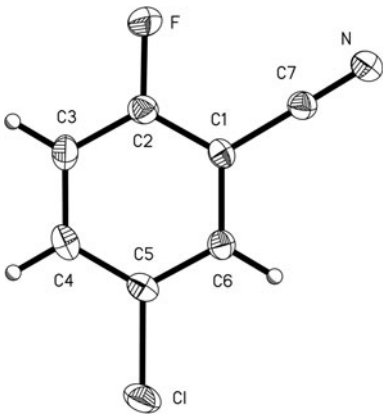

Fig. 4 Molecular structure of 5-chloro-2-fluorobenzonitrile (**2**) with thermal *ellipsoids* at the 50 % probability level. Selected bond lengths (Å) and angles (°): C2–F 1.350(2), C5–Cl 1.732(2), C7–N 1.147(2), C1–C7–N 179.4(2)

(θ_1 and θ_2) that define the C–X···X–C contact [17]. When $\theta_1 \approx \theta_2$, the interaction is classified as type I, whereas when $\theta_1 \approx 90°$ while $\theta_2 \approx 180°$, the interaction is classified as type II. 3-Chloro-2-fluorobenzonitrile (**1**) displays an interaction that is intermediate between the two types, with C2–F···Cl angle $\theta_1 = 123.7(2)°$ and C3–Cl···F angle $\theta_2 = 164.4(1)°$.

5-Chloro-2-fluorobenzonitrile (**2**)

An isomer of 3-chloro-2-fluorobenzonitrile (**1**) is 5-chloro-2-fluorobenzonitrile (**2**), which may also be synthesized by direct fluorination of the chloride *ortho* to the nitrile group in 2,5-dichlorobenzonitrile precursor [18], as well as by substitution of the nitro group in 5-chloro-2-nitrobenzonitrile using methylhexamethylenetetramine fluoride dihydrate [19]. 5-Chloro-2-fluorobenzonitrile (**2**) has been used as a synthon for several biologically active compounds, recently in the synthesis of imidazo-triazolobenzodiazepines [20] and 2-amino-benzothienopyrimidines [21]. Colorless needle shaped crystals obtained from ethyl acetate were used to determine the molecular structure of 5-chloro-2-fluorobenzonitrile (**2**; Fig. 4) which shows that like 3-chloro-2-fluorobenzonitrile (**1**), the molecule is flat, with an rms deviation from the plane of all non-hydrogen atoms of 0.0062. The nitrile C–C–N bond angle is very nearly linear at 179.4(2)°, and the nitrile C≡N bond length of 1.147(2) Å is comparable to that found in the structures of 3-chloro-2-fluorobenzonitrile (**1**), 1.138(4) Å, and benzonitrile, 1.14(1) Å [14]. The C–F and C–Cl bond lengths in 5-chloro-2-fluorobenzonitrile (**2**), 1.350(2) and 1.732(2) Å, respectively, are very similar to those found in 3-chloro-2-fluorobenzonitrile (**1**), 1.346(3) and 1.722(3) Å, respectively. Similarly to 3-chloro-2-fluorobenzonitrile (**1**), the molecules of 5-chloro-2-fluorobenzonitrile (**2**) pack

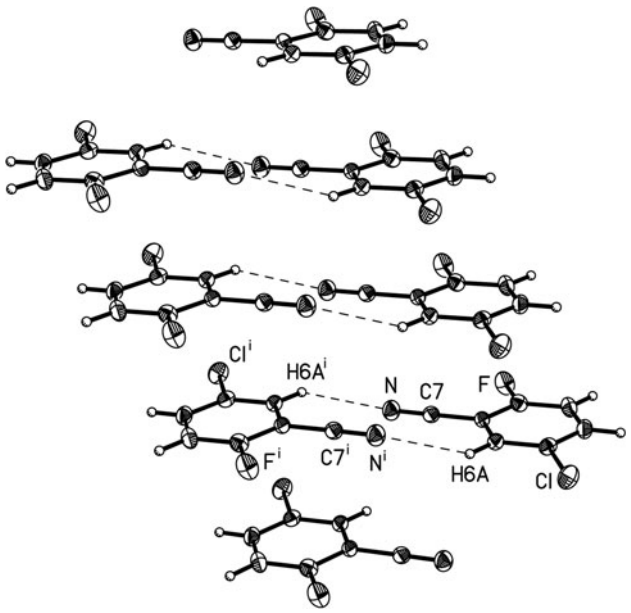

Fig. 5 π-Stacking in the structure of 5-chloro-2-fluorobenzonitrile (**2**) with thermal *ellipsoids* at the 50 % probability level. π-Stacking centroid-to-centroid distance 3.791(1) Å, centroid-to-plane distances 3.408(1) Å, ring offset 1.660(2) Å. Intermolecular C≡N···H distance 2.616(2) Å, CN···H angle 141.0(1)°. Symmetry code i $-x + 1$, $-y + 1$, $-z + 1$

together via an offset face-to-face π-stacking parallel to the crystallographic *a* axis, with centroid-to-centroid distance, *d*, of 3.791(1) Å, centroid-to-plane distances of 3.408(1) Å, and a ring offset, slippage parameters, *r*, of 1.660(2) Å (Fig. 5). Unlike 3-chloro-2-fluorobenzonitrile (**1**), which forms a one-dimensional spiral chain linking two π-stacked columns of molecules via intermolecular Cl···F interactions, 5-chloro-2-fluorobenzonitrile (**2**) forms two π-stacked columns of molecules engaged in a centrosymmetric pairwise nitrile C≡N···H interaction (Fig. 5), with an N···H distance of 2.616(2) Å and C≡N···H angle of 141.0(1)°.

There also exist several Cl···Cl and Cl···F interactions, as depicted in Fig. 6. The shortest Cl···Cl distance of 3.594(1) Å is slightly longer than the sum of the van der Waals radii, 3.50 Å [17]. For comparison, the shortest Cl···Cl distance in 2,5-dichloroaniline is found to be 3.3219(8) Å [22]. The Cl···F interactions of 3.340(1) and 3.562(1) Å are somewhat longer than the sum of the van der Waals radii of chlorine and fluorine, 3.30 Å [17], and the Cl···F interaction observed in 3-chloro-2-fluorobenzonitrile (**1**), at 3.154(2) Å. Such interactions are not uncommon and can vary in length [17, 23]. The Cl···Cl interaction in 5-chloro-2-fluorobenzonitrile (**2**) displays a type I halogen···halogen contact, with angles $\theta_1 = \theta_2 = 147.40(6)°$, whereas the shorter Cl···F interaction is intermediate between the two types, with C2–F···Cl angle $\theta_1 = 117.24(9)°$ and C5–Cl···F angle $\theta_2 = 145.13(6)°$, and the longer one is more similar to a type II interaction, with

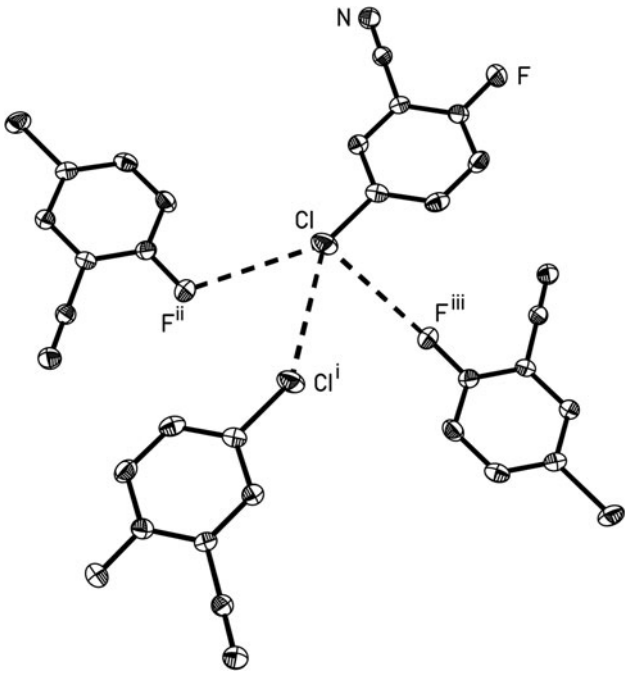

Fig. 6 Depiction of halide–halide interactions in the structure of 5-chloro-2-fluorobenzonitrile (**2**) with thermal *ellipsoids* at the 50 % probability level. Intermolecular halide···halide distances Cl···Cl^{i} 3.594(1) Å, Cl···F^{ii} 3.340(1) Å, Cl···F^{iii} 3.562(1) Å. Symmetry codes *i* $-x + 3, -y + 1, -z + 2$; *ii* $-x + 2, y + 1/2, -z + 3/2$; *iii* $x, -y + 1/2, z + 1/2$

C5–Cl···F angle θ_1 = 79.84(6)° and C2–F···Cl angle θ_2 = 138.7(1)°.

2-Bromo-3′-hydroxyacetophenone (**3**)

Also known as 2-bromo-1-(3-hydroxyphenyl)ethanone, 2-bromo-3′-hydroxyacetophenone (**3**) can be prepared by bromination of 3-hydroxyacetophenone with copper(I) bromide, with dioxane dibromide, or with bromine itself [24]. 2-Bromo-3′-hydroxyacetophenone (**3**), an α-bromoketone, has been employed as a precursor in the synthesis of heterocyclic compounds such as *N*-aryl-*N*-thiazolyls [25], and in non-steroidal anti-inflammatory compounds that are non-ulcerogenic [26].

The structure of 2-bromo-3′-hydroxyacetophenone (**3**; Fig. 7) exhibits two independent molecules in the asymmetric unit ($Z' = 2$) in *P*-1. The independent molecules differ primarily by the C_{aryl}–C(O)–CH_2–Br torsional angle. In the first molecule (Fig. 7, right) the C13–C12–C11–Br1 torsional angle of 82.2(2)° cants the bromine out of the acetophenone plane, whereas in the second molecule (Fig. 7, left), the C23–C22–C21–Br2 torsional angle of 172.9(1)° leaves the bromine almost coplanar with the acetophenone plane, with the bromine *cis* to the carbonyl. Each of the independent molecules forms a centrosymmetric pairwise hydrogen bonding dimer with itself, as shown in Fig. 8, with hydrogen bonding O···O distances of 2.898(2) and 2.810(2) Å. The structure does not exhibit any π-stacking. There is an intermolecular Br1···Br2 interaction at a distance of 3.5087(3) Å, which is significantly shorter than the sum of the van der Walls radii, 3.70 Å [17], as depicted in Fig. 9. The Br···Br interaction in 2-bromo-3′-hydroxyacetophenone (**3**) is best characterized as a type II halogen···halogen contact, with C11–Br1···Br2 angle $\theta_1 = 115.11(6)°$ and C21–Br2···Br1 angle $\theta_2 = 173.58(6)°$. A closely related compound, 2-bromo-4′-hydroxyacetophenone, also crystallizes with two molecules in the asymmetric unit, has similar bond lengths and angles, and exhibits no π-stacking [27]. However, the two independent molecules of 2-bromo-4′-hydroxyacetophenone do not have significantly different C_{aryl}–C(O)–CH_2–Br torsional angles as found in 2-bromo-3′-hydroxyacetophenone (**3**). The C_{aryl}–C(O)–CH_2–Br torsional angles in the two independent molecules of 2-bromo-4′-hydroxyacetophenone are 178.7° and 179.5°, both with the bromine *cis* to the carbonyl. Further, as opposed to the *meta* orientation of the α-bromoketone and hydroxyl moieties in 2-bromo-3′-hydroxyacetophenone (**3**), the *para* orientation in 2-bromo-4′-hydroxyacetophenone results in a different hydrogen bonding motif, namely one-dimensional chains. Also shown in in Fig. 9 are three C–H···O intermolecular interactions present in the structure of 2-bromo-3′-hydroxyacetophenone (**3**), at C–H···O distances 2.547(1) Å (O22···H15^{iii}–C15^{iii}), 2.660(1) Å (O12···H28^{ii}–C28^{ii}), and 2.695(1) Å (O12···H24^{i}–C24^{i}).

3-Chlorobenzoylacetonitrile (**4**)

3-Chlorobenzoylacetonitrile (**4**), or 3-(3-chlorophenyl)-3-oxopropanenitrile, and derivatives can be synthesized by carbonylation of aryl iodides with $Mo(CO)_6$ in the presence of trimethylsilylacetonitrile and a palladium catalyst [28]. The compound has been used in the synthesis biologically active 2-amino-3-benzoylthiophenes [29] and pyrrolopyrimidines [30] that are receptor agonist compounds. 3-Chlorobenzoylacetonitrile (**4**) and other molecules in its class have also been used in the synthesis of 3-aryl-quinoxaline-2-carbonitrile 1,4-di-*N*-oxide derivatives as possible anti-tumor treatments [31].

After recrystallization from hexanes, very thin colorless plates of 3-chlorobenzoylacetonitrile (**4**) were used to determine the crystal structure. The asymmetric unit contains two unique molecules that exhibit different conformations by virtue of a 180° rotation about the C_{aryl}–$C_{carbonyl}$ bond (Fig. 10). In one molecule, the carbonyl is *cis* to the chlorine, with torsional angle C12–C13–C14–C15 of 178.4(2)°, whereas in the other molecule the carbonyl is *trans* to the chlorine, with torsional angle C22–C23–C24–C25 of 1.6(4)°. The two independent molecules form a pairwise dimer linked by an intermolecular C–H···O

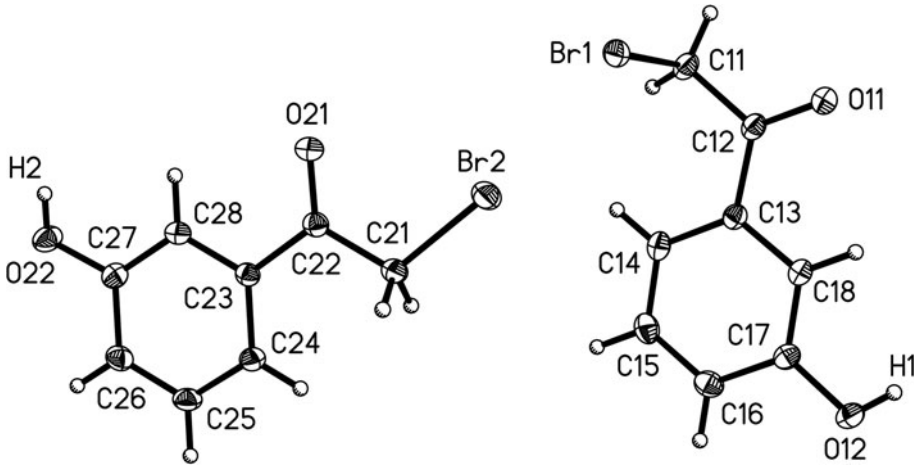

Fig. 7 Molecular structure of 2-bromo-3′-hydroxyacetophenone (**3**) with thermal *ellipsoids* at the 50 % probability level. Selected bond lengths (Å) and angles (°): Br1–C11 1.953(2), Br2–C21 1.924(2), O11–C12 1.220(2), O21–C22 1.219(2), O12–C17 1.367(2), O22–C27 1.372(2). Selected torsional angles (°): C13–C12–C11–Br1 82.2(2), C23–C22–C21–Br2 172.9(1)

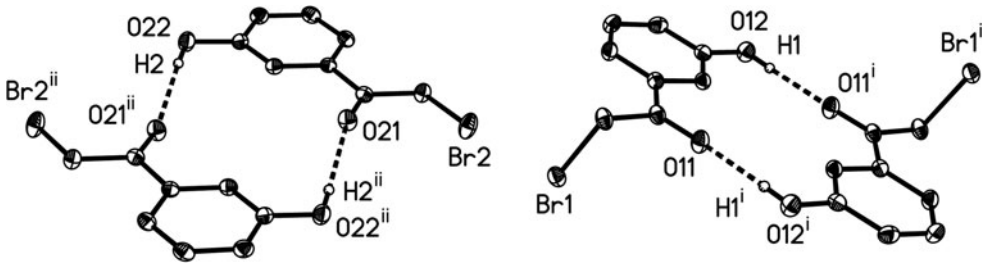

Fig. 8 Depiction of the pairwise hydrogen bonded dimers in the structure of 2-bromo-3′-hydroxyacetophenone (**3**) with thermal *ellipsoids* at the 50 % probability level. Hydrogen bonding distances: O12–H1···O11^{i} 2.898(2) Å, O22–H2···O21^{ii} 2.810(2) Å. Symmetry codes *i* $-x + 2, -y + 1, -z + 2$; *ii* $-x, -y, -z$

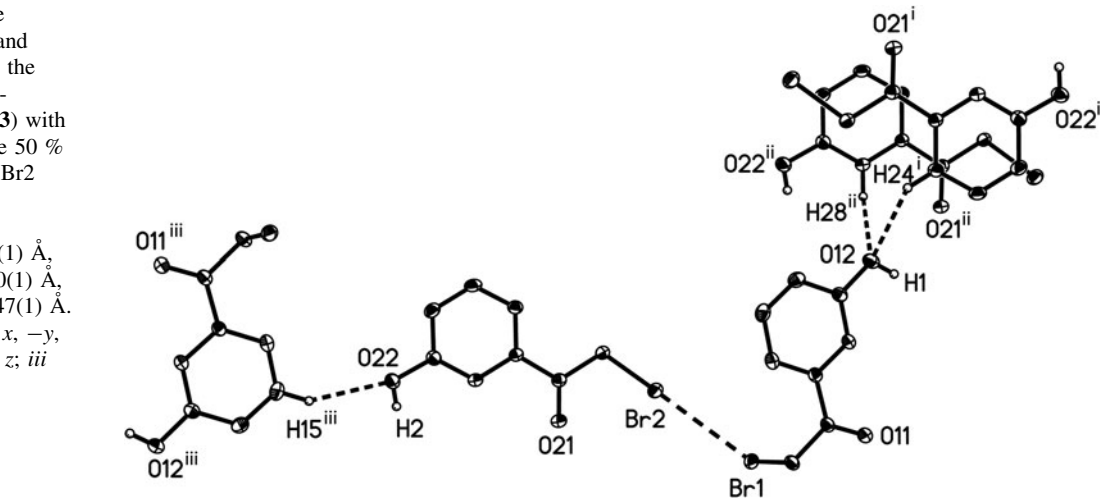

Fig. 9 Depiction of the intermolecular Br···Br and C–H···O interactions in the structure of 2-bromo-3′-hydroxyacetophenone (**3**) with thermal *ellipsoids* at the 50 % probability level. Br1···Br2 3.5087(3) Å. C–H···O interaction distances: O12···H24^{i}–C24^{i} 2.695(1) Å, O12···H28^{ii}–C28^{ii} 2.660(1) Å, O22···H15^{iii}–C15^{iii} 2.547(1) Å. Symmetry codes *i* $2 - x, -y, 1 - z$; *ii* $1 + x, y, 1 + z$; *iii* $1 - x, -y, -z$

(C25–H25A···O1) interaction at a distance of 2.533(1) Å, a C–H···Cl (C15–H15A···Cl2) interaction at a distance of 2.814(1) Å, and a Cl···Cl interaction at 3.580(1) Å. This Cl···Cl interaction distance is similar to that observed in 5-chloro-2-fluorobenzonitrile (**2**) at 3.594(1) Å, and is best characterized as a type II halogen···halogen contact, with C16–Cl1···Cl2 angle $\theta_1 = 95.13(9)°$ and C26–Cl2···Cl1 angle $\theta_2 = 163.5(1)°$. These dimers are further linked into a one-dimensional chain by a carbonyl C=O···H interaction (C23=O2···H17A) with a distance of 2.359(1) Å, as shown in Fig. 11.

4-Bromo-1-indanone (**5**)

4-Bromo-1-indanone (**5**) can be synthesized by direct bromination of 1-indanone with Br_2 in the presence of

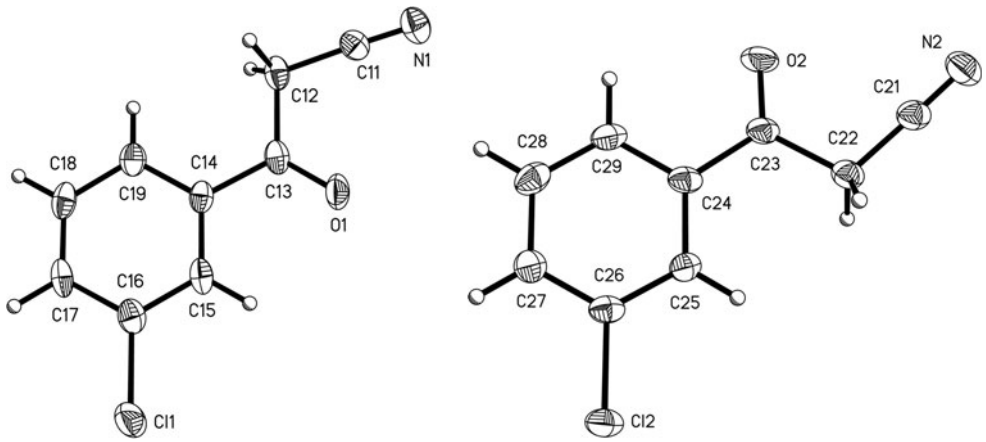

Fig. 10 Molecular structure of of the two independent molecules of 3-chlorobenzoylacetonitrile (**4**) with thermal *ellipsoids* at the 50 % probability level. Selected bond lengths (Å) and angles (°): C11–N1 1.138(4), C21–N2 1.138(4), C13–O1 1.216(3), C23–O2 1.207(3), C16–Cl 1.746(3), C26–Cl2 1.749(3), N1–C11–C12 177.8(3), N2–C21–C22 178.7(3). Selected torsional angles (°): C11–C12–C13–C14 178.6(2), C21–C22–C23–C24 177.9(2), C12–C13–C14–C15 178.4(2), C22–C23–C24–C25 1.6(4)

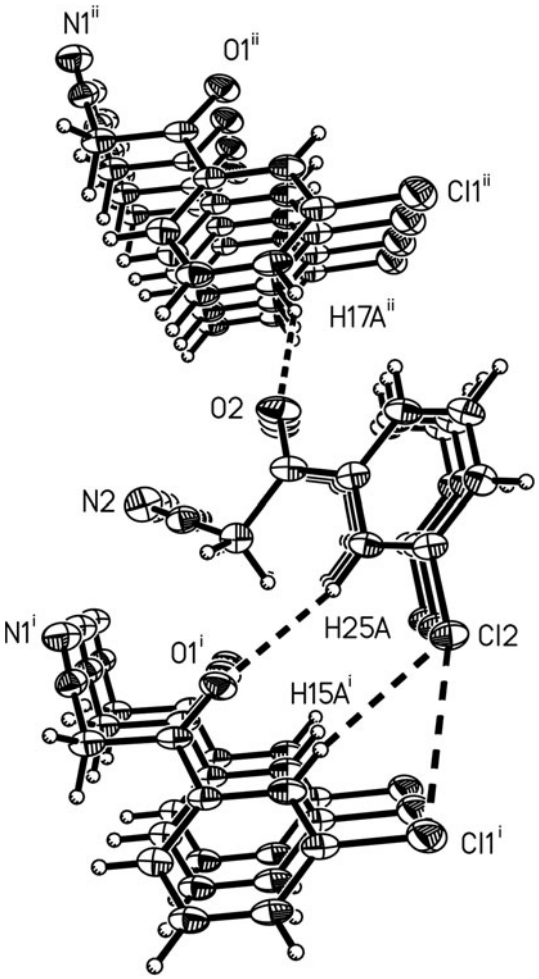

Fig. 11 Important intermolecular interactions in the structure of 3-chlorobenzoylacetonitrile (**4**) with thermal *ellipsoids* at the 50 % probability level. Intermolecular C–H···O distances C25–H25A···O1^{i} 2.533(1) Å and C23=O2···H17A^{ii} 2.359(1) Å, C–H···Cl distance C15^{i}–H15A^{i}···Cl2 2.814(1) Å, and Cl···Cl distance Cl2···Cl1^{i} 3.580(1). Symmetry codes *i* $x + 1, y, z + 1$; *ii* $-1 + x, y, z$

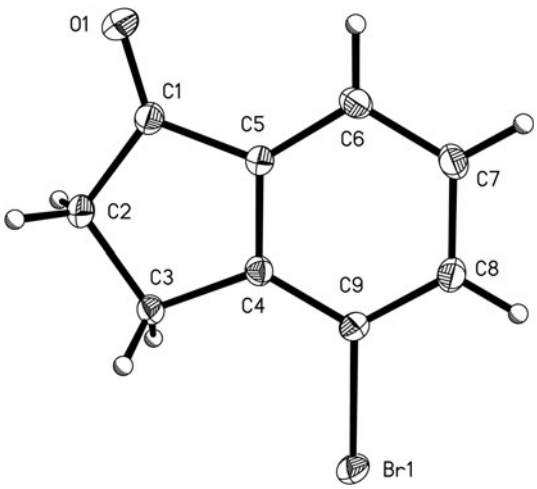

Fig. 12 Molecular structure of 4-bromo-1-indanone (**5**) with thermal *ellipsoids* at the 50 % probability level. Selected bond lengths (Å): C1–O1 1.215(2), C9–Br1 1.894(1)

$AlCl_3$ [32]. It has found use in a potential treatment of HIV [33] and in the synthesis of basket shaped carbon nanotube end-cap precursor molecules [34].

Recrystallization from acetone yielded crystals suitable to determine the molecular structure of 4-bromo-1-indanone (**5**; Fig. 12). With a carbonyl C–O length of 1.215(2) Å and aryl bromide C–Br length of 1.894(1) Å, the structure is similar to that of 4-bromo-5-amino-1-indanone with carbonyl C–O length of 1.220(4) Å and aryl bromide C–Br length of 1.896(3) Å [35].

The molecule is flat with an rms deviation from the plane of all non-hydrogen atoms of 0.0141. The molecules dimerize in the solid state in two different ways. First, the molecules interact via a pairwise centrosymmetric C–H···O (C2–H2A^{ii}···O1) interaction at an H···O distance of 2.550(1) Å (Fig. 13). The same molecular packing interaction is

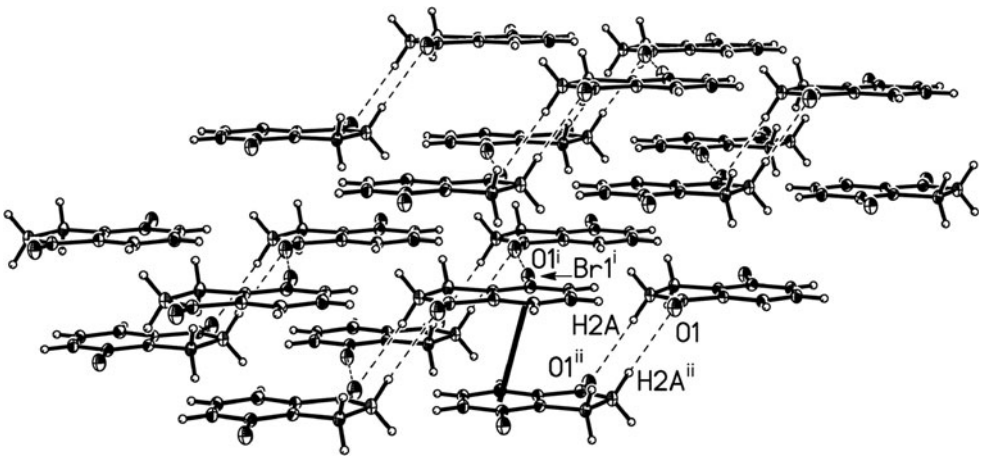

Fig. 13 Important intermolecular interactions in the structure of 4-bromo-1-indanone (**5**) with thermal *ellipsoids* at the 50 % probability level. Intermolecular O···Br distance O1···Br1^{i} 3.129(1) Å, C–H···O distance C2–H2A^{ii}···O1 2.550(1) Å. π-Stacking centroid-to-centroid (*solid line*) distance 3.620(1) Å, centroid-to-plane 3.466(1) Å, ring offset 1.043(2) Å. Symmetry codes i $-1 + x$, y, $1 + z$; ii $-x$, $-y$, $3 - z$

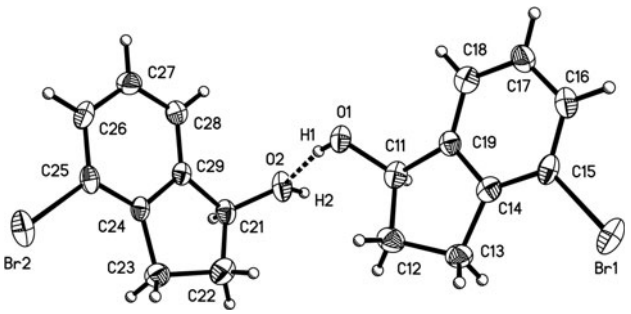

Fig. 14 Molecular structure of 4-bromo-1-indanol (**6**) with thermal *ellipsoids* at the 50 % probability level. The asymmetric unit contains both enantiomers; C11 *R* and C21 *S*. Selected bond lengths (Å): C11–O1 1.426(5), C21–O2 1.427(5), C15–Br1 1.903(5), C25–Br2 1.905(5). Hydrogen bonding distance: O1–H1···O2 2.665(4) Å

found in 4-bromo-5-amino-1-indanone, where the H···O separation is reported at 2.50 Å. Second, there is a pairwise π-stacking interaction with a centroid-to-centroid distance, *d*, of 3.620(1) Å, a centroid-to-plane distance of 3.466(1) Å, and a ring offset, slippage parameters, *r*, of 1.043(2) Å. As shown in Fig. 13, these interactions link the molecules into a two-molecule thick band which is further linked into a two-dimensional sheet by intermolecular O···Br (O1···Br1^{i}) interactions at a distance of distance 3.129(1) Å.

4-Bromo-1-indanol (**6**)

4-Bromo-1-indanol (**6**) may be prepared by the hydrolysis of 4-bromoindanyl acetate, and isolated in optically pure form [36]. Recrystallization of commercially available racemic 4-bromo-1-indanol (**6**) by slow evaporation of an ethanol solution without letting it go to dryness yields crystals suitable for X-ray analysis. The fresh sample was taken from the mother liquor and immediately placed in Paratone N oil, and a crystal quickly selected in a nylon loop and placed in the cold stream on the diffractometer right away. The results show that the compound

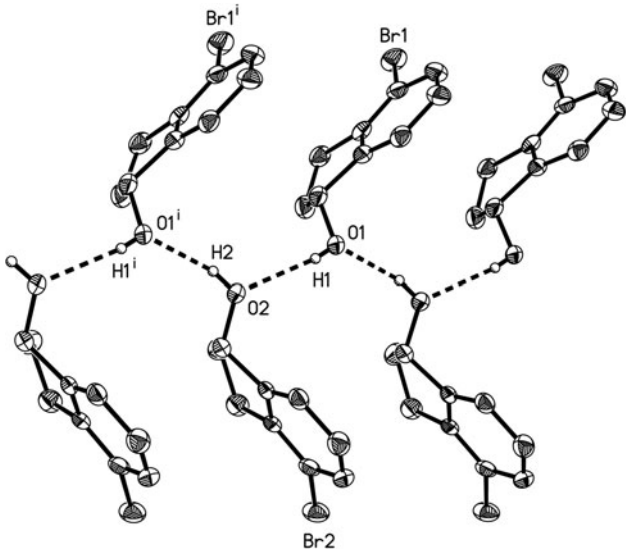

Fig. 15 View of the hydrogen bonding in the structure of 4-bromo-1-indanol (**6**) with thermal *ellipsoids* at the 50 % probability level. A one-dimensional hydrogen bonding chain is collinear with the crystallographic *b* axis. Hydrogen bonding distances: O1–H1···O2 2.665(4) Å, O2–H2···O1^{i} 2.682(4) Å. Symmetry code (i) x, $y + 1$, z

crystallizes in the space group $P2_1/c$ with two independent molecules in the asymmetric unit. These two independent molecules represent the two enantiomers of 4-bromo-1-indanol (**6**), which has an asymmetric carbon center supporting the hydroxyl group. Figure 14 show the two independent molecules; in one molecule the chiral center is of the *R* configuration (C11), and in the other molecule it is of the *S* configuration (C21).

The molecules of 4-bromo-1-indanol (**6**) are linked into an infinite one-dimensional hydrogen bonding chain which runs parallel to the crystallographic *b* axis, as shown in Fig. 15. The two unique hydrogen bonding distances have oxygen–oxygen separations of 2.665(4) Å (O1–H1···O2) and 2.682(4) Å (O2–H2···H1). The unique hydrogen bonds are observed in the IR spectrum of the compound in the

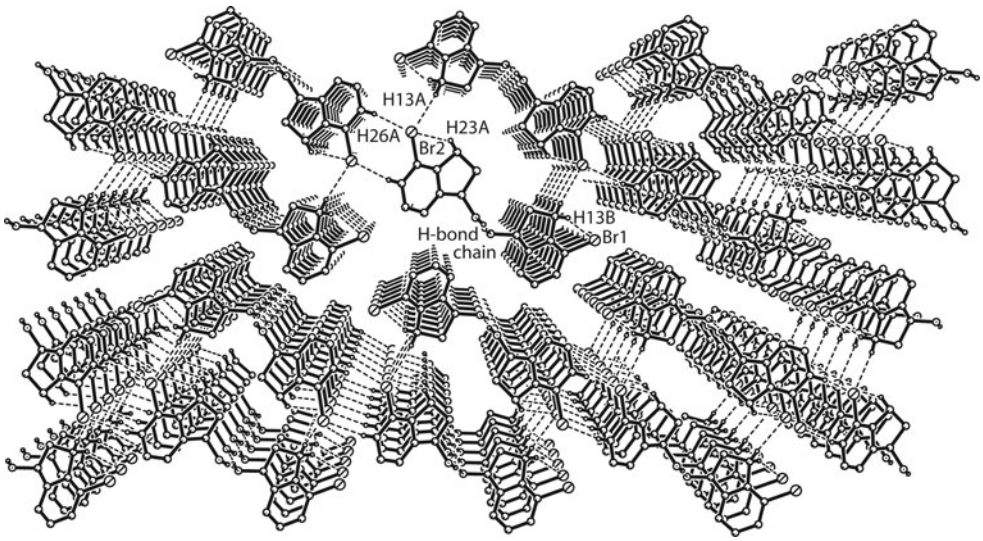

Fig. 16 View of the packing in the structure of 4-bromo-1-indanol (**6**) down the crystallographic *b* axis. C–H···Br distances: Br1···H13B 2.890(5) Å, Br2···H23A 2.910(5) Å, Br2···H26A 3.053(5) Å, Br2···H13A 3.060(6) Å

solid state, which shows O–H stretching bands at 3,281.9 and 3,168.3 cm^{-1}. There also exist several C–H···Br interactions in the crystal lattice. At H···Br distances less than the sum of the van der Waals radii, each enantiomer is linked to its neighbor of the same configuration by methylene C–H···Br interactions also running parallel to the *b* axis at distances of 2.890(5) Å (*R* enantiomer, Br1···H13B) and 2.910(5) Å (*S* enantiomer, Br2···H23A), as shown in Fig. 16. Further, at slightly greater than the sum of the van der Waals radii, Br2 links to the aryl proton H26A at a distance of 3.053(5) Å, as well as methylene proton H13A at a distance of 3.060(6) Å. The linking of the hydrogen bonded chains by these C–H···Br interactions creates zig-zag sheets, two of which are depicted in Fig. 16.

Summary

Chemical crystallography is a valuable pedagogical tool for teaching undergraduate students about molecular structure and intermolecular interactions in the solid state. When students obtain structures that have not yet been reported in the literature, they have the opportunity to participate in the communication of the new structural data. Completed as part of an advanced undergraduate teaching laboratory, the X-ray structures of six small molecule organic compounds reported here also serve to illustrate several different types of intermolecular interactions, including hydrogen bonding, π-stacking, halogen–halogen interactions, and C–H···X (X = O, N, halogen) interactions.

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