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Hydrogen Bonding Interactions in Amorphous Salicyl Salicylate**

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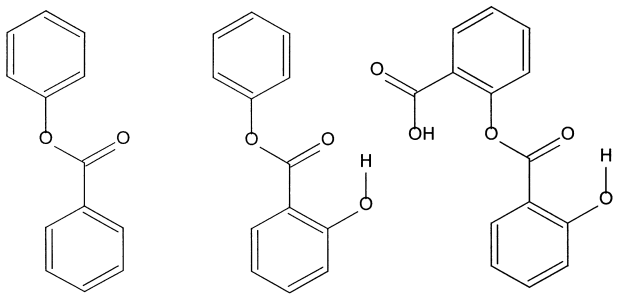
The macroscopic physical properties of a chemical substance are determined by the intra- and intermolecular interactions of each individual molecule comprising it. Presently, reliable prediction of the three-dimensional structure of a multiple-atom chemical species from only its structural formula is not possible,[1] thus the ab initio prediction of bulk physical properties is likewise not currently attainable. To circumvent this obstacle, empirical studies of systematic chemical series have been pursued, and experimentally derived properties, such as crystal structure[2] and melting point,[3] have been correlated with structural formula.

Our research is concerned with the production of supramolecular materials, a field that has promised much.[4] Recent work in the field of supramolecular materials assembly has focused upon the synthesis of molecules containing multiple hydrogen bonding motifs at chain termini[5] and inner-chain sites.[6] We wished to make a departure from this approach to understand the macroscopic physical effect of systematic changes in the chemical structure of simple species. We aimed to maximize the observed change in physical attributes while minimizing the structural change at the molecular level. We studied the molecular series: phenyl benzoate (**1**), phenyl salicylate (**2**), and salicyl salicylate (**3**).



Each compound was melted and allowed to cool at ambient temperature. Compound **1** melted at 342 K and recrystallized at this temperature upon cooling; **2** melted at 317 K and undercooled to ambient temperature without crystallization, the low viscosity undercooled liquid could be maintained in this state for several weeks without difficulty; **3** melted over the range 412–424 K and undercooled to a high viscosity liquid that could be moulded and stress-fractured: a potentially useful material (crystallization in **3** could not be induced by any means, including crystal seeding and holding at the crystallization temperature for several hours. Recrystallization could be achieved only by dissolution and reprecipitation.). Thus we observed gross physical changes with small molecular alterations in the series **1**–**3**.

To elucidate the molecular interactions giving rise to these physical manifestations we reviewed the single-crystal structures of **1**[7] and **2**,[8] and determined the structure of **3**. In addition, **3** was studied extensively by NMR and IR spectroscopy.

The low viscosity of the amorphous **3** at temperatures in the range 373–423 K allowed study by ^{13}C NMR spectroscopy. The spectrum recorded at 423 K is shown in Figure 1, and was assigned by 2D NMR experiments,[9] and comparison with reference spectra.[10] Multiple resonances were observed for many peaks, most notably those carbon atoms lying along the functional backbone: C14, C9, C1, C3, and C4. The acid carbonyl, C2, gave a single resonance signal. The ester carbonyl resonance, C1, was composed of at least five discrete signals, indicating that at least this many environments were stable on the NMR time scale. This multiple-resonance effect persisted, without diminuition, across the observable temperature range. Peak shifting within the multiple-resonance sets was observed over the temperature range, in all cases peaks moved, at various rates, to lower field with cooling (increased hydrogen bonding[11]).

To assess potential structural similarities between the amorphous and crystalline phases of **3**, solid-state ^{13}C NMR spectra of both were recorded at ambient temperature (Figure 1).[12] There was a good correlation between the liquid and solid-state NMR spectra of amorphous **3** and the solid-state NMR spectra of crystalline **3**. The lack of significant chemical shifting of resonances in any of the spectra suggests

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[**] We thank the staff of the University of York NMR service for their time and care in running our samples.

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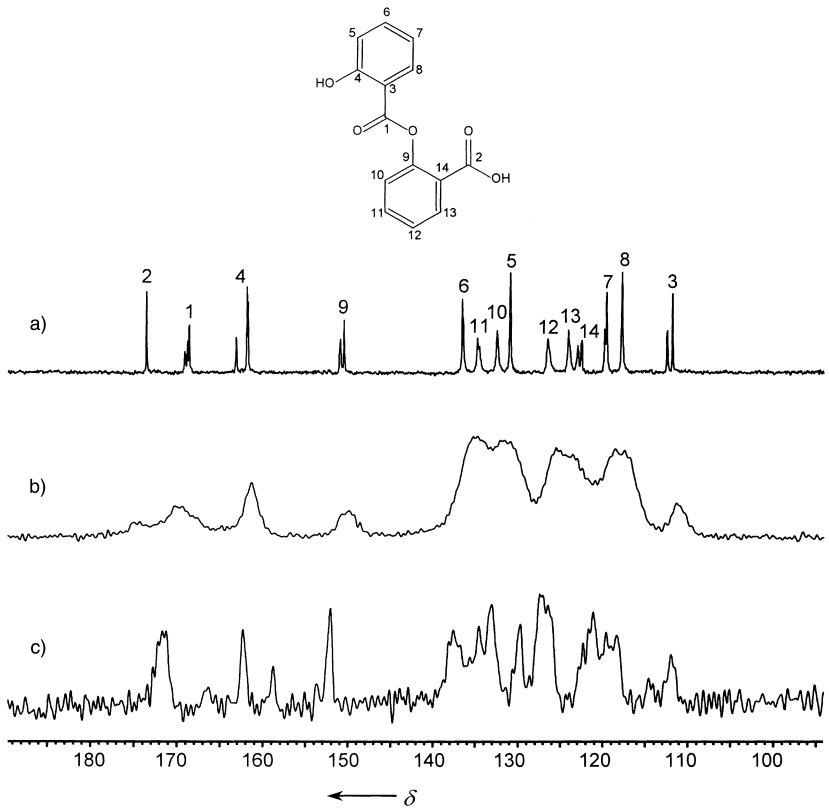

Figure 1. ^{13}C NMR spectra and assignment of amorphous **3** recorded at 373 K (liquid, 126 MHz) (a) and 273 K (solid, 101 MHz) (b),[12] and crystalline **3** recorded at 273 K (solid, 101 MHz) (c).[12]

close structural similarity in the amorphous and crystalline phases. Multiple resonances were not observed in solution ^{13}C NMR spectra of **3** recorded in [D_6]acetone or $CDCl_3$ at ambient temperature but a large shifting of C1 did occur: from $\delta = 165.7$ in [D_6]acetone to $\delta = 168.8$ in $CDCl_3$, and all other resonances were shifted to a significant but lesser extent.[13] Multiple resonances were not observed in neat **2** studied by this method.

In an attempt to elucidate the behavior of the hydrogen-bonded protons in the 373 – 423 K temperature range, ^1H NMR spectra of neat **3** were recorded at 10 K intervals (Figure 2). Integration confirmed that both "alcoholic" and

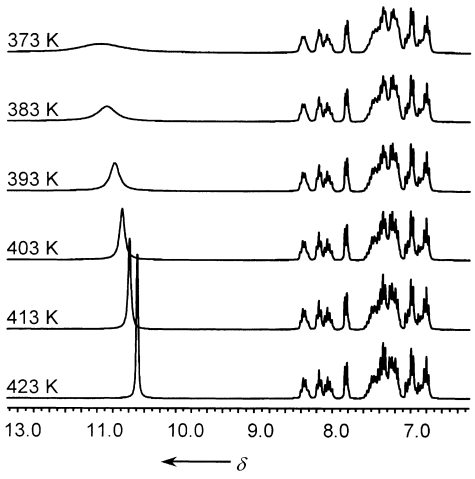

Figure 2. ^1H NMR spectra (liquid, 270 MHz) of amorphous **3** recorded at 373 – 423 K.

"acidic" protons were present as a single resonance, appearing sharp at 423 K and broadening significantly, with shifting to lower field, down to 373 K. Shifting occurred at a constant rate of $9.5 \times 10^{-3}\,\delta\,K^{-1}$ over this temperature range. Both alcohol and acid protons appear chemically equivalent by this analysis technique and the resonance broadening with decrease in temperature is indicative of an exchange phenomenon. The solution spectrum of **3** ($CDCl_3$, 270 MHz), recorded at ambient temperature, contained discrete resonance signals for alcoholic (sharp, $\delta = 10.26$) and acidic (broad, $\delta = 11.24$) protons.[14] Using this resonance separation, we calculated that the observed proton coalescence would occur at exchange rates exceeding 1700 s^{-1}. ^1H NMR spectra of neat **2** were recorded at 10 K intervals in the range 303 – 423 K. Alcoholic proton shifting occurred at a constant rate of $3.4 \times 10^{-3}\,\delta\,K^{-1}$ over this temperature range. The alcoholic proton resonance was composed of at least two environments that became less distinct as the temperature was lowered.

The IR spectra (293 K) of **3** recorded as KBr pressed pellet (crystalline) and film cast from $CHCl_3$ (amorphous) are shown in Figure 3. The amorphous spectrum contained a

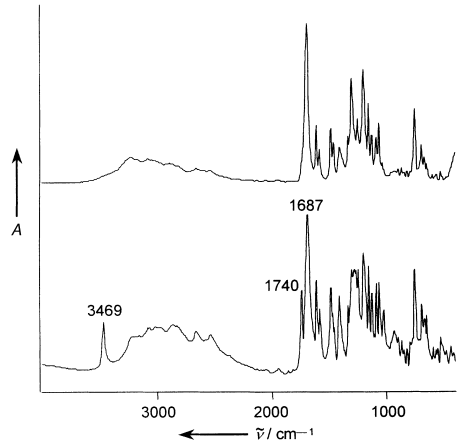

Figure 3. IR spectra of amorphous (top) and crystalline (bottom) **3** recorded at ambient temperature. A = absorbance.

multiple peak carbonyl resonance at $\sim 1685\ cm^{-1}$, indicating that all ester carbonyl groups were in hydrogen-bonded environments.[11] The spectrum of the crystalline sample was identical to that of the amorphous sample with the exception of additional bands appearing at 3469 and 1740 cm^{-1}, consistent with the disruption of an intramolecular hydrogen bond between alcohol and ester carbonyl group. The IR spectrum (293 K) of crystalline **2** contained a broad carbonyl absorbance at 1679 cm^{-1} and a hydroxyl absorbance at 3191 cm^{-1}, these absorbances shifted to higher energy in the amorphous phase (1691 and 3229 cm^{-1}, respectively).

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To further elucidate the intra- and intermolecular interactions present in the crystalline state, **3** was crystallized from acetone – water and its crystal structure determined by single-crystal X-ray diffraction.[15] The disordered structure obtained is shown in Figure 4, labeled to show percentage structural

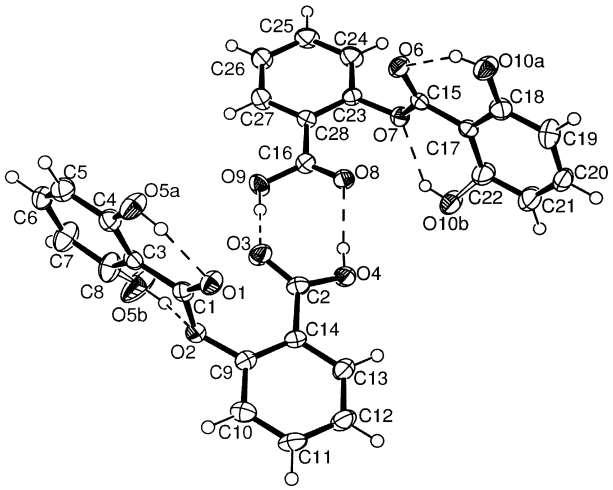

Figure 4. Structure of a dimer of **3** showing positional disorder in the salicylate moiety (ORTEP[20] representation; 50% probability thermal ellipsoids, 150 K): O10a (60%), O10b (40%), O5a (80%), O5b (20%). Selected distances [Å] and angles [°]: O3-O9 2.635(4), O4-O8 2.649(4), O1-O5a 2.662(5), O2-O5b 2.613(2), O6-O10a 2.624(6), O7-O10b 2.661(8); C8-C3-C1-O1 170.7(4), C10-C9-O2-C1 101.0(4); molecular benzene ring dihedrals 86.1(2) and 78.0(2)°.

occupancy. Compound **3** crystallized as noncentrosymmetric hydrogen-bonded carboxylic acid dimers, disordered about the salicylate ring over two geometries with intramolecular hydroxyl hydrogen bond donation to both ester oxygen atoms. Hydroxyl oxygen occupancy varied on each side of the dimer: 80%/20% and 60%/40% in favor of the carbonyl oxygen interaction. The general dimeric structural geometry was consistent with those observed in similar species such as benzoic acid,[16] salicylic acid,[17] and gentisic acid;[18] while the phenyl benzoate section of **3** was isomorphous with those observed in **1**[7] and **2**.[8] Intramolecular hydrogen bond disorder of the type seen in **3** was not observed in **2**.

Small-angle X-ray scattering (SAXS) was measured for amorphous **3** at 150 K.[19] The scattering pattern observed was characteristic of an amorphous material and showed two scattering rings. The two were calculated to arise from close-contact spacings in the range of 4.7 – 5.9 Å and 8.2 – 11.2 Å, similar to intermolecular spacings observed in the crystal structure. The shorter spacing correlated well with the body-center separation of each molecule in the dimeric unit, and the longer spacing correlated well with the nearest-neighbor dimeric separation observed crystallographically. The density of the amorphous material was 1.35 g cm^{-3} (293 K) compared to 1.40 g cm^{-3} (293 K) for the crystalline solid.

X-ray analysis and IR and NMR spectroscopic analysis of **3** are consistent with structural disorder in both the crystalline state and the amorphous state. The ^{1}H NMR spectroscopic observations indicate that rapid acid – alcohol proton exchange is occurring in the amorphous phase, well below the melting point of **3**. The observation of several distinct ^{13}C NMR environments in **3** is consistent with structural conformers that are stable on the NMR time scale. We hypothesize that the amorphous behavior observed in **3** and the undercooling observed in **2** is a consequence of intermolecular hydrogen bond interactions in which protons are undergoing rapid intermolecular exchange. The absence of this structural arrangement in **1** precludes the facile undercooling of this material. We hope that molecules such as **3** will provide the basis for new, amorphous engineered materials, complementing the rapidly expanding field of crystal engineering.[21]

Experimental Section

Compounds **1** and **2** (99%) were used as supplied by Aldrich Ltd. Compound **3** (99%) was used as supplied by Acros Organics. Instrumentation: IR spectra: Mattson Galaxy 5020 FTIR spectrometer; ^{13}C NMR liquid spectra: Bruker 500 MHz NMR spectrometer; ^{13}C NMR solid-state spectra: Bruker DSX400 400 MHz NMR spectrometer; ^{1}H NMR spectra: Jeol 270 MHz NMR spectrometer.

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[9] 2D Gradient COSY and 2D Gradient HMQC NMR spectra were recorded for $CDCl_3$ solutions of **3**.
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[12] Spectra recorded at 100.6 MHz (293 K) using a 2.5 mm CPMAS probe (12 kHz rotation).
[13] **3**: ^{13}C NMR (270 MHz, [D$_6$]acetone): $\delta = 165.7$ (C1), 169.5 (C2), 113.3 (C3), 162.5 (C4), 131.8 (C5), 137.3 (C6), 120.5 (C7), 118.3 (C8), 151.1 (C9), 132.9 (C10), 135.1 (C11), 127.5 (C12), 125.0 (C13), 124.7 (C14); **3**: ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 168.8$ (C1), 169.9 (C2), 111.9 (C3), 162.0 (C4), 130.8 (C5), 136.5 (C6), 119.6 (C7), 117.7 (C8), 150.5 (C9), 132.8 (C10), 135.0 (C11), 126.7 (C12), 124.1 (C13), 122.5 (C14).
[14] **3**: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 11.24$ (s br.; OH), 10.26 (s sh; COOH), 8.11 (dd, $J = 7.8$, 1.9 Hz; H10), 8.04 (dd, $J = 7.8$, 1.6 Hz; H5), 7.65 (dt, $J = 8.1$, 1.6 Hz; H11), 7.51 (ddd, $J = 9.0$, 7.5, 1.9 Hz; H6), 7.38 (dd, $J = 7.8$, 1.2 Hz; H12), 7.23 (dd, $J = 8.1$, 2.6 Hz; H13), 7.01 (dd, $J = 8.4$, 1.2 Hz; H8), 6.91 (ddd, $J = 8.1$, 7.8, 0.9 Hz; H7).
[15] Crystal data for **3**: $C_{14}H_{10}O_5$, $M_r = 258.22$, monoclinic, space group *Cc* (no. 9), $a = 12.965(4)$, $b = 12.982(4)$, $c = 15.530(3)$ Å, $\beta = 114.039(15)°$, $V = 2387.2(11)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.431$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.7107$ Å, $F(000) = 1064$, $T = 150$ K; colorless rhombs, $0.45 \times 0.40 \times 0.35$ mm, Rigaku AFC6 four-circle diffractometer, Oxford Cryosystems N_2 cooler (150 K) 2105 independent reflections. The structure was solved by direct methods, all non-hydrogen atoms were refined anisotropically using full-matrix least-squares based on F^2 to give $R_1 = 0.0341$, $wR_2 = 0.0913$ for 1644 independently observed reflections ($|F_o| > 2\sigma(|F_o|)$) and 366 parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been

deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143946. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[19] SAXS: 0.7 mm diameter cylinder of **3**. Rigaku RU200 rotating anode, graphite-monochromated ($\mu(Cu_{K\alpha}) = 1.5418\ cm^{-1}$, 50 kV, 100 mA) and Marresearch Imaging Plate System, 300.0 mm sample to plate distance.

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Cooperative Asymmetric Catalysis with Dendrimeric [Co(salen)] Complexes**

Rolf Breinbauer and Eric N. Jacobsen*

The synthesis of dendrimers with well-defined architectures has advanced at an accelerating pace since the first examples of cascade-like molecules were introduced in the late 1970s.[1] Indeed, highly pure polyamidoamine (PAMAM) and poly(propyleneimine) dendrimers are now commercially available at a moderate price, and good experimental procedures exist for the preparation of a variety of other dendrimeric compounds. Over the last several years, research in this area has extended from the synthesis and characterization of these compounds to the search for specific properties and functions that are a direct consequence of the dendritic architecture.[1e] One area that has attracted particular interest is in the development of so-called dendrimeric catalysts, and recently several groups have demonstrated that dendrimers bearing catalytic units covalently linked to the terminal sites can combine the best features of homogeneous and heterogeneous catalysts.[2, 3] Thus, a dendrimeric catalyst can present molecularly defined reactive sites in a macromolecule that can be reisolated easily by precipitation[3e,i] or filtration through a membrane.[3p–r]

The relative proximity of terminal sites may be controlled by the nature and generation number of the dendrimer. Therefore, at least in principle, a dendritic framework may be used to enforce and control cooperative interactions between catalyst units. However, while there have been a number of reports of cooperative binding effects with dendrimers incorporating recognition elements such as amino acids or carbohydrates,[4] no examples of enhanced catalytic activity due to cooperative effects have been reported in dendrimeric systems devised thus far.[5, 6]

In our ongoing studies of asymmetric ring opening (ARO) of epoxides by metal–salen complexes (H_2salen = bis(salicylidene)ethylenediamine),[7] substantial mechanistic evidence has been collected in support of a mechanism involving cooperative, bimetallic catalysis.[7, 8] This has led to a proposed mechanism for ARO reactions involving simultaneous activation of both epoxide and nucleophile by different metal–salen units (Figure 1a). Based on this hypothesis, we speculated whether dendrimeric analogues of these catalysts might reinforce cooperative catalytic activity in AROs (Figure 1b).

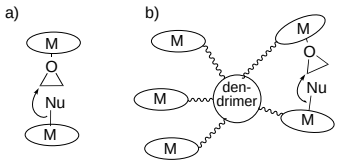
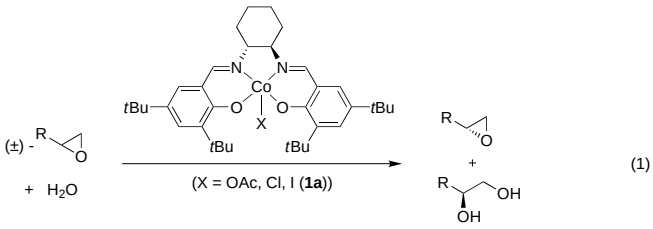


Figure 1. a) Proposed mechanism for cooperative catalysis in the asymmetric ring opening (ARO) of epoxides catalyzed by (salen)metal complexes. b) Cooperative catalytic ARO within a dendrimeric framework.

Herein we report the synthesis of dendrimer-bound [Co^{III}(salen)] complexes, and demonstrate that these catalysts indeed exhibit significantly enhanced catalytic activity in the hydrolytic kinetic resolution (HKR) of terminal epoxides [Eq. (1)].



We selected the commercially available NH_2-terminated PAMAM dendrimers for the syntheses of the dendrimeric [Co(salen)] catalysts. For example, 4-NH_2-PAMAM was derivatized by covalent attachment to chiral [Co^{II}(salen)] units through amide linkages by reaction with pentafluorophenyl ester derivative **1c** following standard peptide coupling methods (Scheme 1).[9] The resulting dendrimeric complex was purified by precipitation of concentrated THF solutions with hexanes followed by size-exclusion chromatography with Sephadex, and was characterized by FAB MS ($[M+Na]^+$: 2888, calcd for $C_{158}H_{224}Co_4N_{18}O_{16}$: 2865). Oxidation of the [Co^{II}(salen)] sites with elemental iodine in THF proceeded in quantitative yield and afforded the catalytically

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[**] Prof. M. T. Reetz (Max Planck-Institut für Kohlenforschung, Mülheim/Ruhr) and Mr. J. Hong (Harvard University) are gratefully acknowledged for stimulating discussions. This work was supported by the NIH (GM 43214). R.B. thanks Fonds zur Förderung der Wissenschaftlichen Forschung, Vienna (Erwin-Schrödinger-Fellowship) and Land Oberösterreich (Sonderförderung außerhalb des KIP-Programms) for postdoctoral fellowship support. H_2salen = bis(salicylidene)ethylenediamine.

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