Oligoamide Conformations

Linear-to-Turn Conformational Switching Induced by Deprotonation of Unsymmetrically Linked Phenolic Oligoamides**

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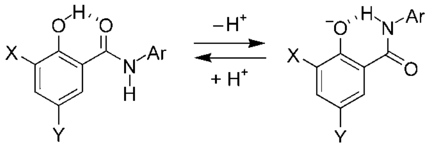
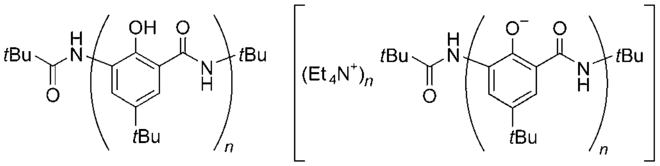
Aromatic oligoamide compounds attract much attention because they form highly ordered structures with intramolecular hydrogen bonds.[1–8] In particular, control of conformational switching within a molecule could lead to the development of molecular machines.[9–11] Salicylamide derivatives are well known to form a highly ordered, planar conformation through hydrogen bonds.[12,13] A rearrangement of the intramolecular hydrogen bond induced by deprotonation of the phenolic OH group was suggested previously[14] and established in our recent study on the crystal structures of protonated and deprotonated salicylamide derivatives (Scheme 1).[15] From these findings, we believe that oligoamide compounds that comprise a salicylamide moiety in a repeating unit have the potential to exhibit conformational switching with the rearrangement of the intramolecular hydrogen bond as the driving force of conformational switching.[9,10] Herein, we report the synthesis and structure determinations of unsymmetrically linked phenolic oligoamides (**1**–**4**) that comprise a salicylamide skeleton in a repeating unit as novel aromatic oligoamide compounds that undergo a conformational switch.



Scheme 1. Conformational switching of a salicylamide derivative by deprotonation and protonation. Ar = 2-chlorophenyl, X = Br, Y = Cl.



1–**4**: *n* = 1–4

The crystal structures of protonated and deprotonated monomer models, namely, **1**′ and $(\mathbf{1}'-H^+)^-Me_4N^+$, which differ from **1** by the replacement of the *t*BuCO group by MeCO, are shown in Figure 1. In **1**′, the phenol OH group forms intramolecular NH···OH and OH···O=C hydrogen bonds with average short distances for O11-N1 and O11-O2 of 2.622 and 2.486 Å, respectively. In the case of $(\mathbf{1}'-H^+)^-Me_4N^+$, the phenolate oxygen anion forms double intramolecular NH···O(oxyanion) hydrogen bonds with short distances for O11-N1 and O11-N2 of 2.605(2) and 2.643(2) Å. The *C*-terminal *N*-*tert*-butylcarbamoyl substituent forms two different types of hydrogen bonds which means that the deprotonation of the phenol OH group induces a conformational change (≈180° rotation about the C12−C2 bond) that leads from a linear-to-turn conformational switching in longer oligoamides. This type of conformational switching was established in our previous study with other salicylamide derivatives (Scheme 1).[15] Intermolecular interactions were found in **1**′ only as NH···O=C hydrogen bonds.

Molecular structures of the dimer in protonated and deprotonated forms, **2** and $(\mathbf{2}-2H^+)^{2-}(Et_4N^+)_2$, are shown in Figure 2. In **2**, each phenol OH group forms intramolecular NH···OH and OH···O=C hydrogen bonds that result in an intramolecular NH···OH···O=C-NH···OH···O=C hydro-

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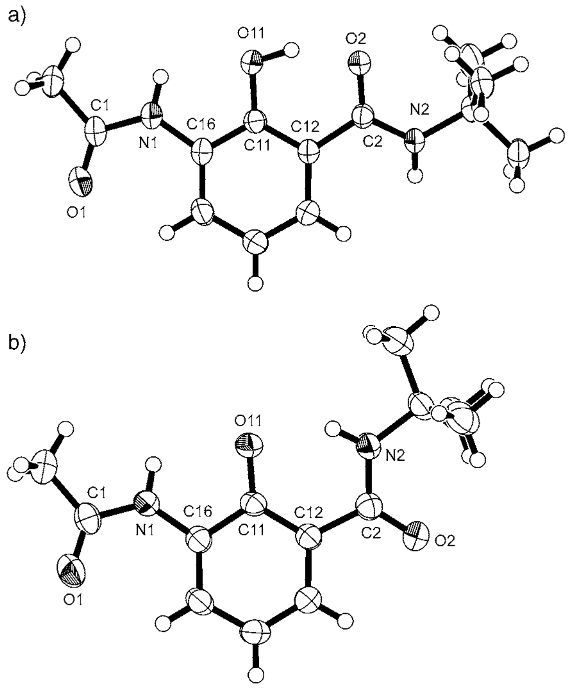


Figure 1. Molecular structures of a) **1**′ (one of the two crystallographically independent molecules is shown) and b) $(\mathbf{1}'-\mathrm{H}^+)^-\mathrm{Me}_4\mathrm{N}^+$. Displacement ellipsoids are drawn at the 50% probability level; the tetramethylammonium cation is omitted for clarity in (b). Selected bond lengths, short contacts [Å], and torsion angles [°] for **1**′: C11–O11 1.3606(16), O11···N1 2.606(1), O11···O2 2.481(1), C1-N1-C16-C11 170.71(15), N2-C2-C12-C11 −167.69(14). Selected bond lengths, short contacts [Å], and torsion angles [°] for $(\mathbf{1}'-\mathrm{H}^+)^-$: C11–O11 1.297(2), O11···N1 2.605(2), O11···N2 2.643(2), C1-N1-C16-C11 173.43(14), N2-C2-C12-C11 7.2(2).

gen-bonded chain. A similar mode of hydrogen bonding was reported for 3,3′,5,5′,6-pentachloro-2′-hydroxysalicylanilide.[16] In $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$, both of the phenolate oxygen anions form double intramolecular NH···O(oxyanion) hydrogen bonds. The NH group in the bridging amide group is involved in a bifurcated intramolecular NH···O(oxyanion) hydrogen bond. This type of intramolecular hydrogen bond is classified as a three-center hydrogen bond and is reported to be strong.[17] Three-center hydrogen-bonded structures are also known to be almost planar.[3,6,17] However, the crystal structure of $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$ has a slightly distorted structure that is different from other oligoamides. Because the optimized structure of simplified $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}$ is planar,[18] this slight distortion may be caused by its packing structure. The difference in the hydrogen-bonding mode between the hydroxyl or phenoxyl group and the neighboring substituents on the *C*-terminal side gives a linear-to-turn conformational switch. Intermolecular hydrogen bonds are formed in the protonated form **2** as NH···O=C hydrogen-bonded chains and not in $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$. This behavior is similar to that of the monomeric protonated pair, **1**′ and $(\mathbf{1}'-\mathrm{H}^+)^-\mathrm{Me}_4\mathrm{N}^+$.

Structures of the oligoamides in solution were determined by ^{1}H NMR spectroscopy of samples dissolved in CDCl_3 and $\mathrm{CD}_3\mathrm{CN}$ (5 mM). Chemical shifts of OH and NH groups indicate hydrogen-bond formation. Dilution experiments from 40 to 1 mM for all oligoamides resulted in no significant changes in the chemical shifts for the OH and NH groups (within 0.04 ppm) which indicates that intermolecular hydrogen bonds are not formed.[3] In the protonated forms of all the oligoamides, the signals for the phenol OH groups were observed at significantly low field ($\delta = 12.49$–13.36 ppm) which suggests the formation of OH···O=C hydrogen bonds. The signals for the NH protons of the *N*-terminal and bridging amide groups were observed at $\delta = 8.24$–8.25 and $\delta = 8.99$–9.06 ppm, respectively. These NH signals were shifted slightly downfield relative to the NH protons in benzanilide ($\delta = 7.76$–7.86 ppm),[19] which indicates the formation of NH···OH hydrogen bonds in the *N*-terminal and bridging amide groups. The amide NH protons in the *C*-terminal amide groups were observed at $\delta = 6.13$ ppm, where signals for non-hydrogen-bonded NH groups of benzamide derivatives are usually observed. NOE correlations between amide NH protons and aryl protons are useful in elucidating the conformations of aromatic amide compounds, including salicylamide derivatives.[20] The NH protons, except in the

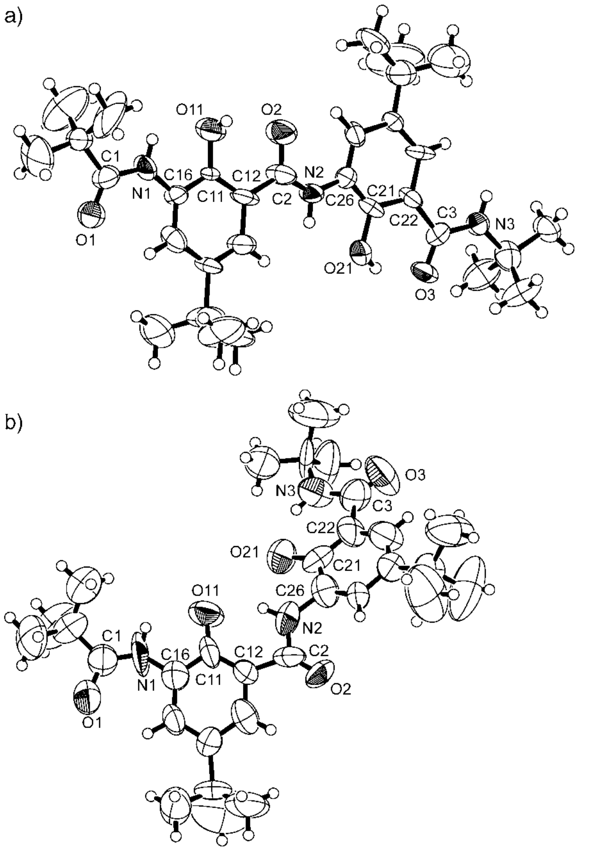
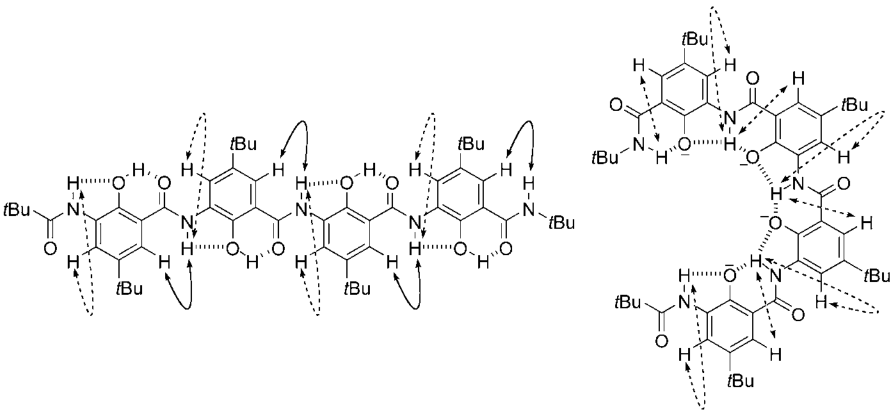


Figure 2. Molecular structures of a) **2** and b) $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$. Displacement ellipsoids are drawn at the 50% probability level; solvent molecules and tetraethylammonium cations are omitted for clarity. Selected bond lengths, short contacts [Å], and torsion angles [°] for **2**: C11–O11 1.332(9), C21–O21 1.414(10), O11···N1 2.584(9), O11···O2 2.472(9), O21···N2 2.584(9), O21···O3 2.462(8), C1-N1-C16-C11 172.8(9), N2-C2-C12-C11 −172.2(10), C2-N2-C26-C21 178.4(10), N3-C3-C22-C21 −175.0(8). Selected bond lengths, short contacts [Å], and torsion angles [°] for $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}$: C11–O11 1.268(14), C21–O21 1.339(13), O11···N1 2.50(1), O11···N2 2.64(1), O21···N2 2.72(1), O21···N3 2.58(1), C1-N1-C16-C11 −176(2), N2-C2-C12-C11 −22(2), C2-N2-C26-C21 153.2(14), N3-C3-C22-C21 7(2).

N-terminal amide group, show NOE correlations with neighboring aromatic protons in each unit. If all oligoamides display a similar mode of hydrogen bonding in solution as that found in the crystal structures of **1**′ and **2**, these results are reasonable. The proposed structure of **4** is depicted in Scheme 2 with arrows representing the observed NOE correlations. The similarities in the ^{1}H NMR spectroscopic results of all the oligoamides show that the longer oligoamides also have linear conformations with the same hydrogen-bonding mode in the protonated forms as shown for **1**′ and **2**.



Scheme 2. Proposed structures of **4** (linear) and the anionic part of $(\mathbf{4}-4\,\mathrm{H}^+)^{4-}$ (turn) in solution. Arrows represent NOE correlations (----- represent correlations that are present only in [D$_6$]DMSO).

For the deprotonated forms of all the oligoamides, the signals for the NH protons were largely shifted downfield relative to the corresponding protons in the protonated forms which suggests strong NH···O(oxyanion) hydrogen-bond formation. The NH protons in the bridging amide groups showed the largest downfield shift relative to other NH protons in each oligoamide. As established in the crystal structure of $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$, the NH proton in the bridging amide group forms a bifurcated NH···O(oxyanion) hydrogen bond. The bifurcated hydrogen bond is stronger and shifts the signal for NH more downfield than a single hydrogen bond would do.[21] No NOE correlations were observed for any of the NH protons in $\mathrm{CDCl_3}$ or $\mathrm{CD_3CN}$. The results also show that the amide NH protons do not direct to aromatic protons but rather to phenolate oxygen anions. The proposed structure of the anion part of $(\mathbf{4}-4\,\mathrm{H}^+)^{4-}(\mathrm{Et}_4\mathrm{N}^+)_4$ is depicted in Scheme 2. The similarities in the ^{1}H NMR spectroscopic results for the longer oligoamides to those for $(\mathbf{1}'-\mathrm{H}^+)^-\mathrm{Me}_4\mathrm{N}^+$ and $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$ indicate that the other oligoamides also adopt the turn conformation in the deprotonated form with the same hydrogen-bonding mode.

Even in a strong intermolecular hydrogen-bonding solvent, [D$_6$]DMSO,[22] the overall conformations of protonated and deprotonated forms are maintained because the observed additional NOE correlations between the NH and aryl protons are very weak.

In terms of the close proximity of the phenol oxygen atoms, the turn conformation in the deprotonated form resembles the conformation of benzoxazine oligomers[23] and calixarenes, although the conformations of the latter are observed for the protonated form. Because the pK_a values of each phenol OH group of these oligoamides are lowered by the intramolecular NH···O(oxyanion) hydrogen bonds,[14,24,25] the OH protons can completely dissociate, unlike the case of calixarenes.[26,27] Our results indicate that as a consequence of lowering the basicity, intramolecular NH···O(oxyanion) hydrogen bonds enable phenolate anions to position themselves close to each other. Charge delocalization of phenolate anions supported by the results of cyclic voltammograms that reveal that all phenolate anions are in a mixed-valence state also means a lowering of the basicity (see Supporting Information).

In conclusion, conformational switching in the unsymmetrically linked phenolic oligoamides, monomer **1** to tetramer **4**, was established in both the solid (for monomers and dimers) and solution states. The deprotonation of a hydroxyl group in each unit induces a rearrangement of the hydrogen-bonding mode within the unit from OH···O=C to NH···O(oxyanion), which leads to linear-to-turn conformational switching.

Experimental Section

X-ray crystal structure analysis: The data were collected at 200 K on a Rigaku RAXIS-RAPID Imaging Plate diffractometer (Mo$_{K\alpha}$ radiation; $\lambda = 0.71069$ Å for **1**′ and 0.71075 Å for others). The structures were solved by direct methods (SIR92[28] for **1**′ and $(\mathbf{1}'-\mathrm{H}^+)^-\mathrm{Me}_4\mathrm{N}^+$ and SIR2002[29] for **2** and SHELXS-97[30] for $(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2$) and refined by full-matrix least-squares on F^2. The non-hydrogen atoms were refined anisotropically. The coordinates of OH and NH protons in **1**′ were refined by using fixed thermal factors, and the rests were included in calculated positions. Crystal data for $\mathrm{C_{13}H_{18}N_2O_3}$ (**1**′): $0.35\times0.35\times0.35$ mm^3, monoclinic, $P2_1/a$ (#14), $a = 16.4062(10)$, $b = 9.9004(7)$, $c = 16.5488(14)$ Å, $\beta = 92.1580(10)°$, $V = 2686.1(3)$ Å^3, $Z = 8$, $\rho_\mathrm{calcd} = 1.238$ g cm^{-3}, $\mu(\mathrm{Mo}_{K\alpha}) = 0.88$ cm^{-1}, $M_\mathrm{w} = 250.29$. 6124 reflections and 349 variables were used to solve the structure, $R_1 = 0.044$, w$R_2 = 0.113$, GOF (F^2) = 1.00. Crystal data for $\mathrm{C_{17}H_{21}N_3O_3}$ ($(\mathbf{1}'-\mathrm{H}^+)^-\mathrm{Me}_4\mathrm{N}^+$): $0.40\times0.20\times0.10$ mm^3, monoclinic, $P2_1/n$ (#14), $a = 6.890(5)$, $b = 15.33(2)$, $c = 18.05(2)$ Å, $\beta = 93.41(8)°$, $V = 1904(4)$ Å^3, $Z = 4$, $\rho_\mathrm{calcd} = 1.128$ g cm^{-3}, $\mu(\mathrm{Mo}_{K\alpha}) = 0.77$ cm^{-1}, $M_\mathrm{w} = 323.43$. 4350 reflections and 209 variables were used to solve the structure, $R_1 = 0.042$, $wR_2 = 0.095$, GOF (F^2) = 0.81. Crystal data for $\mathrm{C_{35}H_{55}N_3O_6}$ ($\mathbf{2}\cdot\mathrm{Et_2O}$): $0.30\times0.10\times0.10$ mm^3, monoclinic, Cc (#9), $a = 16.720(3)$, $b = 10.2219(16)$, $c = 23.907(3)$ Å, $\beta = 93.248(11)°$, $V = 4079.4(11)$ Å^3, $Z = 4$, $\rho_\mathrm{calcd} = 0.999$ g cm^{-3}, $\mu(\mathrm{Mo}_{K\alpha}) = 0.68$ cm^{-1}, $M_\mathrm{w} = 613.83$. 7681 reflections and 427 variables were used to solve the structure, $R_1 = 0.077$, $wR_2 = 0.163$, GOF (F^2) = 0.85. Crystal data for $\mathrm{C_{49}H_{86}N_6O_5}$ ($(\mathbf{2}-2\,\mathrm{H}^+)^{2-}(\mathrm{Et}_4\mathrm{N}^+)_2\cdot\mathrm{CH_3CN}$): $0.20\times0.20\times0.20$ mm^3, monoclinic, $P2_1/c$, $a = 15.223(12)$, $b = 17.143(13)$, $c = 19.901(14)$ Å, $\beta = 101.44(3)°$, 5090(7) Å^3, $Z = 4$, $\rho_\mathrm{calcd} = 1.095$ g cm^{-3}, $\mu(\mathrm{Mo}_{K\alpha}) = 0.71$ cm^{-1}, $M_\mathrm{w} = 839.24$. 8946 reflections and 542 variables were used to solve the structure, $R_1 = 0.095$, $wR_2 = 0.128$, GOF (F^2) = 0.74. CCDC 247765–CCDC 247768 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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