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Facile Formation of Aromatic Cyclic *N*-Methylamides Based on *cis* Conformational Preference

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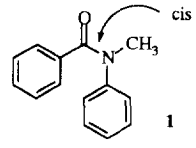
Abstract: Treatment of *meta*-(methylamino)benzoic acid (**2**) with tetrachlorosilane afforded several cyclic oligomers (**3** – **6**). All the amide bonds of the four oligomers are *cis* in the crystal. ^{1}H-NMR spectra of the trimer **3** showed the existence of an equilibrium between chiral truncated cone (*syn*) and *anti* conformations.

Preference of cis conformation is general for *N*-methylated aromatic anilides[1] and often resulted in unique physicochemical[2] and biological[3] properties. The resultant folded aromatic structures of *N*-methylbenzanilide (**1**) and the bis- and trisamides were expected to make possible the formation of oligomeric cyclic amides with moderate ring sizes. Here we report the one-step formation of several cyclic aromatic amides from *meta*-(methylamino)benzoic acid (**2**) and the elucidation of their fascinating chiral cavity conformations.



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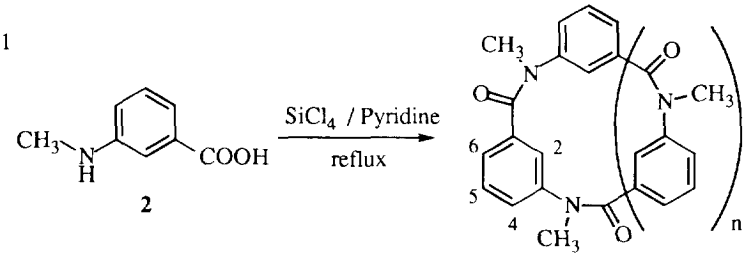
meta-(Methylamino)benzoic acid (**2**, 0.01 M) was refluxed with tetrachlorosilane (1.5 equiv) in dry pyridine for 48 h.[4] After removal of the solvent, the methylene chloride/methanol (1:1 mixture)-soluble portion of the residue was obtained and purified by silica gel column chromatography to afford mainly four compounds, **3** (41%), **4** (11%), **5** (6%) and **6** (8%), all of them being amide compounds with high mp (>300 °C) and with the empirical formula C_8H_7NO from elemental analyses. The cyclic tri-, tetra-, penta- and hexaamide structures for the products **3** – **6**, respectively, were determined by mass spectrometry and X-ray crystallography (Fig. 2).[5] Such cyclic oligomers were not obtained from the reaction of *meta*-aminobenzoic acid under the same conditions. The outcome was considered to have resulted from the advantageous conformations (*cis*-amide structures) of the acyclic *N*-methylated intermediates for the cyclization,[6] in addition to the improvement in solubility compared to the generally poor solubility of secondary aromatic amides in organic solvents. Formation of rather small cyclic products, such as the trimer **3** and tetramer **4**, in one step is in marked contrast to the case of a secondary cyclic aramide with hexameric structure.[7]

Fig. 1



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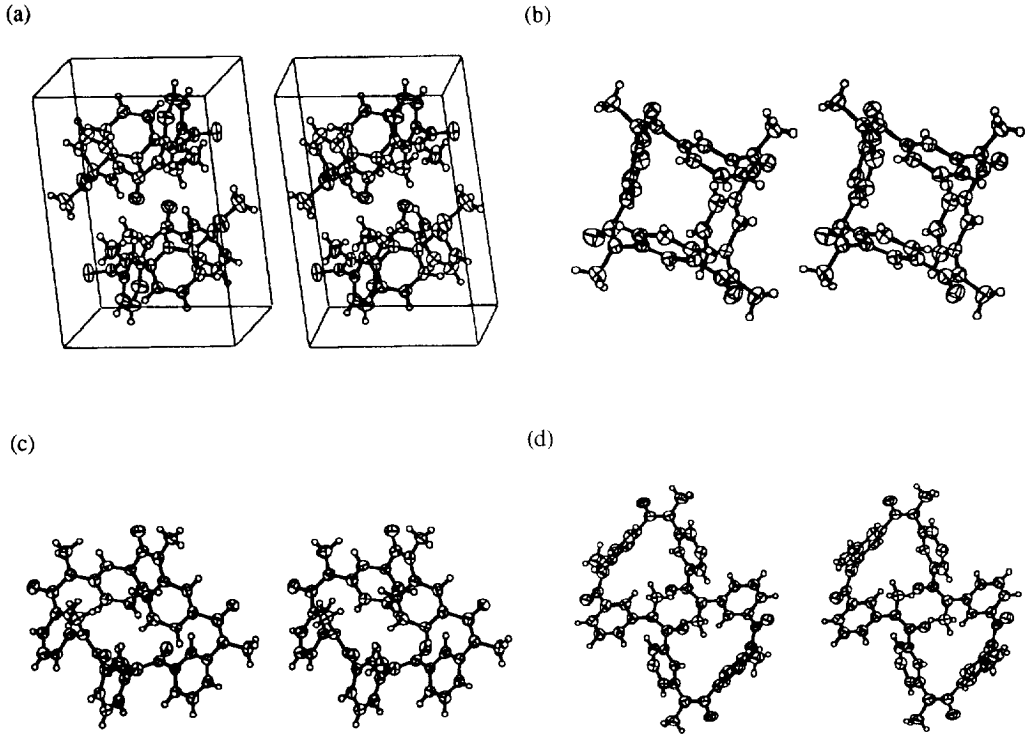
3 (n = 1)
4 (n = 2)
5 (n = 3)
6 (n = 4)

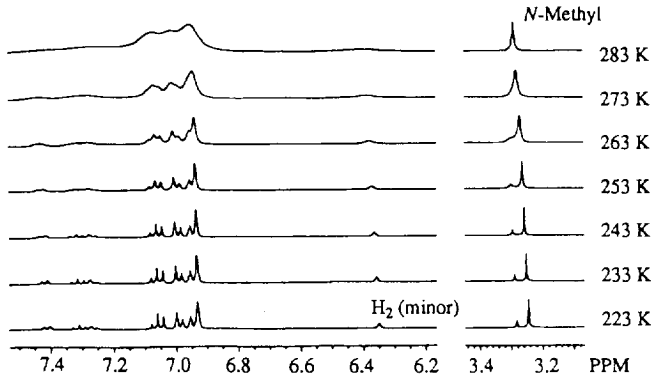
Fig. 2 ORTEP stereoviews of the crystal structures of (a) **3** (a unit cell), (b) **4**, (c) **5** and (d) **6**.



Crystal structures of the cyclic products **3** – **6** showed that all of their *N*-methylamides are *cis*. The structures are characterized by the approximate planarity of the amide bonds and the large torsion angles between the phenyl and amide planes (30 – 70°). *N*-Methylbenzanilide components in each compound have strutures similar to the crystal structure of *N*-methylbenzanilide itself.[1] The molecular shapes of the trimer (**3**) and tetramer (**4**) are a bowl and a ball, respectively. The three 1,3-disubstituted phenyl rings in **3** exist in the same orientation (*syn*) toward the amide bonds in a truncated cone structure (pseudo C_3). The structure has molecular chirality based on the direction of the amide bonds at the *meta* positions. Thus, the rotation of all the phenyl rings around the amide bonds generates the enantiomeric conformer (**3a** and **3a'** in Fig. 4). The unit cell has two molecules of **3**, being enantiomeric to each other (Fig. 2a). In contrast to the structure of **3**, the tetramer **4** has phenyl rings alternately in the same direction (pseudo S_2).

The ^{1}H-NMR spectrum of the trimer **3** in CD_2Cl_2 at room temperature showed broadened peaks that became sharp at low temperature (coalescence point, 263 K, Fig. 3), indicating the existence of two conformers.[12] The ratio of the two conformers is 77:23 at 233 K, as deduced from the integrals of the two singlet *N*-methyl peaks, and significantly depends on the solvent (74:26 in $CDCl_3$, 96:4 in CD_3OD at 233 K), but not on the temperature as in the case of a triamide, *N,N',N''*-trimethyl-*N,N',N''*-triphenyl-1,3,5-benzenetricarboxamide.[2a] The signals for the aromatic protons of the major conformer of **3** at higher field should be assigned to the truncated cone structure (*syn*), as seen in the crystal. Only the signal for the H_2 proton of the minor conformer shifted to higher field (6.33 ppm), which indicated that the minor form is the *anti* conformer with one phenyl ring turning in the other direction (**3b** and **3b'** in Fig. 4). The assignment was supported by the

Fig. 3 The temperature dependence of ^{1}H-NMR signals of **3** in CD_2Cl_2.



observation of NOE enhancement between the *N*-methyl group and H_6 proton only for the minor conformer at 233K in $CDCl_3$. In the minor conformer, interestingly, the signals of the three aromatics and the three *N*-methyls were each observed as equivalent in the NMR spectrum. This suggests that the conversion between **3b** and **3b'**, which includes rotation of the phenyl ring around the amide bond, is fast.

The chiral conformation of **3** observed in the crystal could be distinguished in solution by ^{1}H-NMR in the presence of a chiral reagent. For example, when 7 equiv of (*S*)-1,1'-bi-2-naphthol was added to a solution of **3** in $CDCl_3$, the higher field signal of the two singlet *N*-methyl peaks, which corresponds to the major conformer, was split into two singlets with the ratio of 46:54 at 233 K. In this case, the coalescence point is 278 K, higher than that in the absence of (*S*)-1,1'-bi-2-naphthol. The observation that the *N*-methyl peak for the minor conformer did not split is consistent with the fast conversion between the *anti* conformers (**3b** and **3b'**) that is equivalent to racemization of the minor conformer. As shown in Fig. 4, the racemization of the major conformer **3a** to **3a'** requires three inversions of the phenyl ring. The result indicates that the first inversion (**3a** to **3b**) is much slower than the second inversion (**3b** to **3b'**). The energy barrier (13.5 kcal/mol), calculated from the coalescence point and the chemical shift difference of the *N*-methyl peaks,[13] is responsible for the conversion of **3a** to **3b**.

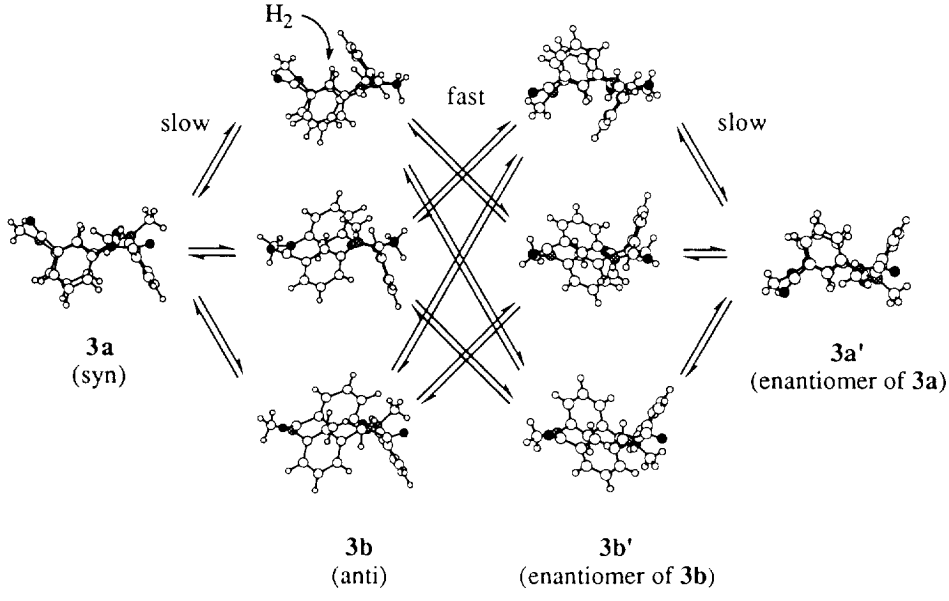


Fig. 4 Schematic representation of equilibria of **3**.

In conclusion, *cis* preference of *N*-methylamide made possible the formation of several cyclic aramides. In view of our previous studies on the spontaneous generation of chiral aromatic *N*-methylamides,[2b] the chiral cavity in the molecules of **3** may be useful in supramolecular chemistry, as is the case with calixarenes[8] and π-prismand.[10] Studies on applications of the compounds and structural investigations on larger cyclic oligomers in solution are in progress.

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5) X-ray structure analyses were carried out using a Rigaku AFC5 for **3**, or Rigaku RAXS IIC for **4** – **6**. Crystal data of **3** ($C_{24}H_{21}N_3O_3$): triclinic; space group, $P\bar{1}$; Z, 2; a, 9.4605(9) Å; b, 13.7285(8) Å; c, 9.2184(6) Å; α, 95.311(5)°; β, 107.373(6)°; γ, 111.252(6)°; *V* 1037.5(2) Å^3; D_{calc}, 1.279 g/cm^3; R, 0.056; **4** ($C_{32}H_{28}N_4O_4$): monoclinic; space group, $P2_1/c$; Z, 4; a, 15.70(1) Å; b, 9.968(2) Å; c, 18.223(6) Å; β, 113.20(3)°; *V* 2623.2100 Å^3; D_{calc}, 1.348 g/cm^3; R, 0.055; **5** ($C_{40}H_{35}N_5O_5 \cdot C_2H_5OH$): monoclinic; space group, $P2_1/a$; Z, 4; a, 30.803(6) Å; b, 12.585(6) Å; c, 9.366(1) Å; β, 95.16(1)°; *V* 3616.1299 Å^3; D_{calc}, 1.223 g/cm^3; R, 0.052; **6** ($C_{48}H_{42}N_6O_6 \cdot iso C_3H_7OH$): triclinic; space group, $P\bar{1}$; Z, 2; a, 14.140(10) Å; b, 15.018(4) Å; c, 11.960(4) Å; α, 90.97(2)°; β, 110.58(4)°; γ, 64.19(3)°; *V* 2140.1899 Å^3; D_{calc}, 1.240 g/cm^3; R, 0.066.
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12) Compounds **4** – **6** also showed broadened ^{1}H-NMR spectra at room temperature. The percentages of the major conformers in $CDCl_3$ at 213 K are 92%, >99% and 50% (1:1), respectively.
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