SYNTHESIS OF NEW MOLECULES ADOPTING A UNIQUE SIGMOID CONFORMATION WITH STACKED AROMATIC RINGS IN THE CRYSTALLINE STATE

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Abstract- Synthesis of new molecules adopting a unique sigmoid conformation in the crystalline state has been achieved. Conformational analysis of these molecules is investigated by utilizing X-ray and ^{1}H nmr analyses.

In the modern science of molecular recognition, exploitation of new molecular devices and functional molecules may be of considerable current interest.[1] Therefore, there have been many reports on the unique molecule involving molecular clefts,[2] molecular tweezers,[3] and receptor models[4] for drug and biologically important substances. In the design of these molecules, a folded or a macrocyclic structural mode seems to be adopted most likely in order to gain a high degree of specificity between the host molecule and the guest molecule.[1-5] Even in the field of drug creation, adoption of a folded conformation in the molecule would be one of novel promising approaches because enzymes, proteins, nucleic acids, and other polar macro molecules never display any stretched molecular aspect.[6]

Recently, we established a general preparation method for the compounds adopting a folded conformation (**A** in Figure 1) with stacked aromatic rings, especially heterocyclic and carbocyclic aromatic moieties.[7] Bridging

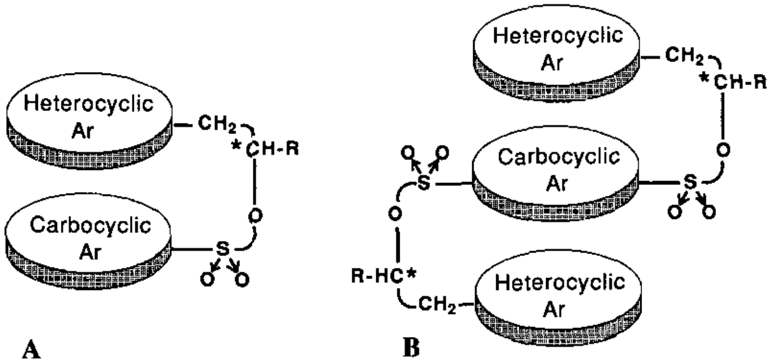
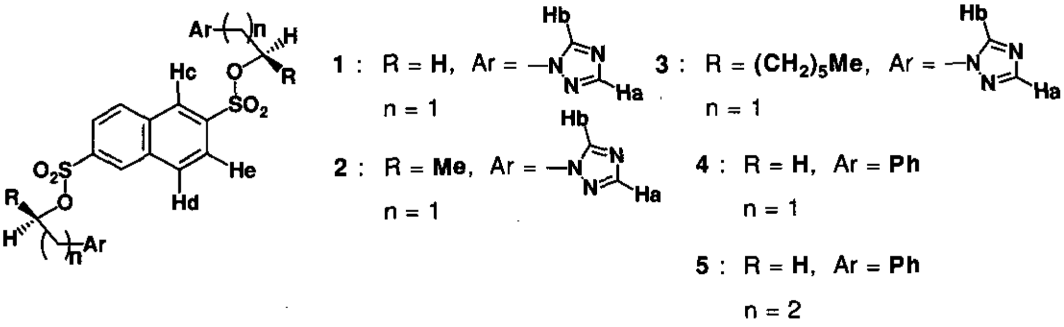
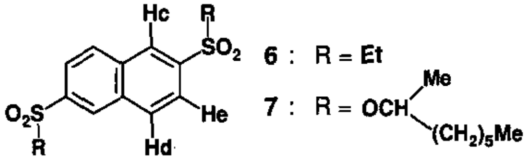
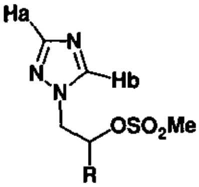


Figure 1. Folded conformation **A** and sigmoid conformation **B**







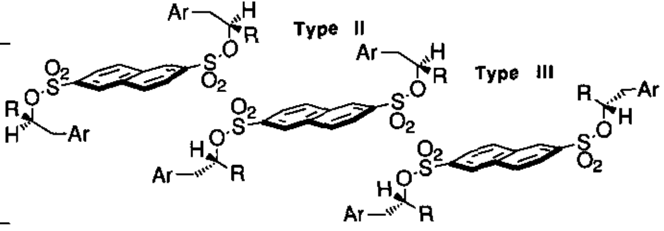
8 : R = H

9 : R = $(CH_2)_5Me$

Table 1. Molecular mechanics calculation of sulfonic esters (**1-4**) adopting type I-III conformations.

Compd	Type I[a)] kcal/mol	Type II[a)] kcal/mol	Type III[a)] kcal/mol
1	4.98	12.71	21.15
2	2.33	5.54	10.18
3	20.78	24.56	32.55
4	12.45	15.56	18.58

a)



two aromatic moieties with a sulfonic ester chain seems to be a considerable factor for design of an **A**-type folded conformation.[7] Thus, we tried to construct new molecules adopting a unique sigmoid conformation illustrated in **B** in Figure 1. Compounds (**1-5**)[8] were synthesized by treatment of 2,6-naphthalenedisulfonyl chloride with the corresponding alcohols in the presence of pyridine or MeLi. Crystalline compounds (**1**), (**4**), and (**5**) were submitted to the X-ray crystallographic analysis.[9] Perspective top and side views of the crystal structures (**1**) and (**4**) are depicted in Figure 2. As is clearly seen in this figure, both compounds (**1**) and (**4**) virtually adopt a beautiful $\underline{S}_2$ symmetric sigmoid conformation in the crystalline state. The compound (**5**), bearing one methylene-longer linkage than that of **1-4**, does not adopt any sigmoid conformation with stacked aromatic rings (Figure 3). Interestingly, each Type I-sigmoid conformation with stacked aromatic moieties was shown to be energetically most stable among the three typical conformers (Type I-III in Table 1) of compounds (**1-4**) based on their molecular mechanics (MM) calculation.[10] From the viewpoint of ^{1}H nmr analysis (Table 2) of compounds (**1**) and (**3**) and the related compounds (**6-9**), a weak intramolecular attraction between a naphthalene ring and two triazole rings was recognized even in DMSO-$\underline{d}_6$ or $CDCl_3$ solution. Namely, all distinctly assignable H_a, H_b, H_c, H_d, and H_e peaks in the ^{1}H nmr (200 MHz) spectra of **1** and **3** appeared at higher field [shifted values ($\Delta\delta$) of H_a (**1**: $\Delta\delta$ 0.21 ppm, **3**: $\Delta\delta$ 0.36 ppm) and H_e (**1**: $\Delta\delta$ 0.21 ppm, **3**: $\Delta\delta$ 0.20 ppm)] than the corresponding peaks on those of the non stacking compounds (**6-9**), respectively (see Table 2). However, the magnitude of upfield shifted values is not yet enough to rationalize their preferential sigmoid conformation in solution. Hence, we also attempted to determine NOE of compounds (**1**), (**3**), and (**4**). We recognized certainly the NOE (CD_2Cl_2, -80 °C) between the benzene protons and the naphthalen protons in the molecule of **4**, while any similar NOE was not observed in the triazole-bearing compounds (**1**) (DMF-$\underline{d}_7$, -55 °C) and (**3**) (CD_2Cl_2, -80 °C), suggesting that the stretched conformations are more favorable for these compounds. This outcome may be explained in terms of "solvation" toward the polar triazole moiety at very low temperature, which would not be available at room temperature. We also realized that the MM calculation result mentioned above is not available for the solution system in the aprotic polar solvent.

Thus, we disclosed a general preparation method for achiral and chiral compounds (**1-4**) adopting a novel $\underline{S}_2$ symmetric (or a non $\underline{S}_2$) sigmoid conformation with stacked aromatic rings in the crystalline state. These unique sigmoid molecules will be useful for developments of new types of functional solid molecules.

Table 2. ^{1}H Nmr (200MHz) spectral data of compounds (**1**, **3**) and the related compounds.

Compd	^{1}H-Chemical shift (δ ppm)				
	Ha	Hb	Hc	Hd	He
1$^{a)}$	7.79	8.48	8.71	8.43	7.86
6$^{a)}$	—	—	8.84	8.55	8.07
8$^{a)}$	8.00	8.53	—	—	—
3$^{b)}$	7.63	8.00	8.40	8.07	7.84
7$^{b)}$	—	—	8.57	8.16	8.04
9$^{b)}$	7.99	8.18	—	—	—

a) Determined in DMSO-$\underline{d}_6$. b) Determined in $CDCl_3$.

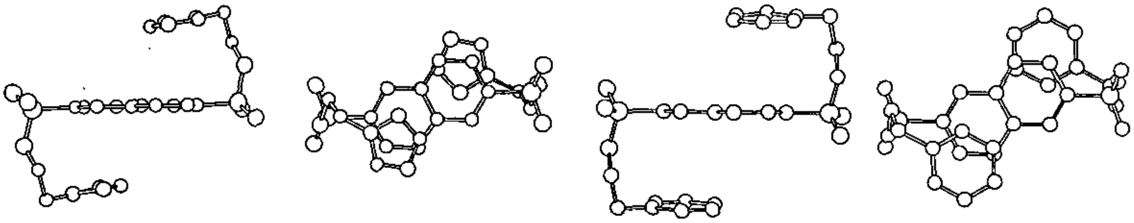

Side view of **1** Top view of **1** Side view of **4** Top view of **4**

Figure 2. $\underline{S}_2$ Symmetric sigmoid conformation in the crystalline state of **1** and **4**

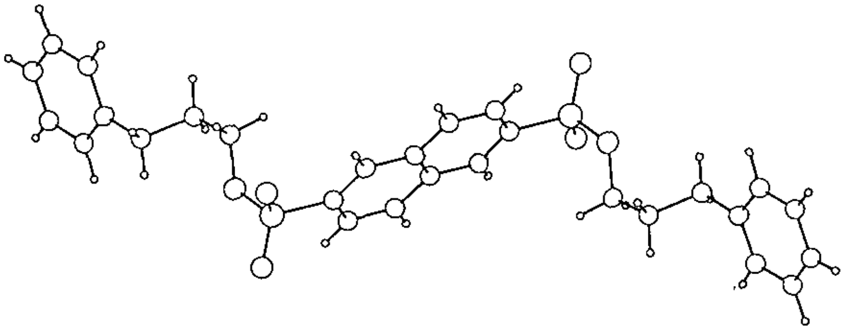


Figure 3. Stretched conformation in the crystalline state of **5**

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8. Compounds **1**: colorless column, mp>250 °C ($CHCl_3$-DMF); **2**: *dl*-diastereomeric mixture, amorphous powder, mp 183-185 °C (EtOH-DMF); **3**: optically pure, $[\alpha]^{22}_{D}$-18.1°(c 0.61, MeOH), colorless plate, mp

109-110 °C (AcOEt-$CHCl_3$); **4**: colorless column, mp 131-133 °C (Et_2O-CH_2Cl_2); **5**: colorless column, mp 121.5-123 °C (Et_2O-CH_2Cl_2).

9. The crystallographic data for **1**, **4**, and **5** are as follows: **1**, $C_{18}H_{18}N_6O_6S_2$, M = 478.498, triclinic, $P\overline{1}$, a = 8.808 (1), b = 8.864 (1), c = 7.315 (1) Å, α = 92.38 (1), β = 112.49 (1), γ = 89.41 (1) °, V = 527.3 (1) $Å^3$, z = 1, D_{cal} = 1.507 gcm^{-3}, R = 0.044; **4**, $C_{26}H_{24}O_6S_2$, M = 496.592, monoclinic, $P2_{1/c}$, a = 5.897 (3), b = 25.923 (11), c = 8.575 (1) Å, β = 115.59 (4) °, V = 1182 (1) $Å^3$, z = 2, D_{cal} = 1.395 gcm^{-3}, R = 0.043; **5**, $C_{28}H_{28}O_6S_2$, M = 524.663, monoclinic, $P2_{1/n}$, a = 5.823 (3), b = 29.513 (2), c = 7.810 (2) Å, β = 106.64 (3) °, V = 1286 (8) $Å^3$, z = 2, D_{cal} = 1.354 gcm^{-3}, R = 0.051.

10. All calculation were performed using the QUANTA software package purchased from Polygen INC., USA, see: B. R, Brooks, R. E. Bruccolei, B. D. Olafson, D. J. States, S. Swaminathan, and M. Karplus, J. Comput. Chem., 1983, **4**, 187.

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