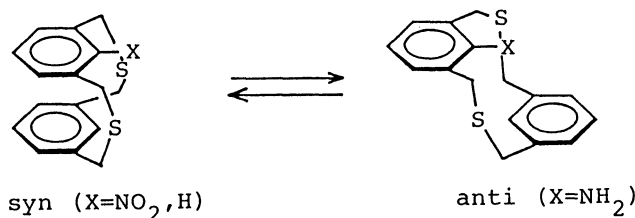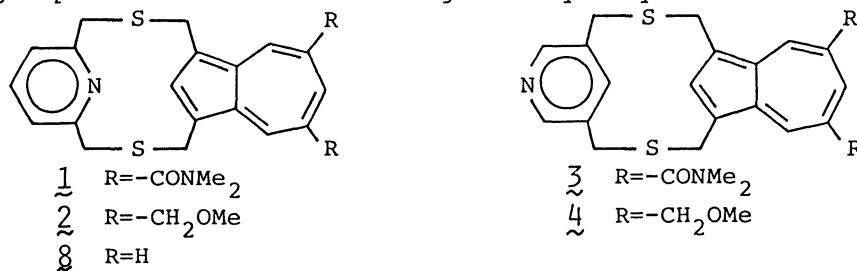Conformation of Dithia[3.3](1,3)azulenopyridinophanes

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The preferred conformations and the dynamic processes of the title compounds have been determined by variable temperature ^{1}H-NMR analysis. Molecular mechanics calculations suggested the detail course of the conformational interconversion.
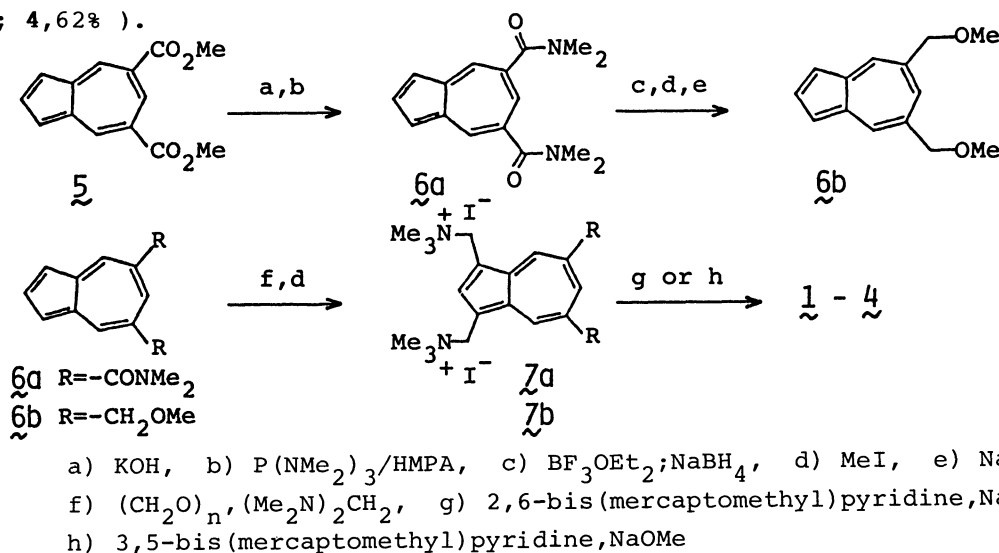
The synthesis and the stereochemical aspect of conformationally mobile [3.3]-metacyclophanes have been of particular interest for the past decades.[1] The pioneering work of the conformational investigation of 2,11-dithia[3.3]metacyclo-phanes by Vögtle suggested that while nitro group at inner aryl position shifts the syn and anti equilibrium to the former side, corresponding amino group works as completely opposite way. Along with the difference of the steric bulkiness of these substituents, the changes of the electron density of benzene rings and hence that of π-π interaction between the two π-systems caused by these substituents, were claimed to be important factor for the preferred conformation in these meta-cyclophanes.[2]

syn (X=NO$_2$,H)   anti (X=NH$_2$)

In the course of the studies on conformation of dithia[3.3]azulenophanes,[3] we have shown that the azulenophanes with 2,6-bridged pyridine ring prefer the syn conformation and Pitzer's type strain in the 2-thiapropano bridge plays an impor-tant role for the conformational equilibrium.[4] However, we could not obtain the clear conclusion about the role of the π-π interaction between the azulene and the pyridine rings. To clarify the influence of the π-π interaction on the conforma-tional equilibrium as well as on the activation energy of the conformational interconversion, we have prepared dithia[3.3]azuleno(2,6)pyridinophanes(1 and 2) and corresponding (3,5)pyridinophanes(3 and 4) bearing electron withdrawing N,N-dimethylamido groups or electron donating methoxymethyl substituents on the azulene ring.


1 R=-CONMe$_2$

2 R=-CH$_2$OMe

8 R=H

3 R=-CONMe$_2$

4 R=-CH$_2$OMe

Dithia[3.3]azulenopyridinophanes were synthesized as shown in Scheme 1. Diamide(6a) was derived from Jutz's dimethyl 5,7-azulenedicarboxylate(5)[5] by hydrolysis and subsequent treatment with $P(NMe_2)_3$ in HMPA. Reduction of 6a by Borch's method[6] and two more steps afforded bis(methoxymethyl) derivative 6b. Azulene-1,3-bis(methyltrimethylammonium) diiodides(7a and 7b) were coupled with bis(mercaptomethyl)pyridine to give dithia[3.3]azulenopyridinophanes(1,19%; 2, 7%; 3,22%; 4,62%).

a) KOH, b) $P(NMe_2)_3$/HMPA, c) BF_3OEt_2;$NaBH_4$, d) MeI, e) NaOMe
f) $(CH_2O)_n$,$(Me_2N)_2CH_2$, g) 2,6-bis(mercaptomethyl)pyridine,NaOMe
h) 3,5-bis(mercaptomethyl)pyridine,NaOMe

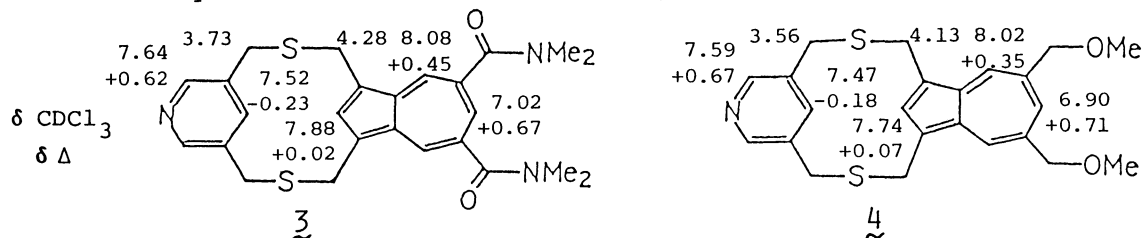Scheme 1.

Two sharp singlets due to methylene hydrogens in the ^{1}H-NMR spectra of 1 and 2 at room temperature suggested a rapid flipping of the two aromatic rings in both cases. The chemical shifts(δ) of their aromatic hydrogens and their differences ($\Delta\delta$; + denote upfield shift) from the reference compounds [2,6-lutidine and the corresponding 1,3-bis(N,N-dimethylaminomethyl) azulenes] are shown below.
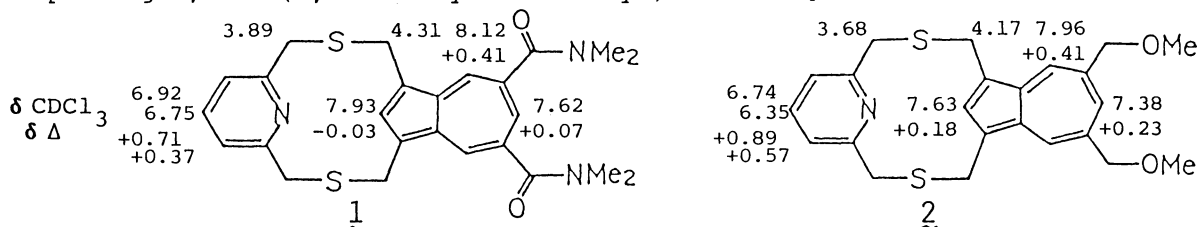
The characteristic upfield shifts of the aromatic outer hydrogens[4] of both rings clearly indicate that the syn forms are predominant in the conformational equilibrium at room temperature. Lowering the temperature, conformational inter-conversion by the aromatic ring flipping slowed down as suggested by the broadened signals of methylene groups. At -100 °C the signals changed to AB quartet indica-ting that the ring flipping was frozen on the NMR time scale. Freezing the inter-conversion usually gives two separate signals corresponding to the components. In these cases, however, the signals of aromatic hydrogens remained unchanged and no extra signals attributable to the anti conformation was detected at this tempera-ture. Therefore, the free energy difference (ΔG^O) between the syn and the anti isomer was estimated to be greater than 1.6 kcal/mol assuming the detection limit of the ^{1}H-NMR signal is 1%.

The ^{1}H-NMR spectral features of 3 and 4 are quite similar to the former compounds. The chemical shift differences shown below suggest also the predominance of the syn conformation. The behavior of the variable temperature NMR of these two is almost the same to the formers, indicating that the syn conformations are exclusively dominant also in these two systems.

δ CDCl$_3$
δ Δ

Compound **3**: 7.64 / +0.62 ; 3.73 ; S ; 7.52 / −0.23 ; 7.88 / +0.02 ; S ; 4.28 ; 8.08 / +0.45 ; —NMe$_2$ (O) ; 7.02 / +0.67 ; —NMe$_2$ (O)

Compound **4**: 7.59 / +0.67 ; 3.56 ; S ; 7.47 / −0.18 ; 7.74 / +0.07 ; S ; 4.13 ; 8.02 / +0.35 ; —OMe ; 6.90 / +0.71 ; —OMe

3   **4**

Since the anti conformation could not be detected in all the compounds **1-4**, neither the electron releasing nor withdrawing substituents on the azulene ring do change the preferred conformation in this system. The π-π interaction between the two rings, therefore, has little influence on the conformational equilibrium. This conclusion was further supported by the free energy of activation($\Delta G^{\ddagger}$) of the ring flipping. The values of $\Delta G^{\ddagger}$ and coalescence temperature(Tc) for these compounds are shown in Table 1 together with those of dithia[3.3](1,3)azuleno(2,6)pyridino-phane(**8**).[4] At the transition state of the ring flipping, the aromatic rings are almost perpendicular with each other and hence there is no π-π interaction between the rings. Therefore, it is reasonable to assume that its energy levels are rather insensitive to the substituents. On the other hand, if the π-π interaction plays an important role and changes the energy levels of the ground states, the $\Delta G^{\ddagger}$ should be changed appreciably. However, it is proven not to be the case from the constant $\Delta G^{\ddagger}$ for **1**, **2**, and **8**. The same conclusion is also deduced for the 3,5-bridged pyridinophanes.

In order to obtain the precise mechanism of the conformational interconversion, we have calculated the steric energy and geometry of six possible conformations by molecular mechanics method.[7,8] The steric energies of six structures are shown in Fig. 1. The calculation successfully reproduced the most stable structure (S_{EE}). The large energy difference between the anti and the syn lowest energy conformers (A_{EX}-S_{EE}, 5.3 kcal/mol) may be another evidence of the absence of ^{1}H-NMR signal due to the anti conformer. From the large energy difference (11.8 kcal/mol) between S_{EE} and A_{EE}, the interconversion between the two seems to be unlikely because it is greater than the observed $\Delta G^{\ddagger}$. Therefore, two pathways for the interconversion (i. $S_{EE} \rightleftarrows S_{EX} \rightleftarrows A_{EX} \rightleftarrows S_{XE} \rightleftarrows S_{EE}$; ii. $S_{EE} \rightleftarrows S_{EX} \rightleftarrows S_{XX} \rightleftarrows A_{XX} \rightleftarrows S_{EE}$) are possible. Since the largest energy difference between the S_{EE} and any one of the intermediates in the former path (A_{EX}-S_{EE}: 5.26 kcal/mol) is smaller than the latter (S_{XX}-S_{EE}: 6.66 kcal/mol), it is suggested that the former route seems to be more likely.[9]

Table 1. Free Energy of Activation(kcal/mol) and Coalescence Temperature(°C)

Compound	Tc	$\Delta G^{\ddagger}$
1	−64	10.2
2	−65	10.2
3	−36	11.6
4	−34	11.7
8	−65	10.2[a]

a) The value reported in Ref. 4 should be corrected.

S_{EE}(17.68 kcal) S_{EX}(20.91) S_{XX}(24.34)

Py.
Flip

A_{EE}(29.50) A_{EX}(22.94) A_{XX}(23.35)

Az.
Flip

S_{XX} S_{XE} S_{EE}

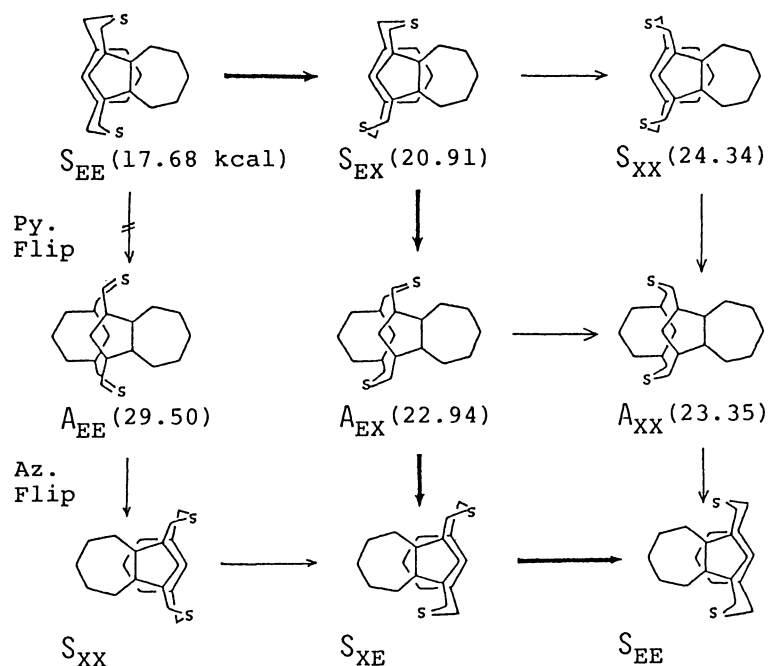Fig.1. Steric energies of the six conformations and plausible route of ring
flipping in 8.

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