The results described above provide experimental support for the external point-charge model which accounts for the bathochromic shifts of the dihydrorhodopsins as well as natural rhodopsins. We have shown that diene models produce wavelength shifts of comparable magnitude (268 nm for **12** vs. 297 nm for **6**) with that seen upon formation of 11,12-dihydrorhodopsin (275 to 315 nm; see above). Moreover, when measured in reciprocal centimeters, the shifts that we have obtained, e.g., for the models **12** vs. **6** (3600 $cm^{-1}$), are even larger than the shifts between the $SBH^+$ of 11-*cis*-retinal (440 nm) and rhodopsin (500 nm), i.e., 2700 $cm^{-1}$. Models **14**–**17** also show that the shifts induced by external negative charges are, in agreement with theoretical calculations, sensitive to their locations relative to the conjugated system. Most probably it is this spatial distribution of charges relative to the retinal $SBH^+$ moiety that leads to the variation in $\lambda_{max}$ of the various pigments and of the intermediates formed during the bleaching process.[16]

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(1) We have employed methanol as the solvent for measuring the electronic spectra of retinal protonated Schiff bases because in such "leveling" solvents, in contrast to the less polar solvents such as *n*-hexane, the $\lambda_{max}$ is independent of the counteranion: J. O. Erickson and P. E. Blatz, *Vision Res.*, **8**, 1367 (1968); P. E. Blatz, J. H. Mohler, and H. V. Navangul, *Biochemistry*, **11**, 848 (1972).
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(11) The compounds were characterized by IR and $^1H$ NMR data.
(12) Owing to the instability of the salt prepared in this manner, it was not possible to obtain the $^1H$ NMR and IR data.
(13) The carboxylate **6** could not be acidified with HCl because the acid degraded it into UV transparent species.
(14) Acetonitrile was the solvent of choice because it dissolved both **10** and **11** but not NaH.
(15) Despite the unstable properties, the salts thus prepared were sufficiently stable for $^1H$ NMR ($CD_3CN$) and IR (neat) measurements.
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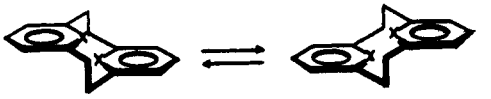
## Anti, Longitudinal Conformational Isomerism in Metacyclophanes

*Sir:*

The stereochemical aspects of cyclophanes have been of particular synthetic and theoretical interest for the past two decades.[1] The molecular geometry of [2.2]metacyclophanes has been exhaustively analyzed and summarized in an excellent review by Vögtle and Neumann.[1f] From crystallographic[2] and NMR[3] studies, [2.2]metacyclophanes possess a "stepped" conformation. The activation parameters for the inversion process (e.g., **1A** ⇄ **1B**) have been determined on the basis of



**1A** **1B**

VT NMR studies. The free energy of activation ($\Delta G^{\ddagger}$) and Arrhenius activation energy ($E_A$) for **1** (X = N) were found to be 14.8 and 15.3 kcal/mol, respectively.[4] Related [2.2]-cyclophanes have been shown to exhibit a similar isomerization process.[5] Syn–anti isomerization has also been reported in metacyclophanes possessing larger bridges;[6] such isomerism is suggested from NMR studies in that the aromatic protons in the syn isomer experience a distinct upfield shift owing to the anisotropy of the juxtaposed ring.

In 1977, we proposed that **2** underwent a syn–anti isomerization (Figure 1) based on 100-MHz VT NMR spectral data. The free energy of activation ($\Delta G^{\ddagger}$) was calculated to be 13.5 ± 0.3 kcal/mol from the coalescence temperature ($T_c$ = 288 K) for the methylene hydrogens and chemical shift difference ($\Delta\delta$ = 137 Hz). The nearly equal syn–anti isomer distribution, suggested by the equal intensity of the two resolved doublets ($J$ = 8.0 Hz) at $\delta$ 6.28 and 6.32 for the 3,5-pyridine hydrogens at 223 K, was a major concern, since this distribution would not be expected to be equal. The chemical-shift differences for the pyridine protons should also have been larger for such syn–anti isomers. A single triplet ($J$ = 8 Hz) at $\delta$ 7.50 for the 4-pyridine hydrogen was observed intact even at 223 K! The alternate mode isomerization (**2a** ⇄ **2b**), for which we suggest the term "anti, transverse", would have afforded only a single doublet for the 3,5-pyridine hydrogens over the entire temperature range, since these are equivalent by symmetry.

In view of recent X-ray crystal data for related macrocycles[8]

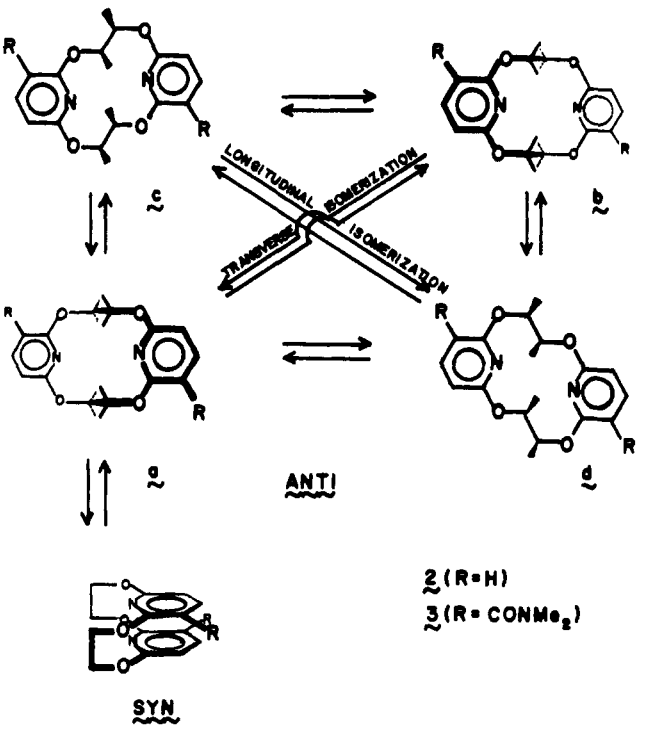



Figure 1.

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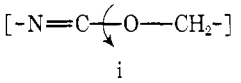
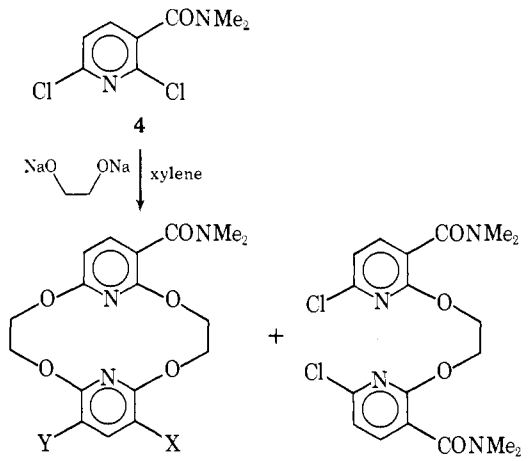
and cryptands[9] possessing the imidate moiety i as well as MINDO-3 calculations of 2,6-dimethoxypyridines,[10] a dihedral angle of 0 ± 10° has been consistently demonstrated for



i

this group. Thus at low temperatures, macrocycles, such as **2**, are now envisioned to possess a nearly coplanar geometry for the pyridine subunits in order to satisfy both the rigid angular constraint imposed by the imidate groups and symmetry considerations. The mode of conformational motion (Figure 1) operative in **2** must be "anti, longitudinal", in which the energy minima would be represented by structures **2c** and **2d.** The NMR data are consistent for isomers **2c** and **2d,** in that equal isomer populations would be expected, and the *3,5-pyridine hydrogens are not magnetically equivalent at low temperatures,* while the 4- and 4′-pyridine protons are magnetically equivalent.

To prove the occurrence of this new isomerization mode, bis amide **3**[11] (mp 270 °C dec) was synthesized from **4**[12] upon




treatment with disodium ethylene glycolate at 140 °C for 40 h via standard procedures.[7] After thick layer chromatography, **3** was isolated (2%) and shown (TLC, NMR, X-ray) to be a single isomer (*E*). Reaction of **5** under the same conditions gave an isomeric mixture of **3** and **6** via transetherification; owing to the limited quantity of **6** further purification was not conducted. At 393 K, the 200-MHz NMR spectrum of **3** shows doublets at δ 7.64 and 6.43 for H-4 and H-5, respectively, as well as a broad singlet at 4.72 for the methylenes and two spikes at 2.93 and 3.11 for the amide methyls. The free energy of activation ($\Delta G^{\ddagger}$) for longitudinal isomerization is calculated to be 14.5 ± 0.1 kcal/mol based on $T_c$ = 301 K and Δδ = 251 Hz. The low-temperature (233 K) spectrum of **3** (downfield region) is shown in Figure 2. The 5-pyridine hydrogen appears as *two* doublets ($J$ = 8 Hz) at δ 6.445 and 6.415 indicative of approximately equal populations of **3c** and **3d.** The two doublets ($J$ = 8 Hz) at δ 7.645 and 7.635 (Δδ = 2 Hz) for H-4 further confirm the magnetic nonequivalence of H-4 in the two isomers.

This anti, longitudinal isomerization (e.g., **c** ⇄ **d**) proceeds through the "stepped" intermediate or transition state. Numerous metacyclophanes have been suggested to possess the anti, stepped (staggered) conformation of the (hetero) aryl rings, and the values for the free energy of activation derived from VT NMR studies used support this hypothesis. Thus if the metacyclophane bridge(s) possess(es) functionality that restricts the rotational freedom via an energetically preferred

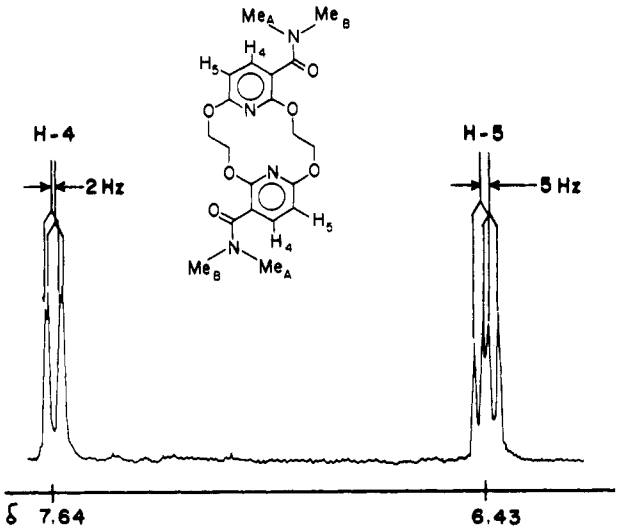



**Figure 2.** Low-temperature (233 K) 200-MHz NMR spectrum of **3** in $CD_2Cl_2$.

conformational orientation (e.g., heteroaryl-X-$CH_2$, $CH_2$-X-X-$CH_2$, $CH_2NHCOCH_2$), the structural representations and isomerization process may deviate considerably from the anti, stepped mode.

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(14) On leave from Kyushu University, Fukuoka, Japan, 1977–1979.

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