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REMOTE SUBSTITUENT EFFECTS ON CONFORMATIONAL RING FLIPPING IN [2.2]METAPARACYCLOPHANES.

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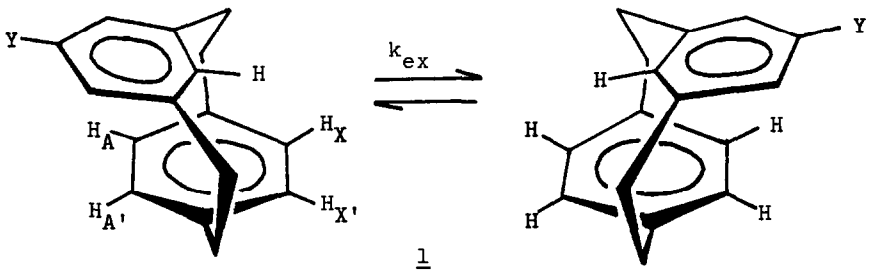
Remote substituent effects on sterically hindered conformational changes have been reported for two classes of compounds. In one class, 4-substituted aniline derivatives[2] and 4-substituted 1-naphthylamine derivatives,[3] the observed effects on the rates of nitrogen inversion correlate well with expectations based on resonance in the transition state. The second class is substituted biphenyls and the related 1,1'-binaphthyls, wherein the effect of remote substituents on hindered rotation about the interannular bond has been the object of several studies.[4] In this class a number of subtle influences may be operative and the data has led to no unifying interpretation.[4f,5] We were attracted by the prospect of measuring remote substituent effects on the rate of conformational ring flipping in [2.2]metaparacyclophanes. The steric barrier to this process is distinctive in the way it requires a hydrogen bound to an aromatic ring to impinge on a benzene π cloud.[6] That this interaction comprises a substantial portion of the barrier to flipping is strongly suggested by our recent measurement of an unusually large steric isotope effect where that hydrogen is replaced by deuterium.[7] We felt that the nature of this interaction might be reflected by substituent effects in well defined and informative trends.

We have synthesized six substituted [2.2]metaparacyclophanes of general formula 1. The syntheses involved coupling reactions between p-xylylenedithiol and substituted m-xylylene dibromides and featured as a key step pyrolysis of bissulfones[7,8] at 500-600° in a flow system, which gave [2.2]metaparacyclo-

phanes in yields of 70-95%.[9] In the course of our isotope effect measurement,[7] we developed a convenient and precise nmr procedure, based on the method of Forsen and Hoffman,[10] which proved to be readily applicable to rate measurements of substituted [2.2]metaparacyclophanes. In the nmr spectra of these compounds the signals due to the parabridged ring protons appear as a pair of narrow, well separated multiplets ($H_{A,A'}$ and $H_{X,X'}$). With a suitable rate of exchange due to ring flipping, saturation of one of these sites results in a



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steady-state reduction in the integrated intensity of the other site, expressible as $M_o/M_{z\infty}$. If the longitudinal relaxation times (T_1) of the sites, measured independently by pulse techniques, are found to be equal, then the rate of conformational exchange is given by $k_{ex} = (1/T_1)(M_o/M_{z\infty}-1)$.[7] Conformational flipping rates determined by this method are presented in Table I.

Obviously, remote substituents do influence the rate, the most marked effect being a five-fold retardation due to the amino group. However, the rate data do not seem to follow a simple linear relationship to any relative property of the functional groups represented. As in the case of biphenyls,[5] no mass effect is indicated, i.e., the heaviest substituent, bromine, is associated with the fastest rate; in theory little mass effect would be expected. Due to the remoteness of the substituents, any correlation with steric bulk would have to be via indirect effects; hence the absence of such a correlation is not surprising. At first sight correlation with electronic factors seems futile also, since both strongly electron releasing and strongly electron donating groups retard ring flipping, but when plotted against σ_p (Fig. 1) the data (excepting the relationship between the acetyl and nitro compounds) are

Table I. Longitudinal Relaxation Times and Ring Flipping Rates in Substituted [2.2]Metaparacyclophanes (1)[a]

Substituent	$(1/T_1^X) \times 10^2$ sec^{-1} [b]	$(1/T_1^A) \times 10^2$ sec^{-1} [b]	$M_o^A/M_{z\infty}^A$ [c]	$k_{ex} \times 10^2$ sec^{-1}	k_{rel}
-Br	9.95±0.34	10.55±0.46	1.694±0.038	7.33±0.54	1.08
-F	8.98±0.13	8.75±0.13	1.819±0.047	7.18±0.42	1.06
-H	7.06±0.11	7.16±0.14	1.949±0.031	6.79±0.16	1.00
$-NO_2$	12.05±0.49	11.90±0.48	1.395±0.012[d]	4.78±0.24	0.705
$-OCH_3$	13.09±0.36	12.98±0.35	1.310±0.012	4.03±0.19	0.595
$-COCH_3$	13.10±0.72	13.34±0.69	1.282±0.011	3.77±0.24	0.556
$-NH_2$	10.78±0.13	11.14±0.21	1.110±0.007	1.29±0.09	0.189

[a]For degassed solutions in $CDCl_3$ at 35.0±0.3°. [b]Error given is standard deviation of the slope based on ten or more points. [c]Standard deviation of the average of four or more determinations, each based on averages of ten or more integrals of both M_o and $M_{z\infty}$. [d]In this case the upfield signal was saturated and the downfield signal was integrated.

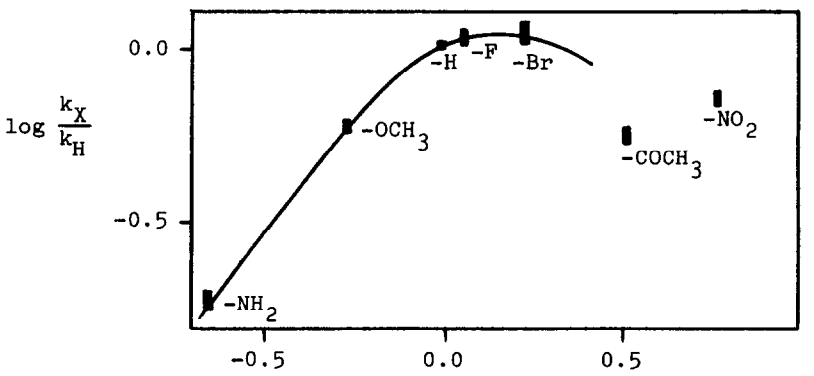

Figure 1. Hammett Plot of Rate Data versus σ_p.

found to define a smooth curve. Simple Hückel molecular orbital theory predicts that endwise interaction of a bond with the face of a benzene ring, such as is envisioned in the transition state for ring flipping, would result in an increase in charge density on the remote end of the bond, due both to polarization of the bond and to donation of charge density from the benzene ring. In keeping with this prediction, the points associated with amino, methoxy, hydrogen, and fluorine are approximately colinear and give a least-squares slope of $\rho = 1.05 \pm 0.09$. If this explanation for the electron releasing substituents is correct, then some opposing effect must be dominant in the case of strongly electron withdrawing groups. We propose that electron withdrawing groups may retard ring flipping by stabilizing the ground state through bonding interaction analogous to that in charge-transfer complexes. The details of our interpretation and the impact upon it of a less approximate molecular orbital treatment will be included in a full paper.

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