Raman band, not the 389-cm$^{-1}$ band. The 389-cm$^{-1}$ band can probably be assigned to a less stable, secondary reaction product, possibly involving two salt molecules and one $F_2$ molecule. Regardless, there is considerable evidence to assign the 461-cm$^{-1}$ Raman band to $\nu_1$ of $F_3^-$ in the $Cs^+F_3^-$ ion pair. This, combined with the $\nu_3$ value of 550 cm$^{-1}$ obtained from the infrared experiments gives two of the three fundamental vibrational bands of the $F_3^-$ anion. The remaining fundamental, the bending mode $\nu_2$, is expected to be considerably less intense, and it was not observed in these studies.

The geometry of the anion may be deduced from this information. As can be seen in traces (c) and (d) of Figure 1, the principle of mutual exclusion holds rigidly within the limits of detectability. $\nu_3$ was not observed in the Raman spectrum, and $\nu_1$ was not observed in the infrared spectrum. This indicates that the $F_3^-$ anion contains a center of symmetry, with a $D_{\infty h}$ structure which is the expected geometry for a symmetrical 22-valence electron species. This result further supports the conclusion that the species formed is a discrete $F_3^-$ anion, and *not* an asymmetric, perturbed $MF \cdot F_2$ species.

The cation in these ion pairs serves to stabilize the anion, and the larger cations $Cs^+$ and $Rb^+$ are much more effective than $K^+$. The yield of $F_3^-$ from the reaction of KF with $F_2$ was considerably less than reactions with RbF and CsF. The $M^+$ ion position in the $M^+F_3^-$ ion pair is probably beside the linear, symmetric $F_3^-$ anion, to maximize cation-anion interaction, rather than at one end of the anion. The absence of a shift in vibrational band position with different cations indicates a pure fluorine vibrational mode not involving the cation.

Finally, a second weak band was observed in the infrared experiments in which a high salt concentration was employed. The species responsible for this absorption was destroyed upon diffusion, which suggests a weakly bound, small aggregate. The second Raman band observed at 389 cm$^{-1}$ may be attributable to this same molecule. A definitive assignment cannot be made, but the sharpness of the bands indicates a well-defined, if weakly bound, species.

The reaction of alkali fluoride salt molecules with $F_2$ in argon matrices has produced a single sharp, intense infrared band at 550 cm$^{-1}$, with a strong Raman counterpart band at 461 cm$^{-1}$. Through analogy to previous salt-molecule reactions, and using $KrF_2$ as a model compound, these two bands have been assigned to $\nu_3$ and $\nu_1$ of the $F_3^-$ anion in the $M^+F_3^-$ ion pair. Mutual exclusion between the infrared and Raman spectra indicates a center of symmetry for the anion, in a $D_{\infty h}$ geometry, and a lack of shift of band position with the different cations indicates a pure fluorine vibrational mode in a distinct trifluoride anion. The salt-molecule reaction has again proven to be a pseudo-ion-molecule reaction, and the matrix isolation technique has provided a method of trapping a transient species of limited stability.

**Acknowledgments.** The authors gratefully acknowledge support of this research by the National Science Foundation under Grant GP-38420X, an Alfred P. Sloan fellowship for Lester Andrews, and helpful discussions with Professor Neil Bartlett.

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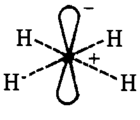
## Four Degenerate Thermal Isomerizations of 1-Methylspiro[2.4]hepta-4,6-diene. A Test for the Smith Mechanism

*Sir:*

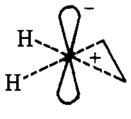
Recent attempts to define mechanisms for thermal geometrical isomerizations of cyclopropanes have uncovered a dominant or sole contribution from two-center epimerizations: at least 96% of the geometrical isomerization shown by 1-phenyl-2-deuteriocyclopropane at 309.5° occurs through simultaneous epimerizations at C(1) and C(2 or 3),[1] while 100% of the geometrical isomerization of (+)-1,2-*trans*-dideuteriocyclopropane may be ascribed to two-center epimerizations.[2] The *O,O*-trimethylene species,[3,4] generated and collapsing through concerted rotations, thus seems favored over either diradical intermediates affording competition between rotations of end methylene units and C–C bond re-formation,[5,6] leading to both one-center and two-center epimerizations as experimental observables, or the Smith mechanism,[7,8] with one-center epimerizations as the exclusive phenomenologically accessible events.

An asymmetrically substituted cyclopropane is one of a set of eight isomers. One-center and two-center epimerizations with rate constants $k_i$ and $k_{i,j'}$ may describe the processes of geometrical isomerizations; there are 48 rate constants but only 9 independent variables. The situation may be simplified by isotopic substitutions and by selecting systems of high symmetry: the 1-phenyl-2-deuteriocyclopropane isomerization may be kinetically described through four independent variables,[1] while optically active 1,2-*trans*-dideuteriocyclopropane[2] requires only two.

All previous experimental work on the geometrical isomerizations of cyclopropanes has been limited to determinations of one or two phenomenological rate constants,[5,6] and, with one exception,[2] experimental results have been interpretable only through the imposition of extreme simplifying assumptions. As a first step toward complete experimental determination of all rate constants for the geometrical isomerizations of an unsymmetrical cyclopropane, we have measured rates for three distinct degenerate processes shown by the cyclopropyl moiety of 1-methylspiro[2.4]hepta-4,6-diene, a system selected to test for a Smith mechanism; given the orbital structure of planar methanes, the planar stereochemical version of a spiro[2.4]hepta-4,6-diene should be particularly favored. Planar methane (**1**) has two electrons in a p orbital and six electrons devoted to four equivalent C–H bonds.[10] While planar methane may be some 125 kcal mol$^{-1}$ less stable than $T_d$ methane,[10] one planar tetracoordinate carbon in a cyclopropane gives a system (**2**) estimated through CNDO calculations including some configuration interaction to lie 67 kcal mol$^{-1}$ above $D_{3h}$ cyclopropane;[11] the same approximate calculations place the *O,O*-trimethylene species 63 kcal mol$^{-1}$ higher than cyclopropane.[11]



1



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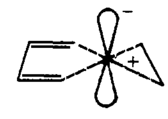
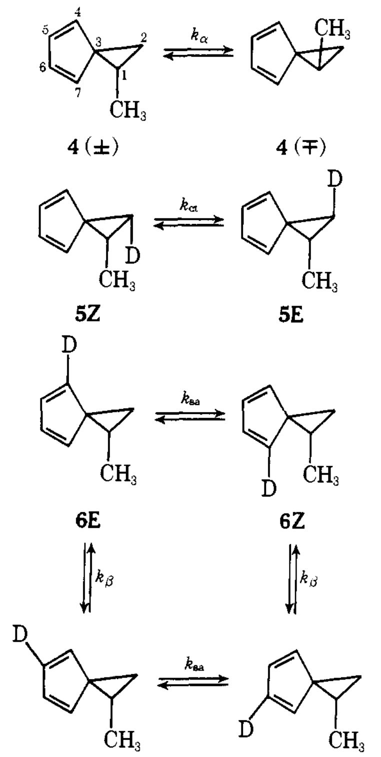


3

Incorporation of the p orbital electron pair in **2** into an aromatic ring as in **3** should afford enhanced stability. If one-center epimerizations are competitive in cyclopropanes generally, they should be the predominant means of geometrical isomerization in spiro[2.4]hepta-4,6-dienes, causing $k_3 > k_{i\neq 3}$ and $k_{i,j'}$.

(+)-1,2-Dibromopropane[12] and cyclopentadiene were condensed using sodium hydride in THF to afford (+)-1-methyl[2.4]hepta-4,6-diene (**4**), $[\alpha]^{25°}{}_{365\text{nm}}$ +16.22° (Scheme I). *Z*-1-Methyl-2-deuteriospiro[2.4]hepta-4,6-diene (**5Z**) was prepared by way of *threo*-1-deuterio-1,2-dibromopropane, obtained from propyne through hydroboration with 9-borabicyclononane, treatment of the intermediate propenyl borane with deuterioacetic acid, and bromination of the *E*-1-deuteriopropene generated. The 1-methyl-4-deuteriospiro[2.4]hepta-4,6-dienes (**6**) were obtained from the undeuterated substrate; it was combined with dichloro ketene,[13] reduced[13] to the corresponding ketene cycloadduct, converted to a trideuterio derivative with sodium deuteroxide in D$_2$O, separated into the four isomeric structural forms by GLC, and, finally, as separated isomers, passed through a hot tube at 300-330° to give dideuterio ketene and the *E* or *Z* versions of the deuterated substrate.

**Scheme I**



From the measured rates of approach to equilibrium at 221.1° determined polarimetrically or NMR spectroscopically (Figure 1), the one-directional rate constants for epimerization at C(1), $k_\alpha = k_1 + k_{12} + k_{13}$; cis-trans isomerization in the three-membered ring, $k_{ct} = k_1 + k_2 + k_{13} + k_{23}$; and syn-anti isomerization of deuterium at C(4) with respect to the methyl group at C(1), $k_{sa} = k_1 + k_3 + k_{12} + k_{23}$, were found to be (7.3 ± 0.4) × 10$^{-5}$, (7.2 ± 0.5) × 10$^{-5}$, and (6.1 ± 0.6) × 10$^{-5}$ s$^{-1}$, respectively. Within the 90% confidence intervals given, $k_\alpha = k_{ct} > k_{sa}$. The process summarized by $k_\beta$, which complicates the kinetics but does not prevent an exact solution, is much slower; $k_\beta$ = (3.1 ± 0.4) × 10$^{-6}$ s$^{-1}$.[14]

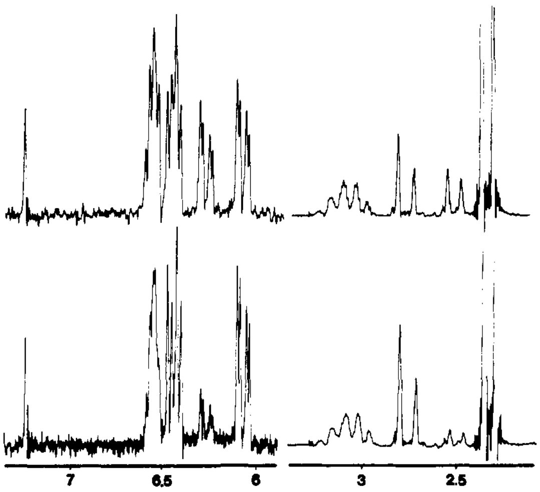


**Figure 1.** NMR spectra of **5E** and **5Z** (right) and **6E** and **6Z** (left): the lower spectra are of the initial mixtures of isomers, while the upper spectra are of mixtures obtained after about 3 h at 221.1°.

The one-center rate constant $k_3$ is thus bracketed: $0 \leq k_3 < k_{13}$. A mechanistic scheme with only one-center epimerizations will not fit. If only two-center epimerizations occur, $k_{13}:k_{12}:k_{23} \approx 40:30:30$.[15] If $k_1$, $k_3$, and $k_{13}$, or $k_3$, $k_{13}$, and $k_{23}$, are taken as the important rate constants, then $k_3 < k_{13}$. In no case can $k_3$ play a predominant role, for $k_{sa}$ is smaller than $k_\alpha$ and $k_{ct}$. Apparently the aromatic stabilization of planar form **3** cannot counterbalance the energetic costs of charge separation.

Even in this favorable case, the first cyclopropane constituted to enhance prospects for one-center epimerization through a planar intermediate and then subjected to kinetic investigation, *epimerization at C(3) is definitely not prominent and may well be zero.*

Other unsymmetrical cyclopropanes suitable for measuring rate constants for all one-center and all two-center epimerizations are being prepared; they should provide a more definitive experimental answer as to the kinetic importance of one-center thermal epimerizations in cyclopropanes.

**Acknowledgment.** This work was supported by the National Science Foundation and by Hoffmann-La Roche, Inc.

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(15) This conclusion based on our experimental data and the two-center-only epimerization model is in conflict with intuitive judgments on the relative magnitudes of these rate constants expressed by two referees, but we know of no conflicting evidence; indeed, $k_{23}$ in 1-phenyl-2-deuteriocyclopropane may, according to our calculations, be only some one-fifth smaller than $k_{12}$.

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## Temperature and pH Dependence of the Tetramer-Dimer Equilibrium of Carbomonoxyhemoglobin A₀

*Sir:*

We wish to report: (1) a new method for measuring the equilibrium constant for the tetramer-dimer dissociation of human hemoglobin, and (2) the temperature and pH dependence of that constant.

We have determined the tetramer-dimer dissociation constant ($K_{4,2}$) of carbomonoxyhemoglobin $A_0$ (HbCO) by the difference in tritium outexchange rates of dimer and tetramer. Differential reactivity of monomers and polymers has been well established as a means for estimating macromolecular subunit dissociation constants.[1] The general principles of the method as applied to the tritium outexchange rates of tetrameric and dimeric hemoglobin can be illustrated as follows. Let each chain of hemoglobin contain the same number of tritium labeled sites and let each state (dimer and tetramer) have a unique set of outexchange rate parameters, as is common in protein systems.[2] Then, at some time after initiation of outexchange, the fraction dissociation, $\alpha$, is given by:

$$\alpha = [(\mathrm{Hrem/Fe})_{\mathrm{C},4} - (\mathrm{Hrem/Fe})_{\mathrm{C},i}] / [(\mathrm{Hrem/Fe})_{\mathrm{C},4} - (\mathrm{Hrem/Fe})_{\mathrm{C},2}] \quad (1)$$

where Hrem/Fe = the amount of tritium left per chain, C,4 and C,2 indicate concentrations of protein where only tetramer or dimer exist, and C,i represents some intermediate concentration at which the two states are both present.

In this manner, fractional hydrogen exchange[3] gives values of the fraction dissociation as a function of protein concentration in a manner strictly analogous to the results obtained from any other physical measurement,[4] provided the protein concentration is well known.

In order to accurately know the concentration of the protein (which must span four or so orders of magnitude) we have labeled the HbCO with trace amounts of $^{14}$C which remains affixed to the chains. The $^{14}$C counts thereby afford a measure of [HbCO] at concentrations well above or well below those suitable for spectrophotometric determination. The relationship between $^{14}$C radioactivity and [HbCO] is established at concentrations where spectral work is feasible.

$K_{4,2}$ at a given set of conditions is determined in a single experiment. A concentrated batch of double-labeled HbCO is apportioned and diluted to yield approximately 18 samples ranging over four orders of magnitude in [HbCO]. Outexchange kinetics in each sample are followed by the rapid dialysis technique.[5] At several times after initiation of outexchange an aliquot is removed from each sample for scintillation counting to simultaneously determine [HbCO] and Hrem/Fe.

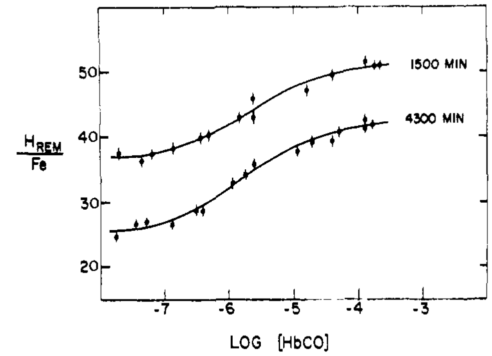

**Figure 1.** Results of a typical experiment: conditions, pH 6.0, 0.1 M phosphate buffer, 15°; vertical axis, amount tritium remaining per chain; horizontal axis, logarithm of the total concentraton of HbCO in moles of tetramer per liter; symbols, Hrem/Fe vs. log [HbCO] at 1500 min (●) and 4300 min (○) after initiation of tritium outexchange; error bars, ±1 SD of Hrem/Fe as calculated from errors in dilutions, scintillation counts, and the $^{14}$C to [HbCO] relationship; solid lines, best fit of data to eq 1 by iterative weighted least-squares analysis; results, at 1500 min, $K_{4,2} = (4.4 \pm 1.2) \times 10^{-6}$, at 4300 min, $K_{4,2} = (3.6 \pm 0.7) \times 10^{-6}$.

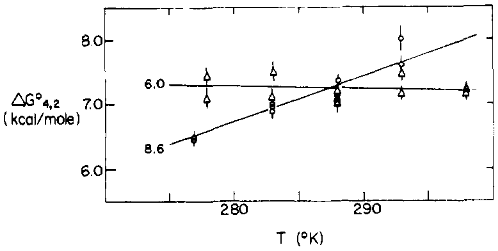

**Figure 2.** Free energy-temperature profile of $K_{4,2}$ as a function of pH: symbols, $\Delta G°_{4,2}$ at pH 6 (△) and 8.6 (○); error bars, ±1 SD of $\Delta G°_{4,2}$; solid lines, weighted least-squares fit to determine enthalpy and entropy of dissociation as $\Delta G°_{4,2} = \Delta H°_{4,2} - T\Delta S°_{4,2}$.

The results of a typical experiment are shown in Figure 1. Experiments at other sets of conditions gave results of equally high quality. The precision of our values of $K_{4,2}$ is about the same as that most recently reported by others,[6] and betters the precision in earlier.[7,8] The accuracy of these values, moreover, is independent of the assumptions needed for data interpretation in gel filtration[9] or in ultracentrifugation studies.[10] In short, measurement of differential tritium exchange, together with the $^{14}$C concentration determination, yields $K_{4,2}$ simply, directly, and precisely.

We have studied the temperature and pH dependence of $K_{4,2}$ for HbCO. The results, displayed as a free energy profile, appear in Figure 2. Weighted least-squares analysis[11] of the data in Figure 2 yields the following thermodynamic quantities: at pH 6, $\Delta H°_{4,2} = 8.2 \pm 1.8$ kcal/mol and $\Delta S°_{4,2} = 4.4 \pm 6.3$ eu; at pH 8.6, $\Delta H°_{4,2} = -13.2 \pm 2.0$ kcal/mol and $\Delta S°_{4,2} = -71.0 \pm 7.1$ eu. These results more than suggest that the liganded or *R* form of hemoglobin has its own measure of conformational lability in response to pH changes. That such should be the case was, in fact, our motivation for undertaking this work. (There had been a report[8] that $\Delta G°_{4,2}$ for HbCO changes substantially with ionic strength but little with pH, findings which to us seemed inconsistent.) The free energy profiles in Figure 2 intersect at about 15° which may indicate that enthalpy-entropy compensation[12] is operative in this system. Regardless, the free energies of dissociation at 20° are not very different which, given the precision of earlier measurements,[8]