former was determined for the diprotonated form of CQ (N-1 and N-3 protonated) while the latter relates to the free base. Electrostatic repulsion between the positive charges would tend to force the CQ molecule into a more open structure with an extended side chain. Interaction with phosphate groups further acts to stabilize the extended form in the cation. On the other hand the unusual buckling of the side chain in solution may arise in part from an intramolecular dipole–induced dipole type of interaction between the N-3 ethyl groups and the π-electron system of the quinoline ring. Such an interaction has its counterpart in the well-known intermolecular dipole–induced dipole interactions between polar aliphatic amides, amines, etc., and various aromatic ring systems. The key factors favoring this type of interaction, namely a polar acceptor and a well-defined π-electron donorr ing, are both present in CQ.

3. Chloroquine Interaction with DNA. Several attempts have been made to relate the conformational features of CQ to its binding interaction with double-stranded DNA. Hahn and O'Brien[34] have recently made the interesting suggestion, based on studies of the effect of CQ on the thermal stability of DNA, that the CQ dication stabilizes the DNA structure by electrostatic interaction between the positive charges on CQ and the phosphate groups on DNA. In this complex the side chain of CQ is visualized as forming a bridge across the minor groove of the double helix. Since the distance across the minor groove, ~10.5 Å, is larger than the maximum possible extended distance between N-2 and N-3, 7.5 Å, and much larger than the distance observed in the crystal, 5.5 Å, a N-2,N-3 complex across the minor groove would appear to be a quite unfavorable possibility. Moreover, the pmr protonation data[33] point to a dication in which positive charges are located at N-1 and N-3 rather than N-2 and N-3. The N-1–N-3 distance in this case is appreciably larger in the crystal, 14.1 Å, and in solution, 6.7 (20°) and 8.1 Å (48°), than N-2–N-3, and a bridging complex would appear to be more favorable. However, the present solution data, though determined for the free base form of CQ, do suggest that the side chain has considerable conformational flexibility and is influenced by a variety of factors including solvent medium, temperature, and pH.

Acknowledgments. The authors wish to acknowledge Dr. Fred E. Hahn for helpful discussions on the properties of antimalarial drugs. We also wish to thank Dr. J. M. Stewart for kindly providing the crystal coordinate data.

[34] R. L. O'Brien and F. E. Hahn, *Antimicrob. Ag. Chemother.*, 315 (1966).

Communications to the Editor

Boat and Chair Transition States of 1,5-Hexadiene[1]

Sir:

The stereospecific Cope rearrangement of acyclic 1,5-dienes continues to attract theoretical interest[2–5] of increasingly more quantitative ambitions.[4,5] Supplementing the previous stereochemical[2] and kinetic[6] investigation, we here report discovery of a second degenerate rearrangement of 1,5-hexadiene—one that requires an additional 5.8 kcal/mol in $\Delta G^{\ddagger}$ (at 250°) but 11.2 kcal/mol more in $\Delta H^{\ddagger}$.[2,6]

To simplify subsequent comparison with theory,[4] we tentatively assign the "boat" stereochemistry to this new, higher energy transition state and accept the "chair" assignment for the lower energy one.[2,6,7] The experimental approach then also becomes more apparent. This begins with the racemic mixture of *ERSZ*[9] and *ESRZ* enantiomers of 1,5-hexadiene-d_4, efficiently obtained by stereospecific cleavage of bicyclo[2.2.0]hexane-*exo*-d_4 at 135–180° (Figure 1).[10] Diene stereointegrity (measured in part by oxidation to the exclusively *meso*-dideuteriosuccinic acid) is retained throughout 22 half-lives[6] of Cope rearrangement at a somewhat higher temperature (233°).

The graphical analysis of Figure 2 then precludes any other structural assignment. It also suggests that leakage into the *ESSE–ERRE–ZSSZ–ZRRZ* quartet might yet be achieved through a "boat" transition state. In practice, identical oxidation of samples recovered at four, still higher temperatures (259–295°) also provided *meso*-dideuteriosuccinic acid but now increasingly contaminated with its racemic diastereomer. The three characteristic pmr areas of the diene remained equal. Fifteen such samples were each oxidized; the derived succinic acid was recrystallized from acetonitrile, accurately weighed ($w \approx 600 \pm 5\ \mu$g), dispersed in KBr, and the racemic content assayed by absorbance (A) at 1215 cm^{-1}.[10,11] An appropriate nonlinear least-squares analysis then provided the best values of either (a) $[(A/w)_\infty - (A/w)_0]$ and λ (eq 1) or (b) $[(A/w)_\infty -$

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[1] Taken in part from the Ph.D. Thesis of M. S. Benzon, Cornell University, Dec 1971.

[2] W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

[3] (a) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4389 (1965); (b) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969); *Angew Chem., Int. Ed. Engl.*, **8**, 781 (1969).

[4] (a) K. Fukui and H. Fujimoto, *Tetrahedron Lett.*, 251 (1966); (b) M. Simonetta, G. Favini, C. Mariani, and P. Gramaccioni, *J. Amer. Chem. Soc.*, **90**, 1280 (1968); (c) A. Brown, M. J. S. Dewar, and W. Schoeller, *ibid.*, **92**, 5517 (1970).

[5] (a) M. J. S. Dewar and W. W. Schoeller, *ibid.*, **93**, 1481 (1971); (b) M. J. S. Dewar, *Fortschr. Chem. Forsch.*, **23**, 1 (1971); (c) M. J. S. Dewar and D. H. Lo, *J. Amer. Chem. Soc.*, **93**, 7201 (1971).

[6] W. von E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971).

[7] Both assumptions are more critically examined in the succeeding communication.[8]

[8] M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 7149 (1972).

[9] E. L. Eliel, *J. Chem. Educ.*, **48**, 163 (1971).

[10] M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 5119 (1972).

[11] C. R. Childs and K. Bloch, *J. Org. Chem.*, **26**, 1630 (1961).

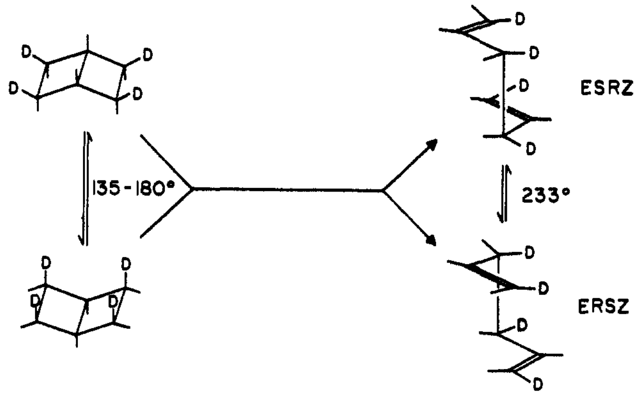

Figure 1. Stereospecific cleavage of bicyclo[2.2.0]hexane (135–180°) and Cope equilibration of 1,5-hexadiene (233°).

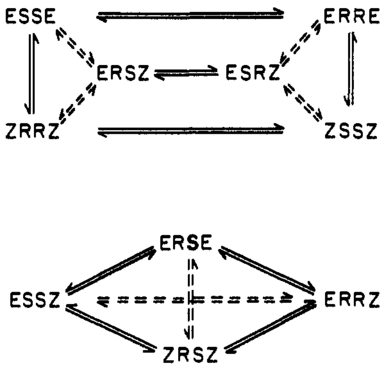

Figure 2. Cope equilibration of the isomeric 1,5-hexadiene-*1,3,4,6*-d_4 through chair ($\rightleftharpoons$) and boat ($\overset{\dashrightarrow}{\dashleftarrow}$) transition states.

$(A/w)_0]$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (eq 1 and 2) which minimized

$$A/w = (A/w)_0 + [(A/w)_\infty - (A/w)_0](1 - e^{-\lambda t}) \quad (1)$$

$$\lambda = (kT/h)e^{-\Delta H^{\ddagger}/RT}e^{-\Delta S^{\ddagger}/R} \quad (2)$$

the sums of squares of deviations in A/w (Table I).

Table I. Comparison of the High and Low Temperature Rearrangements[a]

	Obsd High	Obsd Low[b]
$10^6\lambda(t)$	17.1 ± 2.0 (295.3°) 7.48 ± 0.40 (285.1°) 1.93 ± 0.05 (267.4°) 1.02 ± 0.14 (259.0°)	178 ± 6[c]
$\Delta H^{\ddagger}$	44.7 ± 2.0	33.5 ± 0.5
$\Delta S^{\ddagger}$	−3.0 ± 3.6	−13.8 ± 1.0
$\Delta G^{\ddagger}{}_{523}$	46.3 ± 3.8	40.5 ± 1.0
	Calcd Boat	**Calcd Chair**
$\Delta H^{\ddagger}$	30.2[d] 28.1[e]	23.6[d] 22.8[e]
$\Delta S^{\ddagger}{}_{523}$	−16.9[e]	−16.8[e]

[a] Units are $\sec^{-1}$ for λ; kcal/mol for $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$; cal/(mol deg) for $\Delta S^{\ddagger}$; subscripts are in °K; uncertainties are standard deviations. [b] Reference 6. [c] Reported at 258.2°. [d] Reference 4c, assuming $\Delta H_f{}^{\circ}{}_{298}$(1,5-hexadiene) = 19.8. [e] Reference 4b, assuming $\Delta E = \Delta H_f{}^{\ddagger}{}_{298^{\circ}}$.

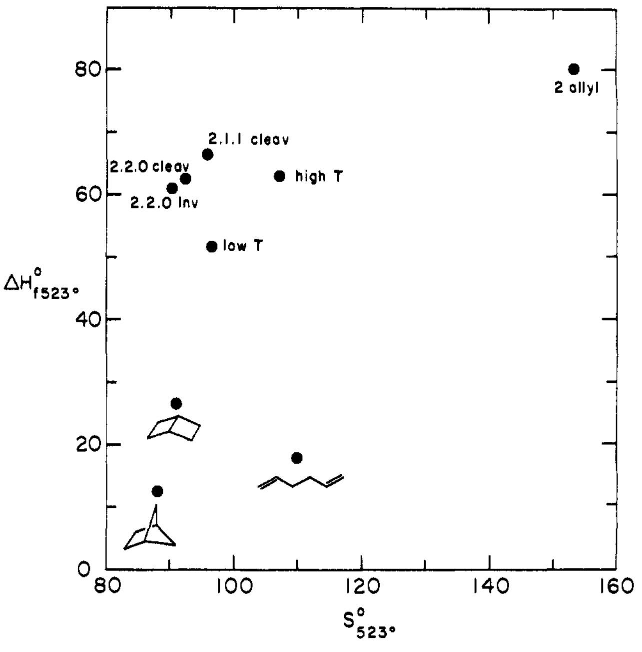

Figure 3. Enthalpies and entropies of isomeric C_6H_{10} substrates, products, and transition states.[14]

The observed difference in $\Delta G^{\ddagger}{}_{523}$ (5.8 kcal/mol) recalls the Doering–Roth experimental estimate ($\Delta\Delta G^{\ddagger} \geqq 5.7$)[2] but also (less appropriately) the theoretically predicted differences between "chair" and "boat": $\Delta\Delta H^{\ddagger} = 5–7$.[4] Such latter estimates must now be regarded as the fortuitous agreement of a naive approach,[4a] of two more sophisticated ones,[4b,c] and, perhaps, of misleading analogy with the boat and chair conformers of cyclohexane.[12,13] The apposite experimental difference is 11.2 ± 2.5. More seriously in error are the theoretically predicted magnitudes of $\Delta H^{\ddagger}$ (Table I).

Figure 3 precludes any confusion of the observed activation parameters with those that would be needed for dissociative recombination.[14] Radical chain processes, the probable source of older erroneous estimates of dissociative requirements,[6] are excluded by the absence of pmr-detectable contaminants.

The stereochemistry of this high-temperature rearrangement is considerably less certain.[7] Should this *not* be the "boat," even at 295°, various experimental considerations would then set the minimal $\Delta G^{\ddagger}{}_{568}$ for that process as >49.0. The predicted $\Delta H^{\ddagger} = 29.1$ would then require that $\Delta S^{\ddagger}$ be <−33—obviously unlikely from Figure 3 and perhaps impossible for any C_6H_{10} unimolecular process.

It thus follows that all currently available theory underestimates the enthalpy needed to achieve both the boat and the chair transition states of the Cope rearrangement—*whether or not such tentative stereochemical assignments be correct.* If they *are* correct, the

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(12) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 8.

(13) Unique in a different sense, the "principle of least motion" fails to detect any difference between "chair" and "boat" transition states: O. S. Tee and K. Yates, *J. Amer. Chem. Soc.*, 94, 3074 (1972).

(14) Estimates of $\Delta H_f{}^{\circ}{}_{298}$ and $\Delta S^{\circ}{}_{298}$ for the three hydrocarbons are from S. W. Benson and H. E. O'Neal, *Nat. Stand. Ref. Data. Ser., Nat. Bur. Stand.*, No. **21**, 328, 331 (1970), and for the allyl radical from D. M. Golden, N. A. Gac, and S. W. Benson, *J. Amer. Chem. Soc.*, **91**, 2136 (1969). Correction to 250° assumes that $C_p{}^{\circ}$ = 36.75, 32.43, and 16.55 cal/(mol deg) for 1,5-hexadiene, each of the two bicyclohexanes, and allyl radical. Bicyclo[2.1.1]hexane activation parameters are from R. Srinivasan and A. A. Levi, *J. Amer. Chem. Soc.*, **85**, 3363 (1963), bicyclo[2.2.0]hexane from ref 10.

errors are 15–17 kcal/mol for the boat and 10–11 kcal/mol for the chair.

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(15) Public Health Service Fellow, National Air Pollution Control Administration, Consumer Protection and Environmental Health Service, 1967–1971.

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The Linear Analysis of Labeling Experiments. An Application to Sigmatropic Rearrangements of 1,5-Hexadiene[1]

Sir:

The increasingly complex labeling studies of pericyclic processes[2] suggest opportunities for a new and more general analysis than has hitherto been customary. Illustratively applied here to the sigmatropic rearrangements[2f] of 1,5-hexadienes, this analysis discovers all ambiguities in previous stereochemical deductions,[3a,4] defines the experiments that might resolve them, and indicates which of these might succeed.

We begin by generating the complete set of nine sigmatropic carbon skeleton rearrangements, first by subjecting the C_{2v} conformer of 1,5-hexadiene to its [3,3] alternatives (Figure 1). Sighting along each axis, first at the front and then from the rear, each rotation is classified as clockwise or counterclockwise.[5] The third mechanism, so generated, is here called "twist" (rather than "antara–antara"[2f,6]), in part because its most symmetric transition state shares D_2 symmetry with the well-known twist conformer of cyclohexane.[7,8] In addition, the (hitherto unrecognized) "plane" transition state is also antara–antara but in an obviously different way.

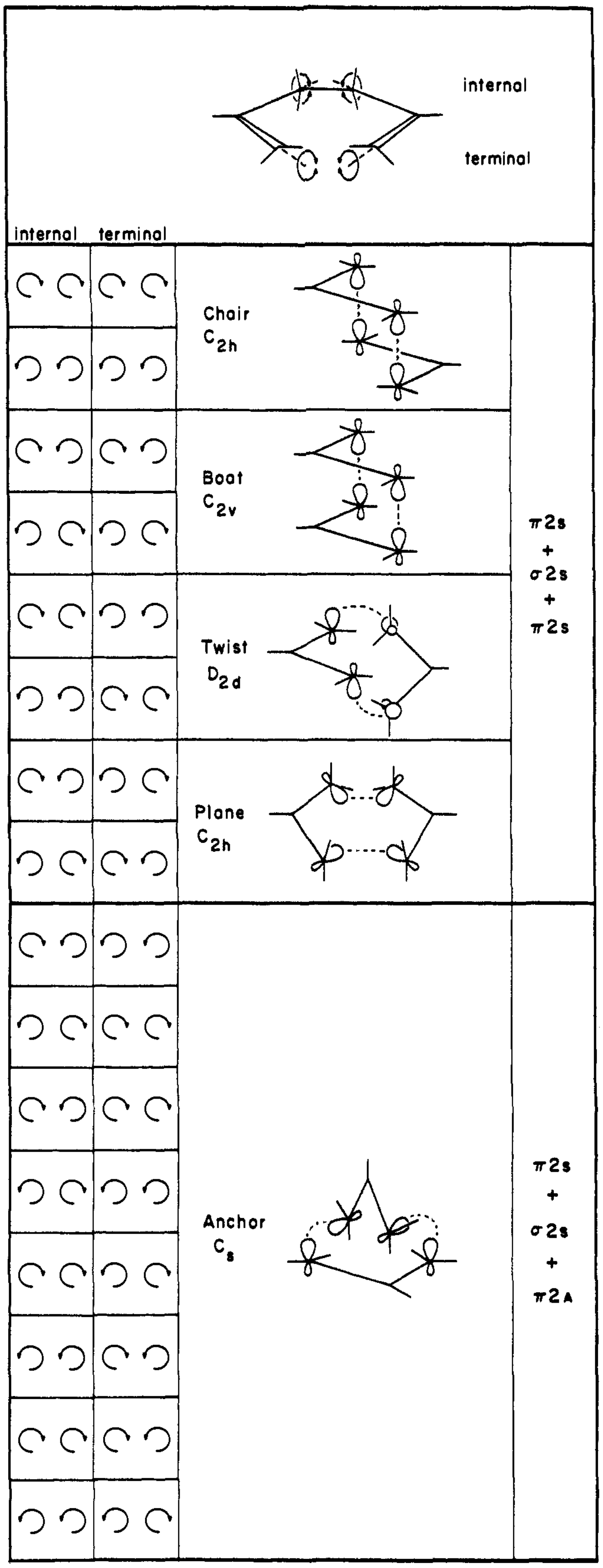

Figure 1. The complete set of [3,3] sigmatropic mechanisms.

All four [1,3] sigmatropic mechanisms (each implicitly fourfold degenerate in Figure 2) have been recognized,[2] if not by such names. These permit each first letter uniquely to label the appropriate mechanistic rate constant—*e.g.*, k_B for rearrangement through a boat transition state.

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(1) Taken, in part, from the Ph.D. Thesis of M. S. Benzon, Cornell University, 1972.

(2) *E.g.*, (a) M. R. Wilcott, III, and C. J. Boriack, *J. Amer. Chem. Soc.*, **93**, 2354 (1971); (b) J. J. Gajewski and L. T. Burka, *ibid.*, **94**, 2554 (1972); (c) W. E. Doering, M. Franck-Neumann, D. Hasselmann, and R. L. Kaye, *ibid.*, **94**, 3833 (1972), and references cited therein; (d) J. E. Baldwin and R. H. Fleming, *J. Amer. Chem. Soc.*, **94**, 2140 (1972), and references cited therein. For reviews, *cf.* (e) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968); (f) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969); *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969); (g) P. D. Bartlett, *Quart. Rev., Chem. Soc.*, **24**, 473 (1970); (h) J. E. Baldwin and R. H. Fleming, *Fortschr. Chem. Forsch.*, **15**, 281 (1970); (i) J. J. Gajewski, *Mech. Mol. Migr.*, **4**, 1 (1972); (j) M. R. Wilcott, R. L. Cargill, and A. B. Sears, *Progr. Phys. Org. Chem.*, **9**, 25 (1972).

(3) (a) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962); (b) W. von E. Doering, V. G. Toscano, and G. H. Beasley, *ibid.*, **27**, 5299 (1971).

(4) M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 7147 (1972) (preceding communication).

(5) *Cf.* R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965), and ref 2f.

(6) (a) T. Miyashi, M. Nitta and T. Mukai *J. Amer. Chem. Soc.*, **93**, 3441 (1971); (b) J. E. Baldwin and M. S. Kaplan, *ibid.*, **94**, 1794 (1972), and references cited therein.

(7) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966, p 76; J. D. Dunitz, *J. Chem. Educ.*, **47**, 488 (1970).

(8) The possibility of less symmetric transition states is not precluded.