agreement with previous work.[8] However, the gas–solid reaction gave, after 30% conversion, a dichloride of which the nmr spectrum showed the *dl* but no detectable amount of the meso isomer.[9] Production exclusively of the *dl* isomer could result from the rigid environment which may constrain both chlorines to attack the double bond from the same side. Gas–solid reactions may have utility in increasing stereoselectivity in cases of this kind.

Acknowledgment. This research was supported by the Advanced Research Projects Agency.

(8) R. E. Buckles and D. F. Knaack, *J. Org. Chem.*, **25**, 20 (1960).

(9) The reaction of *trans*-stilbene is complicated by the appearance of a coating of what seems to be melt in a thin layer on the upper surface. This hardens as reaction proceeds from the sides of the crystal and no general melting occurs. Inspection of the crystal structure of *trans*-stilbene [J. M. Robertson and I. Woodward, *Proc. Roy. Soc.* (*London*), *Ser. A*, **162**, 568 (1937)] shows the molecules to be oriented much more nearly parallel to the most developed (001) face of the crystal. The best planes of the two nonequivalent molecules of *trans*-stilbene are inclined 41 and 43° to that face, whereas the average angle of the two CC(—O)=O planes with the major crystal face is 90° for the *p*-bromo anhydride and 71° for the *p*-chloro anhydride.

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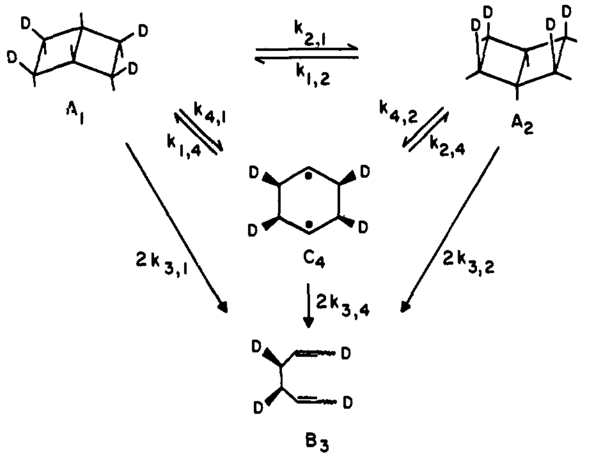
Inversion and Stereospecific Cleavage of Bicyclo[2.2.0]hexane[1]

Sir:

With few exceptions, the kinetic analysis of small hydrocarbon ring pyrolyses has either assumed or else deduced the intercession of a steady-state intermediate—the singlet biradical.[2–4] The relevant stereochemical facts are considerably more varied.[5]

We here report: (a) the discovery of the thermal inversion of bicyclo[2.2.0]-*exo-2,3,5,6-d*$_4$ ($A_1 \rightarrow A_2$, Figure 1),[6] (b) an unbiased kinetic analysis of competition between this process and cleavage to 1,5-hexadiene-*1,3,4,6-d*$_4$, and (c) the deduction of exclusively[7] stereospecific cleavage, fully in accord with predictions based upon naive considerations of orbital symmetry.[8]

A_1 was prepared by an obvious variant of the van Tamelen synthesis[9] and its stereochemical assignment verified by pmr.[10] Two experimental first-order rate constants—those of cleavage (λ_{cle}) and of inversion plus cleavage (λ_{i+c})—were obtained at each of five temperatures by minimizing the sums of squares of the deviations (between calculated and observed areas) in five characteristic regions of the pmr spectra.[11] Concordant, but independently fitted values of the corresponding pairs of activation parameters (19 samples, t = 135–180°, $P \approx 450$ Torr) are listed in column 1 of Table I.[12,13] The pmr spectra of reactant–product mixtures were indistinguishable[7] from the superposition of those of their gc-purified components. Activation parameters for cleavage agree with the original report (footnote *d*, Table I); rate constants are trivially lower.



$$\lambda_{\text{cle}} = k_{4,1}(1-f_{\text{ret}}) + 2k_{3,1}$$

$$\lambda_{i+c} = k_{4,1} + 2k_{3,1} + 2k_{2,1}$$

$$f_{\text{ret}} = k_{1,4}/(k_{1,4}+k_{3,4})$$

Figure 1. Competitive cleavage and inversion of bicyclo[2.2.0]-hexane-*d*$_4$.

In order to avoid mechanistic bias, Figure 1 includes both the concerted and the biradical options. The detailed structure of the biradical (C_4) is not specified beyond its all-cis deuterium assignment. No doubt but that only the subtlest structural changes distinguish it from the transition states of the two alternative concerted processes of mechanistic rate constants $k_{2,1}$ and $k_{3,1}$. A reader who prefers the biradical option need only set $k_{21} = k_{31} = 0$ and consider column 2 of Table I.

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(1) Taken in part from the Ph.D. Thesis of M.S. Benzon, Cornell University, 1971.

(2) The most notable exceptions are pyrolyses of sterically unencumbered cyclobutenes.[3]

(3) For exhaustive reviews, *cf.* (a) H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969); (b) S. W. Benson and H. E. O'Neal, *Nat. Stand. Ref. Data Ser., Nat. Bur. Stand.*, No. **21**, 14 (1970); (c) H. E. O'Neal and S. W. Benson, *Int. J. Chem. Kinet.*, **2**, 423 (1970).

(4) Typical examples are provided by L. K. Montgomery, K. Schueller, and P. D. Bartlett, *J. Amer. Chem. Soc.*, **86**, 622 (1964); R. G. Bergman and W. L. Carter *ibid.*, **91**, 7411 (1969).

(5) (a) P. D. Bartlett, *Pure Appl. Chem.*, **27**, 597 (1971), and references cited therein; (b) H. R. Gerberich and W. D. Walters, *J. Amer. Chem. Soc.*, **83**, 3935, 4884 (1961); (c) G. L. Closs and P. E. Pfeffer, *ibid.*, **90**, 2452 (1968); (d) J. E. Baldwin and P. W. Ford, *ibid.*, **91**, 7192 (1969); (e) A. T. Cocks, H. M. Frey, and I. D. R. Stevens, *Chem. Commun.*, 458 (1969); (f) L. A. Paquette and J. A. Schwartz, *J. Amer. Chem. Soc.*, **92**, 3215 (1970); (g) J. A. Berson, W. Bauer, and M. M. Campbell, *ibid.*, **92**, 7515 (1970); (h) L. A. Paquette and G. L. Thompson, *ibid.*, **93**, 4920 (1971).

(6) Inversion of methylbicyclo[2.1.0]pentanes is long known: M. J. Halberstadt and J. P. Chesick, *ibid.*, **84**, 2688 (1962); J. P. Chesick, *ibid.*, **84**, 3250 (1962).

(7) Except where stated otherwise, such terms denote agreement between observed and anticipated values to within <2%.

(8) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969); *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(9) E. E. van Tamelen, S. P. Pappas, and K. L. Kirk, *J. Amer. Chem. Soc.*, **92**, 6092 (1971); R. N. McDonald and C. E. Reinecke, *J. Org. Chem.*, **32**, 1878 (1967).

(10) The overlapping multiplets of the undeuterated hydrocarbon simplify to a broadened singlet (τ 7.22) and a sharp doublet (τ 7.95, $J \sim 1$ Hz) in the expected 1:2 ratio; *cf.* S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 2870 (1963); R. Steinmetz, W. Hartmann, and G. O. Schenck, *Chem. Ber.*, **98**, 3854 (1965); K. B. Wiberg and D. E. Barth, *J. Amer. Chem. Soc.*, **91**, 5124 (1969), and references cited therein.

(11) τ 3.83–4.50 (C-2,5 of diene), 4.75–5.21 (C-1,6 of diene), 6.98–7.35 (C-1,4 of bicyclohexane), 7.35–7.70 (exo C-2,3,5,6 of bicyclohexane), 7.70–8.16 (endo C-2,3,5,6 of bicyclohexane + C-3,4 of diene).

(12) Copies of the algebraic analysis, experimental data, graphical summaries, and the FORTRAN program were made available to the editor and referees of this paper.

(13) For previous reports of bicyclo[2.2.0]hexane cleavage kinetics, *cf.* (a) C. Steel, R. Zand, P. Hurwitz, and S. G. Cohen, *J. Amer. Chem. Soc.*, **86**, 679 (1964); (b) R. Srinivasan, *Int. J. Chem. Kinet.*, **1**, 133 (1969); for those of substituted derivatives *cf.* (c) E. N. Cain, *Tetrahedron Lett.*, 1865 (1971); (d) E. N. Cain and R. K. Solly, *Int. J. Chem. Kinetic.*, **4**, 159 (1972).

Table I. Experimental and Mechanistic Activation Parameters[a]

Experimental		Mechanistic			
		Biradical[b]		Concerted[c]	
$\Delta H^{\ddagger}_{\text{i+c}}$	35.0 ±0.3	$\Delta H^{\ddagger}_{4,1}$	35.0 ±0.3	$\Delta H^{\ddagger}_{2,1}$	34.4 ±1.3
$\Delta H^{\ddagger}_{\text{cle}}$	36.0[d] ±0.3	$(\Delta H^{\ddagger}_{1,4} - \Delta H^{\ddagger}_{3,4})$	1.58 ±1.03	$\Delta H^{\ddagger}_{3,1}$	36.0 ±0.3
$\Delta S^{\ddagger}_{\text{i+c}}$	1.4 ±0.7	$\Delta S^{\ddagger}_{4,1}$	1.4 ±0.7	$\Delta S^{\ddagger}_{2,1}$	−0.7 ±1.6
$\Delta S^{\ddagger}_{\text{cle}}$	1.5[d] ±0.6	$(\Delta S^{\ddagger}_{1,4} - \Delta S^{\ddagger}_{3,4})$	−2.2 ±1.5	$\Delta S^{\ddagger}_{3,1}$	1.5 ±0.6

[a] Here and elsewhere: units are kcal/mol and cal/(mol deg); uncertainties are standard deviations; kinetic isotope effects are ignored in deriving mechanistic parameters; X_{ij} denotes a reaction parameter for the transformation of *j* to *i*. [b] Assuming that $k_{2,1} = k_{3,1} = 0$: $\Delta H^{\ddagger}_{4,1} = \Delta H^{\ddagger}_{\text{i+c}}$; $\Delta S^{\ddagger}_{4,1} = \Delta S^{\ddagger}_{\text{i+c}}$; $(\Delta H^{\ddagger}_{1,4} - \Delta H^{\ddagger}_{3,4}) = (\Delta H^{\ddagger}_{\text{i+c}} - \Delta H^{\ddagger}_{\text{cle}})/f_R$; $(\Delta S^{\ddagger}_{1,4} - \Delta S^{\ddagger}_{3,4}) = (\Delta S^{\ddagger}_{\text{i+c}} - \Delta S^{\ddagger}_{\text{cle}})/f_R + R \ln f_R + [(1 - f_R)/f_R]R \ln (1 - f_R)$. [c] Assuming that $k_{4,1} = 0$: $\Delta H^{\ddagger}_{3,1} = \Delta H^{\ddagger}_{\text{cle}}$; $\Delta S^{\ddagger}_{3,1} = \Delta S^{\ddagger}_{\text{cle}}$; $\Delta H^{\ddagger}_{2,1} = \Delta H^{\ddagger}_{\text{cle}} + \beta(\Delta H^{\ddagger}_{\text{i+c}} - \Delta H^{\ddagger}_{\text{cle}})$; $\Delta S^{\ddagger}_{2,1} = \Delta S^{\ddagger}_{\text{cle}} + \beta(\Delta S^{\ddagger}_{\text{i+c}} - \Delta S^{\ddagger}_{\text{cle}}) - \beta R \ln \beta$, where $\beta = \lambda_{\text{i+c}}/(\lambda_{\text{i+c}} - \lambda_{\text{cle}})$. [d] These correspond to $E_a = 36.8 \pm 0.3$, $10^{-13}A = 5.3 \pm 1.7$ (lit. values:[13a] $E_a = 36.1 \pm 1.0$, $10^{-13}A = 2.5 \pm 1.9$).

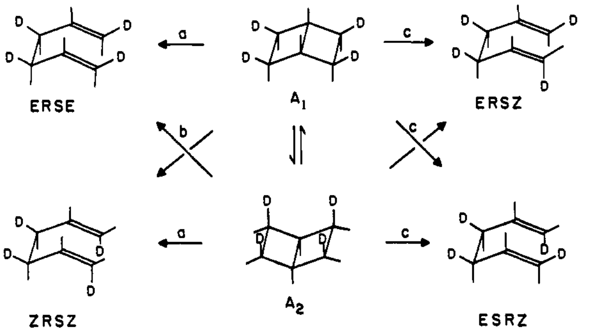

Figure 2. Three distinguishable reaction mechanisms. If regarded as four-electron processes, a and b are $_{\sigma}2_s + _{\sigma}2_s$; c is $_{\sigma}2_s + _{\sigma}2_a$. Six-electron variants will be discussed in the full paper.

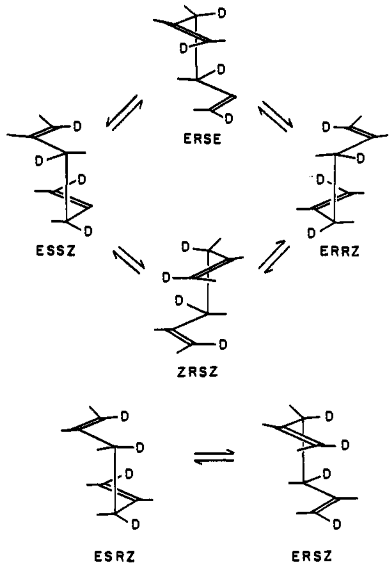

Figure 3. Isomerization of hexa-1,5-dienes-d_4 *via* chair transition states of the Cope rearrangement.

To select the concerted alternative, he sets $k_{4,1} = 0$ and reads column 3.[14] Whichever the option, the magnitudes of pseudothermodynamic parameters of two different transition states (those of $k_{4,1}$ and $k_{3,4}$ *or* of $k_{2,1}$ and $k_{3,1}$) are found to differ negligibly, if at all. Initially a surprise, this observation is fully consistent with expectations based upon recent theoretical analyses of closely related potential energy surfaces.[15]

Figure 2 shows that the different stereochemical consequences of three distinguishable reaction mechanisms remain unaffected by the inversion process. In order to choose among them, samples of isolated 1,5-hexadiene-d_4 were heated at 233° for 48 hr (22 half-lives of a Cope rearrangement).[16] The areas of the three characteristic pmr regions remained equal;[7] permanganate–periodate oxidation[17] provided exclusively *meso*-dideuteriosuccinic acid,[18] both before *and after* such treatment. These results, the assumption that Cope rearrangement proceeds through a "chair" transition state,[19] and Figure 3 then require that the product(s) be the *ERSZ–ESRZ* enantiomers.

A second, independent structure proof is logically less rigorous but quantitatively more precise. The pmr spectral parameters of a hypothetical allyl fragment, first obtained by fitting the olefinic spectral region of undeuterated hexa-1,5-diene,[20] were used to generate the predicted spectra of pure (1*Z*)- and (1*E*)-allyl-*1,3*-d_2 fragments.[21] The relative areas of the three terminal vinyl peaks (Table II) necessarily require equal numbers of *Z* and *E* protons at C-1 and C-6.[7]

Further, both the Cope rearrangement of 1,5-hexadiene[16] and the cleavage of bicyclo[2.1.1]hexane[22] are negligibly slow between 135 and 180°. The first observation identifies the stereospecificity observed as indeed that of the cleavage reaction; the second precludes intercession by the only otherwise credible isomeric intermediate.[23]

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(14) In this case, an unbiased kinetic analysis precludes the use of such data in favor of either option. In other circumstances, a similar analysis can facilitate such a choice; *cf.* M. J. Goldstein and H. A. Judson, *J. Amer. Chem. Soc.*, **92**, 4119, 4120 (1970).

(15) Summarized by L. Salem and C. Rowland, *Angew. Chem.*, **84**, 86, (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972).

(16) W. von E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971). We are grateful to Professor Doering for making these results available to us prior to publication.

(17) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(18) C. R. Childs and K. Bloch, *J. Org. Chem.*, **26**, 1630 (1961). Reliance upon ir spectrometry renders this conclusion less precise than any other. Contamination by as much as 5–7% of the racemic acid would have been undetected.

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

(20) A. A. Bothner-By and S. Castellano, LAOCN3, Vol. 7, Quantum Chemistry Program Exchange, Indiana University, 1971, Program 111.

(21) J. D. Swalen, NMRPLOT, adapted to local conditions.

(22) R. Srinivasan and A. A. Levi, *J. Amer. Chem. Soc.*, **85**, 3363 (1963).

(23) A related stereochemical study of dicarbomethoxybicyclo[2.2.0]-hexane cleavage[5f] explicitly recognized (but made no attempt to rem-

Table II. Integrated Areas of Terminal Vinyl Protons[a]

	Peak maxima at τ		
	4.87 ppm	4.97 ppm	5.14 ppm
Calcd[b]			
(1*Z*)-Allyl-*3*-d_2		0.597	0.403
(1*E*)-Allyl-*3*-d_2	0.674		0.326
1:1 mixture	0.337	0.298	0.365
Obsd[c]			
135°	0.327 ±0.006	0.303 ±0.002	0.370 ±0.006
160°	0.326 ±0.002	0.297 ±0.002	0.377 ±0.002
180°	0.331 ±0.004	0.306 ±0.005	0.364 ±0.004

[a] Normalized to one proton. [b] Consistent results are obtained by analysis as the B part of an ABX spectrum; *cf.* J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 132. [c] Samples obtained at temperatures indicated. Each entry is the mean and standard deviation of six–eight 60-MHz scans.

Although this is now the third report of essentially stereospecific $_\sigma 2_A + {}_\sigma 2_S$ cleavage of a cyclobutane[24] (if also the first to include associated kinetics and activation parameters), it is apparent that failure to observe such stereospecificity is much more common.[5a,b,d–f,h] The possible origins of such diversity will need be discussed elsewhere.

Acknowledgment. We are grateful to Professor E. L. Eliel for suggestions regarding stereochemical nomenclature and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (GP 15863) for partial financial assistance.

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edy) its inability to disentangle cleavage specificity from that of subsequent Cope rearrangement. Isomeric intermediates were not considered. Neither was extensive mechanistic deduction thereby inhibited.

(24) The qualification of apparently incomplete stereospecificity (93–95%,[5c] *ca.* 90%[5g]) is, we suggest, more economically rationalized in footnote 15 of ref 5g than it is in the text above it.

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

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Synthesis and Proton Magnetic Resonance Spectrum of a Selectively Deuterated Dinucleoside Monophosphate, Adenylyl-(3′–5′)-adenosine

Sir:

Proton magnetic resonance studies have yielded much valuable information about key conformational features such as the syn–anti orientation of base and ribose rings,[1] the furanose ring conformations,[2] and the orientation of exocyclic groups[3] in a wide variety of monomeric nucleic acid constituents. It is of considerable importance to extend such detailed studies to higher oligonucleotides in order to establish the influence of chain length upon the nucleotide conformation. Although a number of initial studies along this line have been reported for selected dinucleotides,[4] the full usefulness of nmr measurements in this direction is hampered by extensive overlapping of signals that prevents complete assignments of the spectra, even at the highest operating frequencies currently available. An approach which in principle can circumvent this difficulty involves the synthesis of oligonucleotides in which one (or more) of the nucleotides is replaced by its fully deuterated analog. We have recently developed such an approach, and report the results for the dinucleoside monophosphate adenylyl-(3′–5′)-adenosine, ApA, in this communication.

An illustration of the complete 220-MHz proton spectrum for the protio form of ApA is given in Figure 1a. Assignments of the base-ring (H-2 and H-8) and ribose H-1′ signals reported in extensive earlier studies[4b,5] are essentially indirect in that they are based in part on assumed conformational models for ApA and upon results of measurements on similar model compounds. No direct assignment of the remaining ribose ring proton signals has been reported.

Figure 1b shows the spectrum for 2,1′,2′,3′,4′,5′,5′-heptadeuterioadenylyl-(3′–5′)-adenosine, *ApA, an adenine dinucleoside monophosphate in which all of the 3′ nucleotide (*Ap–) protons (except H-8) are replaced by deuterium atoms. *ApA was synthesized by condensing 2,1′,2′,3′,4′,5′,5′-heptadeuterio-$N,O^{2'},O^{5'}$-tribenzoyladenosine 3′-phosphate[6] with $N,N',O^{2'},O^{3'}$-tetrabenzoyladenosine[7] in the presence of dicyclohexylcarbodiimide. The *ApA was purified by paper and DEAE–cellulose chromatography and the final product was identical chromatographically with a known standard ApA sample. The 2,1′,2′,3′,4′,5′,5′-heptadeuterioadenosine 3′-monophosphate used in the synthesis was isolated by the following procedures. Ribonucleic acid extracts from fully deuterated blue-green algae,[8] *Synechococcus lividus*, were hydrolyzed in alkaline solution yielding 2′,3′ mixtures of all four major ribomononucleotides. The individual 2′,3′ pairs were in turn separated by ion exchange chromatography[9] and the deuterated 3′-AMP was then separated from the 2′ isomer by paper chromatography.

A comparison of the spectra in Figures 1a and 1b permits a straightforward and direct assignment of H-2 and ribose ring proton signals to the individual

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(1) (a) M. P. Schweizer, A. D. Broom, P. O. P. Ts'o, and D. P. Hollis, *J. Amer. Chem. Soc.*, **90**, 1042 (1968); (b) S. S. Danyluk and F. E. Hruska, *Biochemistry*, 7, 1038 (1968); (c) M. P. Schweizer, J. T. Witkowski, and R. K. Robins, *J. Amer. Chem. Soc.*, **93**, 277 (1971); (d) P. A. Hart and J. P. Davis, *ibid.*, **91**, 512 (1969).

(2) (a) M. Smith and C. D. Jardetzky, *J. Mol. Spectrosc.*, **28**, 70 (1968); (b) J. H. Prestegard and S. I. Chan, *J. Amer. Chem. Soc.*, **91**, 2843 (1969); (c) F. E. Hruska, A. A. Grey, and I. C. P. Smith, *ibid.*, **92**, 214 (1970).

(3) (a) T. Schleich, B. J. Blackburn, R. D. Lapper, and I. C. P. Smith, *Biochemistry*, **11**, 137 (1972); (b) F. E. Hruska, A. A. Grey, and I. C. P. Smith, *J. Amer. Chem. Soc.*, **92**, 4088 (1970); (c) B. J. Blackburn, A. A. Grey, I. C. P. Smith, and F. E. Hruska, *Can. J. Chem.*, **48**, 2866 (1970).

(4) (a) F. E. Hruska and S. S. Danyluk, *J. Amer. Chem. Soc.*, **90**, 3266 (1968); (b) S. I. Chan and J. H. Nelson, *ibid.*, **91**, 168 (1969); (c) N. S. Kondo, H. M. Holmes, L. M. Stempel, and P. O. P. Ts'o, *Biochemistry*, **9**, 3479 (1970), and references cited therein.

(5) (a) F. E. Hruska and S. S. Danyluk, *Biochim. Biophys. Acta*, **157**, 238 (1968); (b) P. O. P. Ts'o, N. S. Kondo, M. P. Schweizer, and D. P. Hollis, *Biochemistry*, **8**, 997 (1969).

(6) Y. Lapidot and H. G. Khorana, *J. Amer. Chem. Soc.*, **85**, 3857 (1963).

(7) R. Lohrmann and H. G. Khorana, *J. Amer. Chem. Soc.*, **86**, 4188 (1964).

(8) The deuterated algae were kindly supplied by Drs. H. L. Crespi and J. J. Katz.

(9) F. R. Blattner and H. P. Erickson, *Anal. Biochem.*, **18**, 220 (1967).