conditions applied. As seen from the table, **9** and **10**, which are susceptible to self-condensation under basic conditions, gave DL-threonine and β-hydroxy DL-leucine in good yield, even under these mild reaction conditions.

Detailed investigations of this reaction and those with complexes composed of other metal species and the application of these complexes to the synthesis of polyhydroxy amino acids and related compounds are now in progress in our laboratory.

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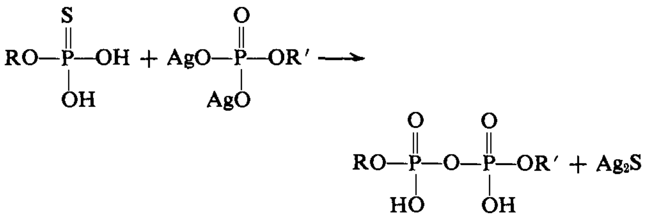
Synthesis of Nucleotide Coenzymes *via* Nucleoside 5′-Phosphorothioate Intermediates

Sir:

Unsymmetrical diesters of pyrophosphoric acid, to which class the nucleotide coenzymes belong, have been synthesized *via* nucleoside phosphoromorpholidates,[1] phosphoroimidazolidates,[2] phosphorochloridates,[3] diphenylphosphoric anhydrides,[4] and *S*-ethyl phosphorothioates.[5] We now wish to report a synthesis of nucleotide coenzymes *via* nucleoside 5′-phosphorothioate intermediates as shown in the following equation.



$$\mathrm{RO{-}\overset{\overset{\Large S}{\|}}{\underset{OH}{\underset{|}{P}}}{-}OH} + \mathrm{AgO{-}\overset{\overset{\Large O}{\|}}{\underset{AgO}{\underset{|}{P}}}{-}OR'} \longrightarrow \mathrm{RO{-}\overset{\overset{\Large O}{\|}}{\underset{HO}{\underset{|}{P}}}{-}O{-}\overset{\overset{\Large O}{\|}}{\underset{OH}{\underset{|}{P}}}{-}OR'} + \mathrm{Ag_2S}$$

R = nucleoside residue
R′ = nucleoside or sugar residue

When 1 equiv of the bis[tri-*n*-butyl]ammonium salt of 2′,3′-*O*-dibenzoyluridine 5′-phosphorothioate[6] was treated with 1.2 equiv of the disilver salt of α-D-glucose 1-phosphate in dry pyridine at room temperature for 5 hr, uridine diphosphoglucose (UDPG) [$\lambda_{\max}^{\mathrm{H_2O}}$ 262 mμ (ε 10,000)] was isolated in 70% yield as the dilithium salt after removal of protecting group.

According to this method, uridine diphosphogalactose (UDPGal) [$\lambda_{\max}^{\mathrm{H_2O}}$ 262mμ (ε 10,000)], flavin adenine dinucleotide (FAD) [$\lambda_{\max}^{\mathrm{H_2O}}$ 264, 375, 450 mμ; $\lambda_{260}/\lambda_{375} = 4.00$; $\lambda_{375}/\lambda_{450} = 0.95$; $\lambda_{260}/\lambda_{450} = 3.80$], P^1-*p*-nitrophenyl P^2-uridine 5′-pyrophosphate [$\lambda_{\max}^{\mathrm{H_2O}}$ 267 mμ (ε 14,000)], P^1-*p*-nitrophenyl P^2-adenosine 5′-pyrophosphate [$\lambda_{\max}^{\mathrm{H_2O}}$ 262 mμ (ε 18,400)], and P^1-*n*-butyl P^2-adenosine 5′-pyrophosphate [$\lambda_{\max}^{\mathrm{H_2O}}$ 260 mμ (ε 15,400)] were obtained in 63, 51, 86, 54, and 61% yields, respectively. The structures were confirmed by paper electrophoresis, paper chromatograms, and ultraviolet spectra, and by detection of the corresponding nucleotides on hydrolysis.

It is noted that this method has three advantageous points, namely: (1) no symmetrical diester of pyrophosphoric acid was detected when only 1.2 equiv of disilver salt of nucleotide was treated with 1 equiv of nucleoside 5′-phosphorothioate; (2) satisfactory yields of nucleotide coenzymes and their analogs are maintained even when the relatively insoluble disilver salts of nucleotides, such as flavin mononucleotide (FMN), are empolyed; (3) these coenzymes and their analogs can be prepared on a relatively large scale by conventional organic techniques.

A complete report of these results will be published later.

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[6] (a) F. Eckstein, *ibid.*, **88**, 4292 (1966). (b) Uridine 5′-phosphorothioate was first prepared by Eckstein[6a] by way of thiophosphorylation using triimidazolyl-1-phosphine sulfide. In this experiment, the nucleoside 5′-phosphorothioates were conveniently prepared in high yields (73–89%) from nucleosides and thiophosphoryl chloride by modification of Murray's method.[7]

[7] A. W. Murray and M. R. Atkinson, *Biochemistry*, **7**, 4023 (1968).

MINDO/2 Study of the Cope Rearrangement

Sir:

As Doering and Roth[1] first pointed out, the Cope rearrangement of biallyl (I) can take place by either of two geometrically distinct reaction paths, the corresponding transition states II and III being analogous to the chair and boat forms of cyclohexane. The reaction is of considerable topical interest since, whereas both processes are "allowed" in terms of arguments based on the conservation of orbital symmetry,[2,3] that proceeding *via* II should be favored in terms of the treatment of electrocyclic reactions based on aromaticity of the transition state,[5] for the interaction between the AO's of the "para" carbon atoms, a and b, in III is predicted to be antibonding. The course of the reaction indicates[1] that the transition state does indeed have the "chair" geometry II.

Recent work[6] in these laboratories has led to the

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

[2] H. C. Longuet-Higgins and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **87**, 2045 (1965); R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 2046 (1965).

[3] In a recent review,[4] Woodward and Hoffmann tried to account for the differences in energy between II and III in terms of orbital correlations during hypothetical dimerizations of two allyl radicals. This rather forced explanation is open to several obvious criticisms; in any case, it is clear that no simple interpretation is possible in terms of orbital correlations during the rearrangement of I.

[4] R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

[5] M. J. S. Dewar, *Tetrahedron, Suppl.*, **8** (1), 75 (1966); article in "Aromaticity," Special Publication No. 21, The Chemical Society, London, 1967, p 177; "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 335.

[6] (a) M. J. S. Dewar and E. Haselbach, *J. Amer. Chem. Soc.*, **92**, 590 (1970); (b) N. Bodor, M. J. S. Dewar, A. Harget, and E. Haselbach, *ibid.*, **92**, 3854 (1970); (c) M. J. S. Dewar, A. Harget, and E. Haselbach, *ibid.*, **91**, 7521 (1969).

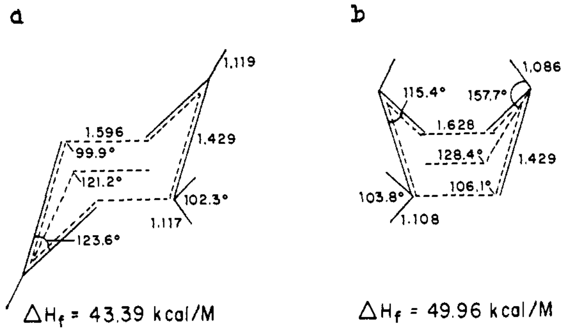
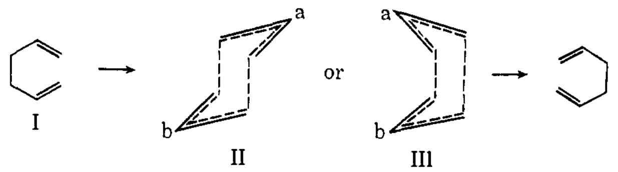


Figure 1. Calculated geometries (bond lengths in Å, angles in deg) and heats of formation (ΔH_f, kcal/mol) for (a) II and (b) III.

development of a semiempirical SCF MO treatment (MINDO/2) which gives good estimates of heats of atomization and other ground-state properties of molecules and which has also been shown to give satisfactory predictions of potential surfaces for a number of reactions of hydrocarbons. Here we report its application to the Cope rearrangement of I. It was assumed that the transition state has a symmetrical structure, II or III, with, respectively, C_{2h} or C_{2v} symmetry. The energies of I, II, and III were minimized with respect to variation of all the bond lengths and bond angles, using a computer program which will be described in detail elsewhere; approximately 200 configurations had to be calculated for each structure. The parameters used in the MINDO/2 treatment were those of ref 6b.



The calculated geometries and heats of formation of the two transition states are shown in Figure 1. It will be seen that II is correctly predicted to have the lower energy. The calculated difference in energy between the two transition states is 6.6 kcal/mol; the experimental evidence indicates the difference in the case of the 3,4-dimethyl derivative of I to be greater than 5.7 kcal/mol.[1] The calculated activation energy (24 kcal/mol) is less than that observed (35.5 kcal/mol[7]); the MINDO/2 method is known to overestimate the stability of six-membered rings by 5–10 kcal/mol, and the same might be expected to hold for each of the cyclic transition states II and III.

Note that whereas the central hydrogen atoms of each allyl moiety in Figure 1a are coplanar with the carbon atoms, those in Figure 1b are tilted out of the planes toward one another. This might be expected if the interaction between the corresponding carbon 2p AO's is antibonding, for the effect will be to replace the 2p AO's by hybrids with less mutual overlap. A similar situation accounts for the transition from linear to bent geometries in triatomic molecules with more than 16 valence electrons,[8] and for the nonlinear geometry of the $\pi-\pi^*$ excited state of acetylene.[9]

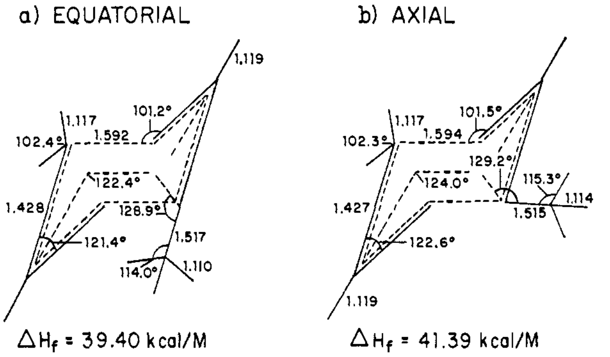


Figure 2. Bond lengths (Å), angles (deg), and heats of formation (ΔH_f, kcal/mol) for (a) "equatorial" and (b) "axial" methyl derivatives of II.

In a recent study[10] of interactions between isolated lone-pair AO's or π MO's, it was shown that the origin of the observed couplings could be established by seeing what happened when the corresponding matrix elements were omitted in a MINDO/2 treatment. When the F_{ab} elements in II and III were omitted, the energy difference between II and III indeed vanished; moreover the central allylic hydrogen atoms in III now reverted to the corresponding C–C–C planes. This entirely confirms the interpretation of the course of the reaction in terms of Evans' principle.[5]

A final calculation was concerned with the effect of "axial" or "equatorial" substituents on the stability of the favored "chair" transition state II. Figure 2 shows calculated geometries and heats of formation for the corresponding methyl isomers; it will be seen that the equatorial isomer is predicted to be the more stable by 2.0 kcal/mol, in excellent agreement with experiment (1.5 kcal/mol[11]). The difference is incidentally very close to the observed difference in heat of formation between the equatorial and axial conformers of methylcyclohexane (1.9 kcal/mol[12]).

The calculations reported here took approximately 5 hr of computer time on a CDC 6600; the experimental studies[1,9] needed to establish the course of the reaction must have cost much more than this. Since the system studied here is quite a complicated one, since the MINDO/2 method has proved effective in a number of other connections, and since the method is certainly capable of further refinement, it seems likely that it will prove of practical value as an aid in the elucidation of reaction mechanisms.

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