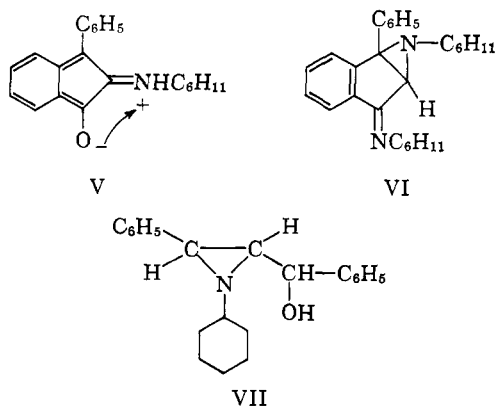


The ultraviolet spectrum of IIIa exhibits maxima at 265 m μ (ϵ 57,600) and 525 (13,900); the latter undoubtedly is responsible for the dark purple color. We suggest that this latter maximum is associated with the considerable electron delocalization implied by forms such as V,⁴ which involves electron mobility between the oxygen and nitrogen atoms implied by the arrow in V.



Treatment of IIIa with concentrated sulfuric acid at 0° and then addition of the brown solution thus formed to water at 70° resulted in hydrolysis of the cyclohexylamino group and precipitation of 3-phenylindandione (IIIb) in 84.5% yield, m.p. 145–147°, $\nu_{\text{OH}}^{\text{CCl}_4}$ 3500 cm.⁻¹, $\nu_{\text{C=O}}^{\text{CCl}_4}$ 1725 cm.⁻¹, $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 252 m μ (ϵ 32,000), and $\delta_{\text{OH}}^{\text{DMSO}}$ 10.6 p.p.m. The diketone was identical in all respects with an authentic sample prepared by the method of Koelsch.⁵

An independent synthesis of IIIa was undertaken involving the addition of cyclohexylamine to 2-bromo-3-phenylindandione (IIIc).⁶ However, when 1 mole of IIIc was treated with 4 moles of cyclohexylamine in benzene, a white solid was obtained which we believe, on the basis of spectral and analytical data, to have structure VI (73%), m.p. 157.5–158.5°, $\nu_{\text{C=N}}$ 1658 cm.⁻¹, and $\lambda_{\text{max}}^{\text{isooctane}}$ 252 m μ (ϵ 17,950). *Anal.* Calcd. for C₂₇H₃₂N₂: C, 84.33; H, 8.39; N, 7.29. Found: C, 84.10; H, 8.46; N, 7.16. All attempts to partially hydrolyze VI to IIIa have been unsuccessful. However, hydrolysis in concentrated sulfuric acid, as in the case of IIIa, results in the formation of IIIb.

- (3) N. H. Cromwell, *et al.*, *J. Am. Chem. Soc.*, **71**, 3337 (1949).
 (4) N. H. Cromwell and R. S. Johnson, *ibid.*, **65**, 316 (1943).
 (5) C. F. Koelsch, *ibid.*, **58**, 1321 (1936).
 (6) R. Weisz and S. Luft, *Monatsh.*, **48**, 338 (1927).

Secondary amines on the other hand readily form purple compounds analogous to IIIa. Thus treatment of 1 g. (0.0035 mole) of IIIc with 1.19 g. (0.014 mole) of piperidine in benzene at room temperature yields in 4 days 32.7% IIIId, m.p. 77–79°. *Anal.* Calcd. for C₂₀H₁₉NO: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.45; H, 6.74; N, 4.79. The infrared spectrum exhibits strong carbonyl absorption at 1710 cm.⁻¹. In the ultraviolet IIIId absorbs strongly at 271 m μ (ϵ 31,000) and 521 (1700). These values are consistent with those found for IIIa and thus lend further support for the structure of IIIa. Hydrolysis of IIIId in concentrated sulfuric acid again leads to IIIb identical in all respects with authentic material.

Surprisingly enough, *trans*-ethylenimine ketone II is unchanged by *N*-methylanilinolithium. Neither *t*-butylaminolithium nor cyclohexylaminolithium have any effect on I or II. Diisopropylaminolithium does effect the rearrangement of I to IIIa in low yield (<5%). This reagent with II effectively reduces the carbonyl group, yielding the corresponding carbinol VII (60.2%), m.p. 141–142°, identical in all respects with that obtained through lithium aluminum hydride reduction of II. *Anal.* Calcd. for C₂₁H₂₅NO: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.41; H, 8.12; N, 4.70. The detailed mechanism by which I is transformed into IIIa is currently under investigation and will be discussed in a later communication.

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A. E. Pohland, M. C. McMaster
 R. C. Badger, N. H. Cromwell

Department of Chemistry, University of Nebraska
 Lincoln, Nebraska

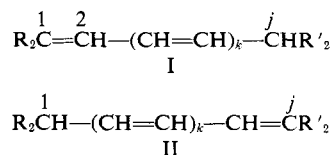
Received April 8, 1965

Selection Rules for Sigmatropic Reactions

Sir:

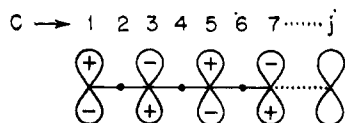
We define as a *sigmatropic change of order* [i,j] the migration of a σ -bond, flanked by one or more π -electron systems, to a new position whose termini are *i* - 1 and *j* - atoms removed from the original bonded loci, in an uncatalyzed intramolecular process. Thus, the well-known Claisen and Cope rearrangements are sigmatropic changes of order [3,3]. It is our purpose here to point out that orbital symmetry relationships must play a determinative role in the course of sigmatropic transformations similar to that operative in electrocyclic reactions¹ and concerted cycloadditions.²

Consider first the [1,j] sigmatropic migration of hydrogen within an all-*cis* polyolefin framework (I \rightarrow II). There are two conceivable ways in which



- (1) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).
 (2) R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 2046 (1965).

hydrogen might be transferred from C- j to C-1. In each case the transition state for the change may be envisaged as made up by the combination of a hydrogen atom with a radical containing $2k + 3$ π -electrons. In the first process, here designated *suprafacial*, the hydrogen atom is associated at all times with the same face of the π -system, and the transition state possesses a plane of symmetry, σ . In the second, *antarafacial* process, the migrating atom is passed from the top face of one carbon terminus to the bottom of the other, through a transition state characterized by a twofold axis of symmetry, C_2 . We note now that the highest occupied orbital of the framework system possesses the symmetry shown in III. Consequently, in order that positive overlap between this framework



III

orbital and the migrating hydrogen orbital be maintained, the isomerization I \rightarrow II must occur thermally by the suprafacial route when k is odd, and by the antarafacial path when k is 0 or even. Analogous considerations lead to the conclusion that these relationships are precisely reversed for sigmatropic changes taking place within first-excited-state species. Our calculations by the extended Hückel method³ fully support the generalizations deduced from simple orbital symmetry arguments.

The symmetry-allowed [1, j] sigmatropic transformations for $j \leq 7$ are summarized in Table I.⁴ In apply-

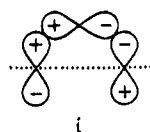
Table I

[1, j]	Thermal	Excited state
[1,3]	Antarafacial (C_2)	Suprafacial (σ)
[1,5]	Suprafacial (σ)	Antarafacial (C_2)
[1,7]	Antarafacial (C_2)	Suprafacial (σ)

ing these generalizations, several special factors should be borne in mind: (i) Antarafacial processes are obviously impossible for transformations which occur within small or medium-sized rings. (ii) In all cases, the carbon framework must not be so distorted during reaction as to cause serious impairment of coupling within the π -electron system; for example, this factor makes the antarafacial process difficult or impossible for $j = 3$, but is not a serious impediment to the similar process for $j = 7$. (iii) Sigmatropic reactions which

(3) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963), and subsequent papers.

(4) In the above discussion of [1, j] sigmatropic changes, we have assumed throughout that a σ -orbital of the migrating group interacts with a π -system in the transition state. If the migrating group possesses an available relatively low-lying π -orbital and is not so substituted as to create an impossible steric situation in the transition state, alternative processes with relationships reversed from those in Table I can be envisaged (*cf.* i).



i

violate the selection rules may take place through multi-step processes, involving diradical intermediates, but such transformations may be expected to require relatively vigorous conditions.

For sigmatropic reactions of order [1, j], in which both i and $j > 1$, proceeding through transition states possessing a plane of symmetry,⁵ it is easy to show, following the lines laid down above, that thermal changes are symmetry-allowed when $i + j = 4n + 2$, while excited-state transformations are permitted when $i + j = 4n$.

The selection rules deduced here for sigmatropic reactions are in striking agreement with experience accumulated so far. To our knowledge there are no established examples of thermal, uncatalyzed [1,3] hydrogen shifts. On the other hand, specific [1,5] thermally induced hydrogen migrations, uncomplicated by competing [1,3] or [1,7] processes, have been observed in both cyclopentadienes⁶ and cycloheptatrienes,⁷ and in acyclic cases.⁸ An important [1,7] thermally induced hydrogen shift in an open-chain system has been known for some time in the precalciferol-calciferol equilibrium.⁹ By contrast [1,3] hydrogen shifts, as well as [1,3] carbon shifts, have been reported in photochemically activated cyclic systems,¹⁰ and irradiation of cycloheptatrienes brings about highly specific [1,7] migrations.¹¹ Light-induced [1,5] hydrogen shifts have been observed in open-chain but *not* in cyclic systems.¹² Thermal sigmatropic reactions of order [3,3] have already been alluded to as the best known of all such processes. The [3,5] process has very probably been observed in a photoactivated system,¹³ but if it occurs thermally at all it does so only with relatively great difficulty.¹⁴

In some of the cases cited above, the selection rules are permissive of alternatives which have not been observed. Thus, in the thermal rearrangement of precalciferol, a suprafacial [1,5] hydrogen migration could compete with the observed antarafacial [1,7] shift, while [1,3] migrations could accompany the photochemically induced [1,7] isomerizations in cycloheptatriene. The fact that only the transformations with the higher values of j are observed may be explicable in terms of a preference for processes with the maximum degree of linear conjugation in the transition state.

Of special interest is the fact that a cyclopropane ring may replace a π -bond in the framework system for a sigmatropic change. The symmetry-allowed, supra-

(5) Additional symmetry elements may be present and can be definitive in determining the preferred *conformation* for such sigmatropic changes. This point will be discussed in a subsequent communication.

(6) W. R. Roth, *Tetrahedron Letters*, 1009 (1964); S. McLean and R. Haynes, *ibid.*, 2385 (1964).

(7) A. P. ter Boorg, H. Kloosterziel, and N. van Meurs, *Rec. trav. chim.*, **82**, 717, 741, 1189 (1963); E. Weth and A. S. Dreiding, *Proc. Chem. Soc.*, 59 (1964).

(8) J. Wolinski, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.*, **84**, 2775 (1962).

(9) *Cf.* J. L. M. A. Schlatmann, J. Pot, and E. Havinga, *Rec. trav. chim.*, **83**, 1173 (1964).

(10) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964); J. J. Hurst and G. H. Whitham, *J. Chem. Soc.*, 2864 (1960).

(11) A. P. ter Boorg and H. Kloosterziel, *Rec. trav. chim.*, **84**, 241 (1965).

(12) R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 3982 (1962); K. J. Crowley, *Proc. Chem. Soc.*, 17 (1964).

(13) K. Schmid and H. Schmid, *Helv. Chim. Acta*, **36**, 687 (1953).

(14) P. Fahrni and H. Schmid argue persuasively, but perhaps not entirely conclusively, that they have observed such a case [*ibid.*, **42**, 1102 (1959)].

facial, [1,5] hydrogen shift in the transformation of *cis*-1-methyl-2-vinylcyclopropane to *cis*-hexa-1,4-diene, which occurs very readily at 160° [$E^* \sim 31$ kcal.],¹⁵ exemplifies this process.

It is also worthy of note that orbital symmetry arguments are applicable to sigmatropic changes within ionic species. Thus, the suprafacial [1,2] shift within a carbonium ion is symmetry-allowed and is very well known. The as yet undetected [1,4] migration within a but-2-en-1-yl cation must proceed through an antarafacial transition state, which may be difficult of access because of serious uncoupling within the framework π -system. By contrast, it may be predicted that the [1,6] shift within a hexa-2,4-dien-1-yl cation should take place through a readily accessible suprafacial transition state.

(15) R. J. Ellis and H. M. Frey, *Proc. Chem. Soc.*, 221 (1964); cf. also W. Grimme, *Chem. Ber.*, **98**, 756 (1965).

(16) Junior Fellow, Society of Fellows, Harvard University.

R. B. Woodward, Roald Hoffmann¹⁶

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

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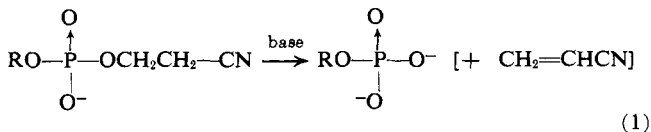
A New Phosphorylation Procedure

Sir:

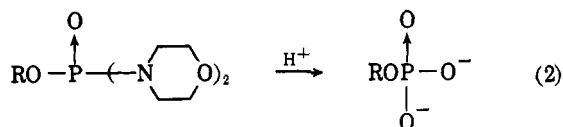
Monoesters of phosphoric acid, a class of compounds of considerable interest in biology, are frequently synthesized chemically by condensation of a properly activated derivative of phosphoric acid with an alcohol.¹ Because of the nature of phosphoric acid, means had to be found to prevent the formation of di- or triesters as well as anhydrides by further reaction of the desired condensation product. This is customarily accomplished by blockade of at least one, and sometimes two, of the substituents on the central phosphorus atom with a masking group which can be selectively removed subsequent to the desired condensation.² We wish to report on the use of the alkylthio substituent on phosphorus as a shielding group which can be replaced under mild conditions appropriate for the treatment of acid- or base-sensitive molecules of biological interest.⁵

(1) See H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961.

(2) This "unmasking" is typically brought about by rather drastic hydrolytic or hydrogenolytic procedures: thus, in the widely useful phosphorylation method of Tener,³ a cyanoethyl ester blocking group is split off *via* β -elimination by means of alkaline reagents (1). On the other hand, the method of Montgomery and Turnbull⁴ uses acidic



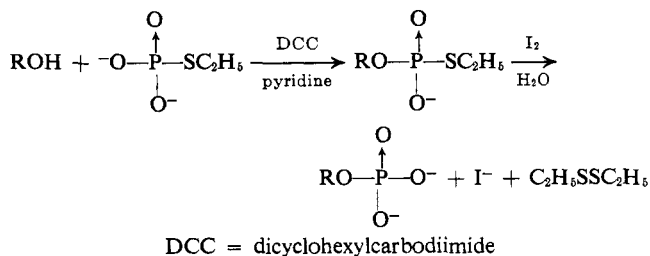
hydrolysis (2) to remove blocking groups in the alkyl phosphorodimorpholides formed in the primary condensation.



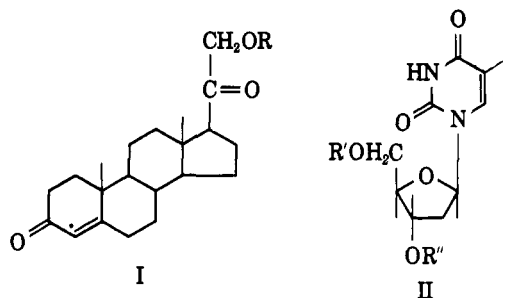
(3) G. M. Tener, *J. Am. Chem. Soc.*, **83**, 159 (1961).

(4) H. A. C. Montgomery and J. H. Turnbull, *J. Chem. Soc.*, 1963 (1958).

It has been observed that S-alkylphosphorothioic acids are converted to organic phosphate at pH 7 in the presence of iodine.⁶ We therefore studied the monophosphorylation of alcohols with S-ethylphosphorothioic acid⁷ according to the scheme



The feasibility of this procedure was tested by studying the phosphorylation of a steroidal alcohol, 11-desoxycorticosterone (I, R = H). Condensation of the latter with pyridinium S-ethylphosphorothioate by means of DCC in pyridine gave a crude phosphate which was directly treated with iodine in aqueous acetone. Fractionation by ion-exchange chromatography on DEAE⁸-cellulose, using gradient elution with



a bicarbonate buffer, gave 11-desoxycorticosterone 21-monophosphate (I, R = PO_3^{3-}), eluted with buffer strength 0.04 M, in 35% yield. This material traveled as a single spot in paper electrophoresis (16 cm. toward the cathode during 1 hr., 20 v./cm., pH 7.3 with 0.05 M ammonium acetate), absorbed maximally at 243 m μ , and was split completely to the starting steroidal alcohol with bacterial alkaline phosphatase.⁹ A comparison sample prepared by Tener's procedure^{3,10} had the same properties. The material was lyophilized to give the bistriethylammonium salt; it contained 1.06 μ moles of organically bound phosphate per 16 optical density units (theory: 1.0 μ mole). This demonstrates the capability of the alkylthio substituent to function as a blocking group in DCC condensations.¹¹

(5) The use of an enzyme at pH 8.8 (rattle snake venom phosphodiesterase) to strip a *p*-nitrophenyl substituent has been described: see R. W. Chambers, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **79**, 3741 (1957). Aqueous acetic acid has been used to unmask nucleoside phosphates blocked with *t*-butyl groups: F. Cramer, H. Neunhoeffer, K. H. Scheit, G. Schneider, and J. Tennigkeit, *Angew. Chem.*, **74**, 387 (1962).

(6) S. Åkerfeldt, *Svensk. Kem. Tidskr.*, **75**, 4 (1963).

(7) S. Åkerfeldt, *Acta Chem. Scand.*, **16**, 1897 (1962).

(8) DEAE = diethylaminoethyl.

(9) E. C. 3.13.1, Worthington Biochemical Corp., Freehold, N. J.

(10) A number of steroidal phosphates have been prepared by this latter procedure: see R. B. Brownfield and W. Shultz, *Steroids*, **2**, 597 (1963).

(11) The possibility that the alkylthio substituent acts as an activating group in its own right has been investigated by T. Wieland and R. Lambert, *Chem. Ber.*, **89**, 2476 (1956). These authors reported that when S-alkylthiophosphates are alcoholized in the presence of iodine, the corresponding phosphomonoesters can be demonstrated. It would seem, however, that a large excess of the alcohol is required: an at-