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Stereochemistry of the Conant–Swan Fragmentation: The Absence of a Phenonium Ion Intermediate

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Abstract: In the accompanying paper, the kinetics and mechanism of the Conant–Swan fragmentation are considered. A *p*-methoxy substituent in an appropriate β-bromophosphonate increases the rate by a factor of 25. The question arose as to whether this acceleration was caused by a pathway through a phenonium ion intermediate. The stereochemistry of the fragmentation is controlled by its mechanism. The configuration of one enantiomer of the *RS*/*SR* diastereomer of dihydrogen (2-bromo-1-(4-methoxyphenyl)-3-phenyl-3-oxo-1-propyl)phosphonic acid was determined by X-ray crystallography; this compound was found to fragment to the (*E*)-chalcone. Its diastereomer fragments to the (*Z*)-chalcone. These facts are shown to rule out a phenonium ion intermediate for the fragmentation.

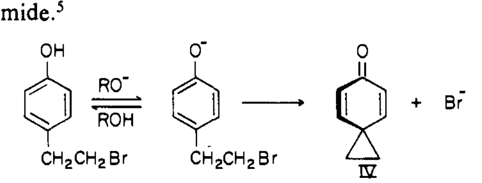
The dianions of β-halophosphonates rapidly undergo fragmentation in solution to yield an olefin, halide ion, and monomeric metaphosphate ion.[1] This latter ion is a strong electrophile and reacts indiscriminately with water, various alcohols, amines, or the carbonyl group of ketones or esters.[2] Its chemistry is of significance for biochemistry,[3] since phosphorylations with ATP may involve this electrophile as an intermediate. The stopped-flow kinetics of the reaction of certain β-halophosphonates that fragment to chalcones and a discussion of the mechanism of the process are presented in the accompanying paper.[4] In particular, the fragmentation of the dianion of the *RS*/*SR* enantiomeric pair of dihydrogen (2-bromo-1-(4-methoxyphenyl)-3-phenyl-3-oxo-1-propyl)phosphonate (II) proceeds with a rate constant of 600 s^{-1} in methanol as solvent at 14 °C (eq 1). This rate constant is 25

$$\underset{\text{II}}{p\text{-}CH_3OC_6H_4CH(PO_3^{2-})CHBrCOC_6H_5} \rightarrow p\text{-}CH_3OC_6H_4CH{=}CHCOC_6H_5 + PO_3^- + Br^-$$

$$PO_3^- + CH_3OH \rightarrow CH_3OPO_3H^- \qquad (1)$$

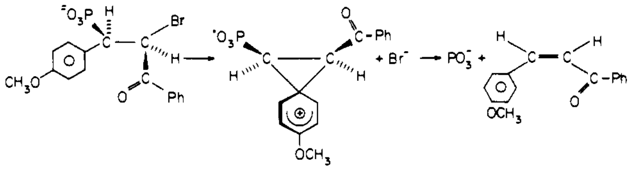
times that of the unsubstituted compound I, which is consistent with a direct fragmentation, but the rate constants for a series of substituted analogues of I do not give a good Hammett plot.[4] These facts raise the question of whether the methoxyl derivative II may decompose by a special mechanism and in particular whether it might not fragment by way of the phenonium ion III as intermediate.

The possibility of the intermediacy of III in the reaction cannot be dismissed lightly, in view of the isolation of IV by Winstein and his collaborators from the solvolysis of (*p*-hydroxyphenyl)ethyl bromide.[5]



(2)

The question of the intermediacy of the phenonium ion III in the fragmentation of II has been settled in the negative by a determination of the stereochemistry of the process. In prior work, Kenyon and Westheimer[6] had found that the fragmentation of the dianion of (1,2-dibromo-1-phenyl-1-propyl)phosphonic acid (V) is antiperiplanar, that is to say that the *RR*/*SS* diastereomer yields the *E* olefin, whereas the *RS*/*SR* diastereomer yields the *Z* olefin. Parallel stereochemistry was found for the monoanions of the monomethyl ester of V.[7] The same type of direct antiperiplanar fragmentation for II would demand that the *RS*/*SR* diastereomer yield the (*E*)-chalcone VI and the *RR*/*SS* diastereomer yield the (*Z*)-chalcone VII. (The peculiarities of the standard numbering system, not stereochemical differences, account for the change in the identification of the diastereomer that yields the *E* olefin in the two cases.) On the other hand, if reaction takes place by way of a phenonium ion, then the *RS* isomer of II would yield III, with the stereochemistry as shown, and this ion, on opening, would yield the (*Z*)-chalcone. Conversely, the *RR*/*SS* diastereomer of II would yield the (*E*)-chalcone. Finally, if the reaction is not concerted but proceeds, for example, by way of a carbonium ion, then both diastereoisomeric pairs of II would be expected to yield the same mixture of *E* and *Z* olefins, a mixture in which the thermally more stable *E* isomer would presumably dominate.



(1R, 2S)-IIa III VII

Results and Discussion

This paper describes the preparation of the pure 1*R*,2*S* enantiomer of II, the determination of its stereochemistry by X-ray analysis, and the identification of the product of the fragmentation of its dianion as the (*E*)-chalcone, as shown in eq 1. We have not been successful in purifying the *RR*/*SS* diastereomer of II but have obtained a 1.16:1 mixture of the *RS*/*SR* to *RR*/*SS* diastereomers and found that the mixture fragments to a 1.17:1 mixture of the *E* and *Z* olefins, respectively. Each diastereomer,

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Table I[a]

Non-Hydrogen Bond Lengths (Å)[b]	
C(1)-P	1.820 (9)
C(1)-C(2)	1.554 (12)
C(1)-1	1.505 (13)
C(2)-Br	1.958 (8)
C(2)-C(3)	1.526 (13)
C(3)-O(4)	1.200 (12)
C(3)-1′	1.495 (11)
1-2	1.397 (12)
1-6	1.382 (12)
2-3	1.385 (13)
3-4	1.365 (13)
4-5	1.384 (13)
4-O(5)	1.357 (11)
5-6	1.375 (13)
O(5)-C(Me)	1.419 (14)
P-O(1)	1.490 (14)
P-O(2)	1.571 (6)
P-O(3)	1.552 (7)
Bond Angles[c]	
P-C(1)-O(1)	104.8 (4)
P-C(1)-O(2)	111.3 (4)
P-C(1)-O(3)	104.3 (4)
P-C(1)-H(C(1))	112.1 (3)
P-C(1)-C(2)	107.0 (6)
P-C(1)-1	111.4 (6)
C(1)-H(C(1))-C(2)	108.1 (5)
C(1)-H(C(1))-1	103.4 (5)
C(1)-C(2)-H(C2)	103.7 (5)
C(1)-C(2)-Br	113.0 (6)
C(1)-C(2)-C(3)	112.1 (7)
C(1)-C(2)-1	115.0 (7)
C(2)-Br-C(3)	104.5 (6)
C(2)-Br-H(C(2))	111.5 (2)
C(2)-H(C(2))-C(3)	112.3 (5)
C(2)-C(3)-O(4)	119.7 (8)
C(2)-C(3)-1′	119.4 (7)
C(3)-1′-O(4)	120.9 (8)
C(3)-1′-2′	121.8 (4)
C(3)-1′-6′	118.1 (4)
1-2-C(1)	118.5 (8)
1-2-6	117.9 (8)
1-H(2)-2	119.5 (5)
2-3-H(2)	119.5 (5)
2-3-H(3)	120.0 (5)
2-3-4	120.3 (9)
2-3-1	121.0 (9)
3-4-H(3)	119.7 (5)
4-3-O(5)	116.6 (8)
4-3-5	119.0 (9)
5-4-O(5)	124.3 (8)
5-4-H(5)	119.4 (5)
5-4-6	121.2 (9)
6-5-H(5)	119.4 (6)
6-5-H(6)	119.8 (6)
6-5-1	120.6 (9)
6-1-H(6)	119.4 (5)
6-1-C(1)	123.6 (8)
P-O(1)-O(2)	112.9 (4)
P-O(1)-O(3)	107.1 (4)
P-O(2)-O(3)	115.6 (4)
C(Me)-O(5)-4	119.6 (8)
O(5)-C(Me)-H(Me-A)	113.6 (6)
O(5)-C(Me)-H(Me-B)	103.5 (6)
O(5)-C(Me)-H(Me-C)	111.1 (6)

[a] Numbering corresponds to that indicated in Figure 1. [b] All other bond lengths were constrained to ideal values during least-squares minimization (1.395 for phenyl carbons, 0.96 for hydrogens). [c] All other bond angles were constrained to ideal values during least-squares minimization (120.0 for phenyl ring).

then, decomposes stereospecifically to give the product expected for an antiperiplanar fragmentation. These experiments rule out the phenonium ion III as an intermediate in the Conant-Swan fragmentation of II.

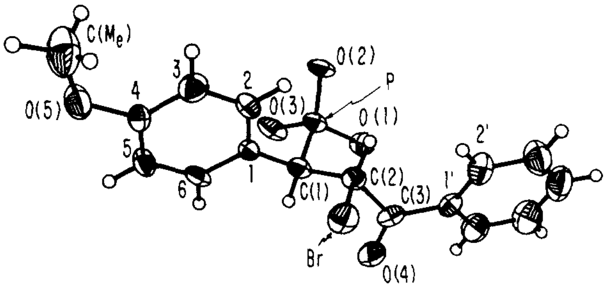

Figure 1. Structure of IIa obtained from the X-ray obtained from the X-ray crystal analysis. The numbering system indicated is that used in Tables I and II; 50% probability elipsoids are used.

Table II. Non-Hydrogen Atom Fractional Coordinates (×10^4)

atom	*x*	*y*	*z*
Br	10428 (2)	4131 (1)	8848 (1)
P	5742 (4)	6625 (2)	9417 (1)
O(1)	5405 (11)	7174 (4)	8901 (2)
O(2)	7373 (11)	7184 (5)	9737 (2)
O(3)	3707 (10)	6465 (5)	9646 (3)
O(4)	6260 (11)	5122 (6)	8214 (3)
O(5)	8240 (11)	2871 (5)	10989 (3)
C(1)	6674 (15)	5298 (7)	9270 (4)
C(2)	8624 (13)	5409 (7)	8897 (3)
C(3)	7815 (16)	5607 (7)	8370 (3)
1′	9028 (10)	6575 (5)	8050 (2)
2′	11155 (10)	6725 (5)	8166 (2)
3′	12200 (10)	7467 (5)	7865 (2)
4′	11118 (10)	7859 (5)	7448 (2)
5′	8991 (10)	7509 (5)	7331 (2)
6′	7946 (10)	6767 (5)	7632 (2)
1	7202 (14)	4682 (7)	9731 (3)
2	5695 (16)	3917 (6)	9889 (3)
3	6102 (14)	3320 (8)	10309 (4)
4	7988 (15)	3474 (7)	10578 (3)
5	9480 (16)	4237 (8)	10426 (3)
6	9096 (15)	4832 (7)	10009 (3)
C(Me)	10265 (19)	2906 (10)	11256 (5)

The structure of compound II is shown below in Figure 1. Although, presumably both enantiomers of IIa crystallized with spontaneous resolution, the crystal chosen for analysis contained only the 1*R*,2*S* enantiomer. The R_w value computed for the *RS* enantiomer is 0.0550, whereas that computed for the *SR* is 0.0614. This result,[8] combined with inspection of the Friedel pairs collected, demonstrates that the enantiomorph chosen is correct. The stereochemistry of the fragmentation requires only that the particular diastereomer be the *RS*/*SR* isomer. The bond angles and distances (Table I) are those expected for a phosphonic acid such as II. In particular, there are no irregularities in regard to the P-C and Br-C bond distances. The crystal structure indicates a torsion angle between the phosphorus and bromine atoms of 162.4°. The nonhydrogen atom coordinates calculated for II are presented in Table II.

Experimental Section

Materials. (*E*)-4-Methoxychalcone melted at 75 °C (lit.[9] 74 °C). A mixture of the corresponding *Z* isomer with the more stable (*E*)-chalcone was prepared by irradiating a water-cooled solution of 89 mg of the *E* isomer in 50 mL of isooctane in a quartz tube for 90 min with the unfiltered light of a 250-W General Electric sunlamp. The *E* isomer was preferentially crystallized from the mixture from hexane at -20 °C; after three crystallizations, a 9:1 mixture of (*Z*)- to (*E*)-4-methoxychalcones was obtained from the mother liquor. The mixture was analyzed by its ^{1}H NMR spectrum (Figure 2). The signal from the methoxyl group of the *Z* isomer is 6.4 Hz upfield from that of the *E* isomer; the vinylic resonances from the *Z* isomer are also upfield from those of the *E* isomer. This shift for the signal from the hydrogen atoms of the cis double bond is analogous to that for the unsubstituted chalcone.[10] The IR spectra

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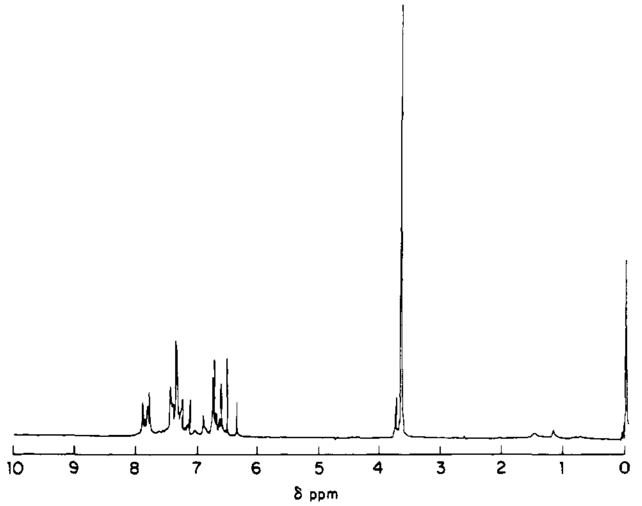

Figure 2. ^{1}H NMR ($CDCl_3$) spectrum of the 9:1 ratio of (*Z*)- to (*E*)-1,3-diphenyl-2-propen-1-one. As indicated in the Experimental Section, the methoxyl signal for the (*Z*)-chalcone (δ 3.72) is shifted upfield relative to that from the (*E*)-chalcone (δ 3.80). The vinylic resonances are similarly shifted (*Z*, δ 6.58, *E*, δ 6.88).

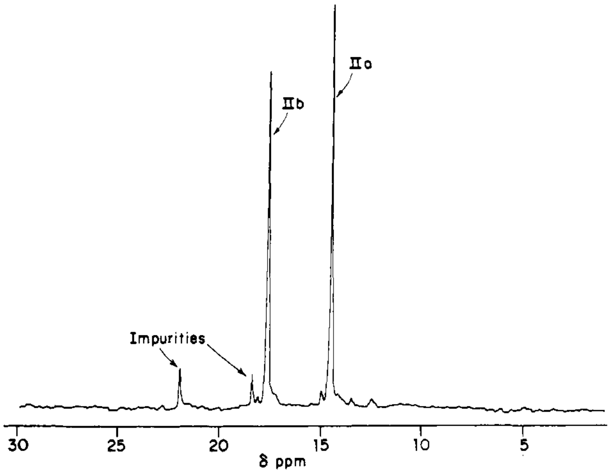

Figure 3. Proton-decoupled ^{31}P NMR ($CDCl_3$) spectrum of the mixture of diastereomers of II. The ratio of IIa to IIb is 1.16, and the sum of the signals represents more than 90% of the total phosphorus. Decomposition of this mixture yielded a ratio of 1.17 of (*E*)- to (*Z*)-chalcone.

of the two isomers are also consistent with the stereochemical assignment here advanced. The stereochemistry of the *E* isomer has been established by X-ray crystallography.[9]

About 7.0 g of II was synthesized in 80% yield (a mixture of both diastereomers) from the (*E*)-chalcone by the same procedure as that for the preparation of the unsubstituted β-bromophosphonate I from chalcone itself. Although both diastereomers of II were present in the reaction mixture (in 2.5:1 ratio by ^{31}P NMR analysis), the major diastereomer, IIa, was selectively crystallized by cooling a benzene solution of the two. The mother liquor contained a 1.16:1 ratio of IIa to the second diastereomer, IIb. Although we have so far been unsuccessful in obtaining IIb in pure form, it was identified in the reaction mixture by both ^{31}P and proton NMR spectroscopy; the appropriate spectrum is shown in Figure 3. The ^{31}P shift for IIb in deuterochloroform is 17.76, whereas that for IIa is 14.64, relative to 85% phosphoric acid as standard; their J_{HP} coupling constants are 17.0 and 7.6 Hz for IIb and 21.0 and 8.0 Hz for IIa. Crystals of IIa, suitable for X-ray structure determination, were obtained by cooling an acetone solution of the racemic mixture from room temperature to 4 °C over 24 h.

Products. Fragmentation of 30 mg of IIa was carried out in 10 mL of methanol in the presence of 10 mL of 0.03 N sodium methoxide. The reaction mixture was dried, and the product was isolated by extraction of the residue with chloroform; the ^{1}H NMR, IR and UV spectra indicated that only the *E* isomer of 4-methoxychalcone had been formed.

Table III. Crystal Data for (1*R*,2*S*)-II

formula	$C_{16}H_{16}BrO_5P \cdot C_3H_6O$
fw	457.25
space group	$P2_12_12_1$
a, Å	6.038 (6)
b, Å	12.692 (8)
c, Å	27.000 (18)
V, Å^3	2069 (2)
Z	4
d_{calcd}, g/cm^3	1.468
crystal size, mm	0.5 × 0.4 × 0.15
data collecn instrument	Nicolet-R3
radiatn	Mo Kα (λ ā = 0.71073 Å); graphite monochromated
scan method	θ–2θ variable scan rate
data collecn range	$3° \le 2\theta \le 30°$ $(+h,+k,\pm l)$; $30° \le 2\theta \le 52°$ $(+h,+k,+l)$
no. of unique data ($F_o^2 \ge 3\sigma(F_o^2)$)	1827
no. of parameters refined	235
R^a	0.0537
$R_w{}^b$	0.0550
quality of fit indicator^c	1.416
largest shift/esd, final cycle	0.003
absorption correction	semiempirical (ψ scan)
max transmissn	0.939
min transmissn	0.457

[a] $R = \sum||F_o| - |F_c|| / \sum|F_o|$. [b] $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$; $w = 1/[\sigma^2(|F_o|) + g|F|^2]$, $g = 0.001$. [c] Quality of fit $= [\sum w(|F_o| - |F_c|)^2 / (N_{obsd} - N_{parameters})]^{1/2}$.

When 40 mg of the 1.16:1 mixture of the two diastereomers was subjected to fragmentation under the same conditions as those for the pure IIa, the reaction products consisted of a 1.17:1 mixture of the (*E*)- and (*Z*)-chalcones, identified by an examination of the proton NMR spectrum of the chloroform extract obtained as for the products from IIa.

X-ray Crystallography. A portion of a needle (0.5 × 0.4 × 0.15 mm) of IIa was wedged into a glass capillary, which was then sealed at both ends. The crystal was subjected to Mo Kᾱ graphite monochromated radiation (λ = 0.71073 Å). Intensities were measured with a Nicolet R3 diffractometer at 22 °C with the θ–2θ variable-scan-rate technique. Data of the form $+h,+k,\pm l$ were collected for the angles $3° < 2\theta < 30°$ and $+h,+k,+l$ for the range $30° < 2\theta < 52°$. The unit cell parameters (Table III) were determined by a least-squares analysis of 25 reflections with $20° \le 2\theta \le 25°$. The asymmetric unit contains one molecule of IIa and one acetone molecule. The space group was determined to be $P2_12_12_1$ on the basis of systematic absences. Intensities were corrected for absorption effects and Lorentz–polarization factors. Check reflections were measured every 60 reflections and showed no significant fluctuations. The structure was solved by the heavy-atom method and refined by least-squares analysis on the basis of 1827 observed reflections having $F^2 > 3\sigma(F^2)$. All data processing and refinement were carried out with the SHELXTL system. The hydrogen atoms bound to carbon were included in their calculated positions with C–H distances of 0.96 Å and temperature factors equal to 1.2 times that of the attached carbon atoms. No hydrogen atoms could be located in the phosphate group. The unsubstituted phenyl ring and the methyl group were constrained to idealized geometries. The refinement, including anisotropic temperature factors for atoms other than hydrogen, converged to $R_w = 0.0550$. The coordinates were inverted and the structure was again refined to convergence yielding $R_w = 0.0614$.

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Supplementary Material Available: Temperature factors, hydrogen coordinates, and the observed and calculated structure factors (13 pages). Ordering information is given on any current masthead page.