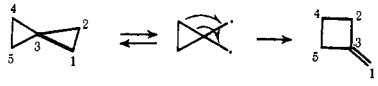
Alkyl Shifts in Thermolyses. IV.[1] Carbethoxyspiropentane–Carbethoxymethylenecyclobutane Isomerization. Evidence for Orbital Symmetry Control and an Intermediate

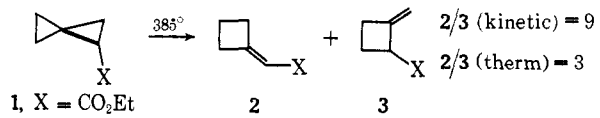
Sir:

The spiropentane–methylenecyclobutane thermal rearrangement,[2] which in most cases proceeds by initial C_1–C_2 (peripheral) bond fission, followed by migration of C_4,[1] bears a close resemblance to the cyclopropane–propylene isomerization.[3] With deuterium[4] and methyl[5]

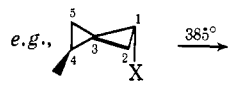


substitution on the spiropentane system, the initial peripheral bond fission is reversible with epimerization of starting materials occurring at least ten times faster than structural rearrangement.

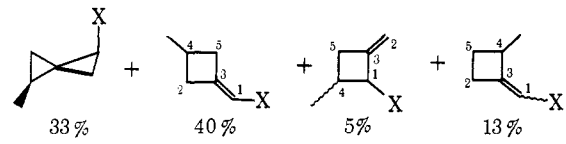
In order to examine the overall stereochemistry of the rearrangement, it was necessary to select a substituted spiropentane in which initial cleavage would occur to the carbon bearing the substituent even with heavy methyl substitution elsewhere in the system. Further, the substituent could not enter into the reaction nor allow rapid epimerization at C_1 relative to rearrangement. Carbethoxyspiropentane (**1**) appeared to satisfy these requisites. Upon pyrolysis at 385° for a short contact time in a gold tube, **1** was cleanly converted to carbethoxymethylenecyclobutane (**2**) and 2-methylene-1-carbethoxycyclobutane (**3**) in a ratio of 9:1,



1, X = CO_2Et 2 3



4, X = CO_2Et



(1) For part III, see J. J. Gajewski and L. T. Burka, *J. Amer. Chem. Soc.*, **93**, 4942 (1971); for part II, see J. J. Gajewski, *ibid.*, **92**, 3688 (1970).

(2) (a) M. C. Flowers and H. M. Frey, *J. Chem. Soc.*, 5550 (1961); (b) P. J. Burkhardt, *Diss. Abstr.*, **23**, 1524 (1962).

(3) (a) The cyclopropane pyrolysis has been the subject of experimental[3b] as well as theoretical studies[3c] which revealed that the initial geometric isomerization proceeds *via* a trimethylene biradical which is formed without concert. However, no information is available on the second step, that is, whether or not the structural isomerization is independent of the geometric isomerization (and possibly concerted). (b) For a review, see R. G. Berman and W. L. Carter, *J. Amer. Chem. Soc.*, **91**, 7411 (1969). (c) L. Salem, *Bull. Soc. Chim. Fr.*, 3161 (1970); Y. Jean and L. Salem, *J. Chem. Soc. D*, 382 (1971); J. A. Horsely, Y. Jean, C. Moser, L. Salem, R. M. Stevens, and J. S. Wright, *J. Amer. Chem. Soc.*, **94**, 279 (1972).

(4) J. C. Gilbert, *Tetrahedron*, **25**, 1459 (1969).

(5) J. J. Gajewski and L. T. Burka, submitted for publication to *J. Amer. Chem. Soc.*

Table I. Products[a] from Short-Term Pyrolysis of the Dimethylcarbethoxyspiropentanes[b]

	% conversion	8	9	10	11
5	20%	58	17	9	1
6	24%	1	70	Trace	8
7	20%	9	8	18	22
12	7%	72[c]	2	10	2[d]
13	9%	8	40[c]	12[d]	3
14	3%	25	0[d]	61[c]	0

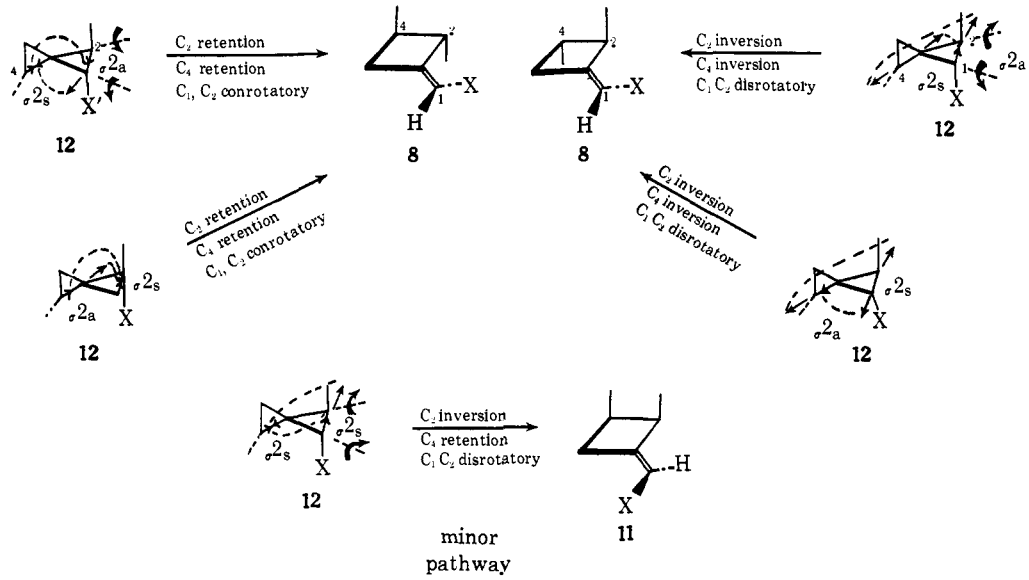
[a] Reported as percentages of rearranged product. The remainder of the material was either an epimer of starting material (with **5**–**7**) or other isomeric products. The cis compounds corresponding to **12**–**14** gave different products, and the products reported interconverted at about the same rate as they were formed so these short-term pyrolyses are a close approximation to a kinetically controlled distribution. [b] X = CO_2Et. [c] Orbital-symmetry controlled product with retention at C_2 and C_4 or inversion at C_2 and C_4. [d] Orbital-symmetry controlled product with retention (inversion) at C_2 and inversion (retention) at C_4.

kinetically; the equilibrium mixture of **2** and **3** was 3:1. No 3-methylene-1-carbethoxycyclobutane was formed. Thus, C_1–C_2 bond fission must have occurred, and formation of the α,β-unsaturated ester was preferred kinetically. Pyrolysis of the 4-methyl-1-carbethoxypentanes (**4**)[6] indicated rearrangement was faster than C_1 epimerization and that the reaction rate varied between 0.5 and 2 times as fast as the parent compound and that there was a 3.5–16-fold preference for migration of the methyl bearing carbon over the methylene group. The remainder of the product in each case was the starting material epimerized at C_4.

In order to examine the stereochemistry of the migrating carbon, the *trans,anti-*, *trans,syn-*, and *cis,anti*-4,5-dimethyl-1-carbethoxyspiropentanes, **5**, **6**, and **7**, respectively,[7a] were pyrolyzed, and at short reaction

(6) J. J. Gajewski and L. T. Burka, *J. Org. Chem.*, **35**, 2190 (1970).

(7) (a) Prepared by copper-catalyzed addition of ethyl diazoacetate to *trans-* and *cis*-2,3-dimethylmethylenecyclopropane. The stereochemical assignments at C_1 are based on steric considerations, those at C_4 and C_5 are fixed in the starting olefin. (b) Prepared by the Emmons–Wittig reactions of *cis-* and of *trans*-2,3-dimethylcyclobutanone using pmr to distinguish between syn and anti isomers, *i.e.*, a downfield shift of the proton at C_2 in the syn isomers. (c) Prepared by cuprous chloride catalyzed addition of diazomethane to each of the four 2-ethylidene-3-methylcarbethoxycyclopropanes whose relative configurations at C_1 and C_2 were easily determined by pmr, *i.e.*, an upfield shift of the proton on C_1 in the trans compounds. In the spiropentane esters produced, the relationship between the methyls



times the distribution of the *trans*- and *cis*-2,3-dimethyl-1-carbethoxymethylenecyclobutanes **8** → **11**[7b] indicated substantial retention (7.5 and 9:1 from **5** and **6**, respectively, and 2:1 from **7**; Table I). Furthermore, these compounds (**5**–**7**) rearranged at the same rate as **1** (±25%).

Finally, in order to ascertain the stereochemistry at the migration terminus and the direction of rotation of C_1, the 2,4-dimethyl-1-carbethoxyspiropentanes **12**, **13**, and **14**[7c] were pyrolyzed. Examination of the 2,3-dimethyl-1-carbethoxymethylenecyclobutane product at very short reaction times revealed partial stereospecificity in the rearrangement (Table I).

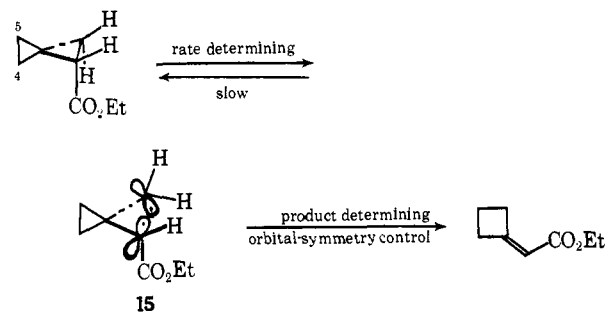
If the reaction were entirely controlled by conservation of orbital symmetry, it must be a $_{\sigma}2_s + {}_{\sigma}2_a$ reaction[8] and there are eight ways to choose and use bonds, s or a; however, only four of these paths give a prediction of experimentally discernible possibilities at each center, but only two different products, each as an enantiomeric pair, can result *via* a concerted process from each compound **12**, **13**, or **14**.

For example, retention at C_2 and C_4 with conrotatory[9] opening of the C_1–C_2 bond predicts formation of trans,-syn material **8** from **12** in a concerted manner; also possible is inversion at both C_2 and C_4 with disrotatory[9] opening of the C_1–C_2 bond to give the opposite enantiomer of **8**. Inversion at C_2 and retention at C_4 with conrotatory opening of the C_1–C_2 bond or retention at C_2 and inversion at C_4 with disrotatory opening of the C_1–C_2 bond are also concerted processes giving only both enantiomers of cis,anti material, **11**, but this compound is only a minor product of the reaction.

A similar analysis reveals that **13** should give trans,-anti material, **9**, with an anti-ward rotation of the C_1 substituent if there is retention at both C_2 and C_4 or inversion of both of these centers. In fact, **9** represents about 70% of the four cyclobutyl products at low conversions of **13**. Likewise, **14** is predicted to give cis-syn material, **10**, by a syn-ward rotation of the C_1 substituent if there is retention at C_2 and C_4 or inversion at C_2 or C_4, and indeed it is the major product. Finally, since the experiments with the 4,5-dimethylcarbethoxyspiropentanes **5**–**7** revealed predominant retention at C_4, the retention–retention pathway at C_2 and C_4 is preferred over the inversion–inversion pathway.[10]

The observed partial stereospecificity in the carbethoxyspiropentane thermal rearrangement is clearly in accord with the predictions of orbital-symmetry control[8] upon which may be superimposed least-motion control, *i.e.*, the retention–retention pathway. However, there is the suggestion that at least part of each pyrolysis is nonconcerted. Product interconversions are slow enough so that the product distributions from **12** to **14** at short reaction times are reasonably indicative of relative transition-state energies.

Besides the stereochemical data, the facts that the rate constants for rearrangement of the mono- and dimethyl esters **4**–**7** are very similar yet migration of the methyl-substituted carbon (C_4 in **4**) is greatly preferred over methylene (C_5 in **4**) migration should be considered. These facts are incompatible with a single-stage reaction unless heretofore unrecognizable steric effects are operating in all four isomers of **4**. We therefore suggest[11] a two-step pathway with the first step being rate



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was established by reductive decarboxylation to the 1,4-dimethylspiropentanes,[6] since the initial relationship between the ester group and one of the methyls was established, and the structures of all eight 2,4-dimethylcarbethoxyspiropentanes were easily assignable.

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

(9) Note that the rotation of C_2 is related to the position of the migrating carbon (C_4). Note also that in the pathways involving inversion at C_2, the rotation of C_2 is only one of meeting C_4, not a 90° rotation as with C_1.

(10) W. R. Roth and K. Enderer (*Justus Liebigs Ann. Chem.*, 733, 44 (1970)) have examined the stereochemistry of the migrating carbon in a spiropentane system where only disrotatory opening of the C_1–C_2 bond is possible and found little stereospecificity.

(11) A number of other intermediates such as a π-cyclopropane, or an orthogonal biradical (the edge-to-edge or edge-to-face biradicals of

determining, leading to an intermediate having a stretched C_1–C_2 bond, *e.g.*, **15**, which may retain enough interaction between the orbitals at C_1 and C_2 to allow the stereospecificity observed with **12–14**, yet able to discriminate between C_4 and C_5 migration. This suggestion of a potential well on the energy surface is in accord with that made by Benson[12] and not with that by Salem[3c] for the possibly structurally related cyclopropane energy surface.

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund (2754-AC1,4), administered by the American Chemical Society, for partial support of this work.

Hoffmann and Salem), or an ethoxyoxaspiroheptene *via* a carbonyl-cyclopropane rearrangement were considered and discarded as major contributors in view of all the stereochemical data.

(12) S. W. Benson, *J. Chem. Phys.*, **34**, 521 (1961); H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, **72**, 1866 (1968).

(13) Fellow of the Alfred P. Sloan Foundation, 1971–1973.

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Synthesis of the Central Iron Core of Rubredoxin

Sir:

Rubredoxin from *Micrococcus aerogenes*, an anaerobic bacterium, is a linear polypeptide of 53 residues and contains an iron that is coordinated to the cysteine residues at positions 6, 9, 38, and 41 in the molecule (Figure 1).[1] The chelate structure of this specific protein has been studied by various physical techniques,[2,3] but considerably more work exists on the rubredoxin from *Clostridium pasteurianum*,[4–8] which includes the preparation of several simple inorganic models.[9–11] A detailed X-ray study of this last rubredoxin showed recently that the metal was in a strained tetrahedral configuration and was located at one side of the molecule.[12] Furthermore, the iron connected two separate, secondary hairpin turns of the main chain that involves the regions between residues 5–10 and 37–42. Most importantly, the large, middle peptide section consisting of residues 11–36 was not in bonding contact with the metalloorganic region. Such information suggested that the synthesis of a small, model peptide area might produce an "active site" or, at least, give evidence as to the stability of the existing central core of rubredoxin.

We now wish to report the partial realization of this idea, in terms of the rubredoxin from *M. aerogenes*, by two related chemical approaches. In the first, the protected pentapeptide R_{6-10}, methyl N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucinyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (I),[13] on reaction with hydrazine gave the corresponding hydrazide II.[14] This compound was joined by the organic azide procedure[15] to the pentapeptide R_{38-42}, methyl *S*-*p*-methoxybenzyl-L-cysteinyl-L-prolyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (III), to yield the decapeptide, methyl N^{α}-*tert*-butyloxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-threonyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycyl-*S*-*p*-methoxybenzyl-L-cysteinyl-L-prolyl-L-leucyl-*S*-*p*-methoxybenzyl-L-cysteinylglycinate (IV). Alternatively, the same compound was prepared by the mild base hydrolysis of I to the pentapeptide acid (V), followed by a mixed carbonic anhydride[16] coupling with the amine III. The addition of sodium to a liquid ammonia solution of IV cleaved the *S*-*p*-methoxybenzyl protecting groups[17] and generated the partially deblocked peptide, methyl N^{α}-*tert*-butyloxycarbonyl-L-cysteinyl-L-threonyl-L-leucyl-L-cysteinylglycyl-L-cysteinyl-L-prolyl-L-leucyl-L-cysteinylglycinate (VI). If the decapeptide IV was hydrolyzed to the acid VII, then the remaining blocking groups could be removed by warming with trifluoroacetic acid–anisole to afford the salt, L-cysteinyl-L-threonyl-L-leucyl-L-cysteinylglycyl-L-cysteinyl-L-prolyl-L-leucyl-L-cysteinylglycinate trifluoroacetate (VIII). Iodometric titration of both VI and VIII showed the presence of 3.50 and 3.60 free cysteinyl groups, respectively.[18]

Both VI and VIII (0.1 mmol) were suspended separately in water (20 ml), mercaptoethanol (20 mmol) was added, and the pH was adjusted to 10 by addition of triethylamine. The clear liquid was deaerated with nitrogen, and an aqueous solution of ferrous ammonium sufate (0.5 mmol) was introduced, after which the reaction was cooled to 0°. The admission of air into the flask produced an immediate dark red-brown coloration. The failure to see any precipitate under these conditions means that the ferrous ion has been incorporated into a chelate structure and subsequently is oxidized to the ferric state. Each solution was passed through a Sephadex LH-20 column, previously equilibrated to a pH value of 9.5 (μ = 0.06), to yield one brown and two pale yellow fractions. The former possessed a continuous band spectrum, which was different in shape from those produced by mixing the various reactants in any two combinations.[19] It should be noted that a match to the exact spectrum of rubredoxin would not be expected (Figure 2), as no aromatic residues are present in compounds VI and VIII. Lyophilization of either product produced a pale-green

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(2) H. Bachmayer, L. H. Piette, K. T. Yasunobu, and H. R. Whiteley, *Proc. Nat. Acad. Sci. U. S.*, **57**, 122 (1967).

(3) H. Bachmayer, K. T. Yasunobu, and H. R. Whiteley, *ibid.*, **59**, 1273 (1968).

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(6) T. V. Long, II, and T. M. Loehr, *J. Amer. Chem. Soc.*, **92**, 6384 (1970).

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