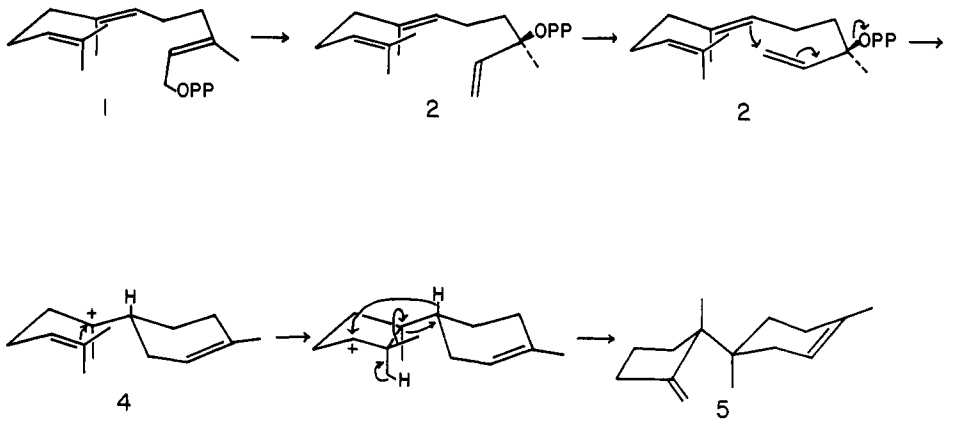
Scheme IV



$HClO_4$, THF:H_2O, 1:1/48 h/0 °C) and thence to the corresponding 9,10-bis(dinitrobenzoate) (**11**) which was recrystallized to constant activity and isotope ratio ($^3H/^{14}C = 8.23 \pm 0.12$; atom ratio 1.8:2), mp 220 °C dec. Rearrangement of a further portion of the epoxide with lithium perchlorate in benzene[21] (4 equiv/48 h/reflux) gave the 10-ketone (**12**) which epimerized to the more stable equatorial isomer **13** and lost all tritium activity (>99%) upon exchange with sodium deuteroxide in refluxing dioxane–D_2O for 30 h. The latter experiment thus located all the tritium isotope at the expected site,[7] C-11, of trichodiene.[22] In further confirmation of the above results, the corresponding 9-hydroxy-10-phenylselenide (**14**), obtained by reaction of the remaining epoxide with sodium phenylselenide (EtOH/20 h/reflux), lost one-half the total tritium activity upon treatment with sodium periodate (H_2O/THF/MeOH/0 °C/3 h and then reflux/4 h) and elimination of the selenoxide to yield the allylic alcohol (**15**).[23]

The above described experiments (Scheme III) conclusively demonstrate that the enzymatic cyclization of *trans,trans*-farnesyl pyrophosphate to trichodiene takes place without loss of isotope from C-1 of the precursor. This result, together with the previously cited findings of both Croteau and Arigoni, as well as related studies by Arigoni on the biosynthesis of a group of closely related cadalane- and humulane-derived sesquiterpenes[24] clearly exclude all redox mechanisms proposed to date and strongly favor an alternative isomerization–cyclization mechanism involving the tertiary allylic isomer nerolidyl pyrophosphate.[25] As illustrated in Scheme IV, isomerization of *trans,trans*-farnesyl pyrophosphate will give nerolidyl pyrophosphate, a conversion which we have previously shown takes place with syn stereochemistry via the allylic cation–pyrophosphate anion pair.[13] Rotation about the 2,3 single bond and anti allylic displacement[3] via the cisoid ion pair generates the bisabolyl cation en route to trichodiene. All operations are assumed to take place at a single enzyme active site. It is unnecessary to invoke *cis,trans*-farnesyl pyrophosphate as an intermediate, since, as previously pointed out,[13] further reaction of this substrate would proceed by way of the same ion pair from which it had been formed. Indeed, for bornyl pyrophosphate synthetase, Croteau has already demonstrated that the V_{max}/K_m for geranyl pyrophosphate is more that 20 times that for the cis isomer, neryl pyrophosphate.[11c] A coherent picture of terpenoid cyclization has therefore begun to emerge. Further investigations of the stereochemistry of farnesyl pyrophosphate isomerization–cyclization are in progress and the results will be reported in due course.[26]

Acknowledgment. 270-MHz ^1H spectra were recorded at the Southern New England High Field NMR Facility at Yale University. We should like to thank Professor Rodney Croteau for kindly sending us a preprint of ref 11a in advance of publication.

(21) B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, **93**, 1693 (1971).
(22) The alternative locus of tritium, C-10, is excluded by the known derivation of H-10 from 4-H_{re} of mevalonate.[7]
(23) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973); T. Mori and K. B. Sharpless, *J. Org. Chem.*, **43**, 1689 (1978); H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow, and D. F. Wendelborn, *ibid.*, **43**, 1697 (1978).
(24) (a) D. Arigoni, ref 4; (b) P. Bernasconi, Dissertation ETH Zurich No. 6024, 1977; F. Dorn, *ibid.*, No. 5554 (1975); F. Dorn and D. Arigoni, *Experientia*, **30**, 851 (1974); F. Dorn, P. Bernasconi, and D. Arigoni, *Chimia*, **29** (1), 24 (1975).
(25) See, however, H. Mackie and K. Overton, *Eur. J. Biochem.*, **77**, 101 (1977); K. H. Overton and D. J. Picken, *J. Chem. Soc., Chem. Commun.*, 105 (1976).
(26) This work was supported by NSF Grants PCM 74-07924 and PCM 78-13230.

Thermal Rearrangement of 2,2-Difluorovinylcyclopropane. A Concerted Pathway?

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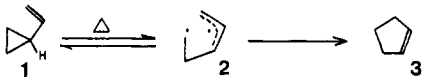
A reaction which has certainly been studied in great mechanistic detail is the rearrangement of vinylcyclopropane to cyclopentene. The bulk of the accumulated evidence is compatible with a diradical mechanism. Kinetic data (log A = 13.6, E_a = 49.7 kcal/mol)[1] are consistent with the formation of the allylically stabilized 1,3-diradical intermediate **2**, as are numerous elegant stereochemical investigations.[2] (That is not to say that "completely equilibrated" diradicals are involved, since stereoselectivity certainly is observed in a number of substituted vinylcyclopropane systems.)



As expected, radical-stabilizing substituents in the 2 position lower the activation energy for the rearrangement. For example, *trans*-2-methyl-, -phenyl-, and -methoxyvinylcyclopropanes each rearrange with cleavage of the C_1–C_2 bond and with lowered activation energies (48.6, 44.7, and 41.0 kcal/mol, respectively).[3,4] In recent years we have probed the quantitative effect of *fluorine* substituents, particularly gem-difluoro substituents, on thermal isomerizations of cyclopropane systems. The 9 kcal/mol incremental lowering of E_a for homolytic cleavage of 1,1-difluoro-2,3-dimethylcyclopropane[5] was consistent with the theoretical

(1) Flowers, F. C.; Frey, H. M. *J. Chem. Soc.* **1961**, 3547.
(2) (a) Willcott, R. M., III; Cargle, V. H. *J. Am. Chem. Soc.* **1967**, *89*, 723. (b) *Ibid.* **1969**, *91*, 4310. (c) Mazzocchi, P. H.; Tamburin, H. J. *Ibid.* **1970**, *92*, 7220. (d) Doering, W., von E.; Sachdev, K. *Ibid.* **1975**, *97*, 5512. (e) Andrews, G. D.; Baldwin, J. E. *Ibid.* **1976**, *98*, 6705.
(3) (a) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 5578. (b) Roth, W. R.; Konig, J. *Liebigs Ann. Chem.* **1965**, *688*, 28.
(4) Simpson, J. M.; Richey, H. G., Jr. *Tetrahedron Lett.* **1973**, 2545.

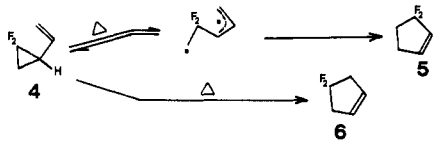
0002-7863/81/1503-2138$01.25/0

Table I. Rates for 4 → 6

T, K	194.91	203.38	208.32	213.38	218.55	224.25
k (× 10^5)	0.751	1.62	2.46	4.01	6.24	9.45

predictions,[6] structural determinations,[7] and earlier qualitative studies[8] which indicated that the bond *opposite* to the CF_2 group is weakened substantially. On the other hand, there is much evidence which indicates that the bond *adjacent* to the CF_2 group *is not* weakened substantially.[9]

Thus, it was reasonable to expect that 2,2-difluorovinylcyclopropane (**4**) would rearrange to 3,3-difluorocyclopentene (**5**) via cleavage of the weaker C_1–C_3 bond. However, when the isomerization of **4** was carried out in the gas phase, in a well-conditiond Pyrex vessel, the *only* product was 4,4-difluorocyclopentene (**6**), obtained in >90% yield.[10] Compound **6** could only have resulted from preferential ring expansion using the *stronger* C_1–C_2 bond. Rate constants were obtained for six temperatures (see Table I), and an Arrhenius plot of this data gave a good straight line, with the frequency factor and energy of activation being calculated by the method of least squares:



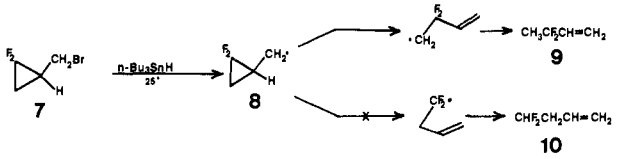
$$\log A = 13.7 \pm 0.2$$

$$E_a = 40.3 \pm 0.5 \text{ kcal/mol}$$

It should be noticed that there is a *substantial lowering* of E_a for **4** relative to **1**. In *no other cases* where adjacent bond cleavage is involved have we ever detected a significant bond weakening. This includes our earlier mentioned studies of difluoromethylenecyclopropane and difluorospiropentane.[9]

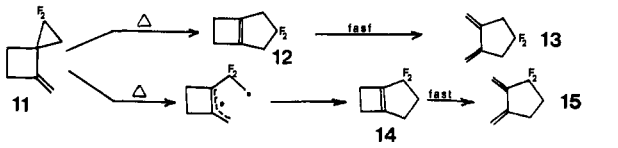
To one unfamiliar with the effects of fluorine, C_1–C_2 cleavage in **4** might not appear at all unusual. After all, 2,2-dichlorovinylcyclopropane rearranges exclusively via C_1–C_2 cleavage and with a significant rate enhancement.[11] Unlike most other substituents, however, fluorine does not seem to provide stabilization to a carbon radical site.[12]

In order to test further the effect of a CF_2 group in a cyclopropane ring on *homolytic* cleavage, we have generated the 2,2-difluorocyclopropylcarbinyl radical (**8**) and examined its rearrangement to an allyl carbinyl system. The *only* product observed from this reaction, using neat *n*-Bu_3SnH at 25 °C, was 3,3-difluoro-1-butene (**9**) which results from cleavage of the *opposite* C_1–C_2 bond.[13] No **10** could be detected.



This result demonstrates clearly the preference for C_1–C_3 cleavage in a homolytic process,[14] and the question thus remains as to *why* **4** *does* rearrange via C_1–C_2 migration. Since C_1–C_2 homolytic cleavage of **4** to a diradical would seem to be an unlikely competitive process, we would like to propose the possibility of *a concerted pathway* for the rearrangement from **4** to **6**. It, however, is not yet clear as to why a concerted mechanism should involve the stronger C_1–C_2 bond exclusively in the rearrangement.

As a test of this hypothesis, the synthesis and thermal rearrangement of 1,1-difluoro-4-methylenespirohexane (**11**) was carried out.[16] In the case of **11**, the vinylcyclopropane system



has a geometry which should diminish the probability of a concerted mechanism.[17] The results show a partitioning between products **13** and **15**,[18] and when compared to the results from **4**, they are best interpreted as deriving from a *competition* between concerted and nonconcerted processes, the concerted process being inhibited relative to **4** because of the structural constraints inherent to **11**.[17]

Out suggestion of a possible concerted mechanism for the rearrangement from **4** to **6** has certainly not been unambigously demonstrated. It is, however, a reasonable explanation for a very puzzling result. Moreover, it is possible that other substituents, such as methoxy, may well induce similar mechanistic deviation in vinylcyclopropane and related rearrangements. While the 2-methoxy-1-vinylcyclopropane rearrangement[4] was discussed entirely in terms of a diradical process, other thermal studies, on 5-methoxybicyclo[2.1.0]pentane systems,[20] indicate that the concerted mechanism should be considered here also. The intriguing possibility that concerted pericyclic reactions of a difluorocyclopropyl group may prefer to utilize the adjacent bond, while reactions involving diradicals prefer opposite bond homolysis is being tested further.

Acknowledgment. We acknowledge with thanks the support of this research in part by the National Science Foundation.

(5) Dolbier, W. R. Jr.; Enoch, H. O. *J. Am. Chem. Soc.* **1977**, *99*, 4532.
(6) (a) Hoffmann, R.; Stohrer, W. P. *Ibid.* **1971**, *93*, 6941. (b) Hoffmann, R. *Tetrahedron Lett.* **1970**, 2907. (c) Gunter, H. *Ibid.* **1970**, 5173.
(7) Perretta, A. T.; Laurie, V. W. *J. Chem. Phys.* **1975**, *62*, 2469.
(8) (a) Sargeant, P. B. *J. Am. Chem. Soc.* **1969**, *91*, 3061. (b) Jefford, C. W.; Mareda, J.; Gehret, J. C. E.; Karbengele, T.; Graham, W. D.; Burger, U. *Ibid.* **1976**, *98*, 2585.
(9) (a) Dolbier, W. R., Jr.; Fielder, T. H. Jr., *Ibid.* **1978**, *100*, 5577. (b) Dolbier, W. R., Jr.; Al-Sader, B. H.; Sellers, S. F.; Elsheimer, S *Ibid.* **1981**, *103*, 715.
(10) Spectral properties of **4**: IR (gas) ν_{max} 1475, 1225 cm^{-1}, $\nu_{C=C}$ 1640 cm^{-1}; NMR ($CDCl_3$) δ 5.0–5.8 (vinylic *H*, complex m, 3), 2.0–2.6 (CH, complex m, 1), 0.9–2.0 (CH_2, complex m, 4); ϕ 135.0 (midpoint) (AB further splitting, J_{AB} = 156.5 Hz, $\Delta\nu_{AB}$ = 1235.6 Hz, $J_{F\text{-}cis\text{-}H}$ = 12.5 Hz, $F_{F\text{-}trans\text{-}H}$ = 4 Hz). MS gave M^+ 104.94317 [standard deviation = 0.00225 (21.6 ppm)]. Calculated M^+ 104.04376 [deviation = −0.00054 (5.6 ppm)]. Spectral properties of **6**: NMR ($CDCl_3$) δ 5.97 (complex m, 2) δ 3.00 (t with further splitting, J = 16 Hz, 4) ϕ 70.42 (t of p, J_t = 2.5 Hz, J_p = 16 Hz). MS gave M^+ 104.04303 [standard deviation = 0.00103 (9.9 ppm)]. Calculated M^+ 104.04376 [deviation = −0.0096 (7.0 ppm)].
(11) Ketley, A D.; Berlin, A. J.; Gorman, E.; Fisher, L. P. *J. Org. Chem.* **1969**, *31*, 305.
(12) (a) O'Neal, H. E.; Berson, S. W. *J. Chem. Phys.* **1968**, *72*, 1866. (b) Cocks, A. T.; Egger, K. W. *Helv. Chim. Acta* **1973**, *56*, 1516, 1537. (c) Dolbier, W. R., Jr.; Piedrahita, C. A.; Al-Sader, B. H. *Tetrahedron Lett.* **1979**, 2957.
(13) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024.
(14) It should be mentioned that the effect of substituents *in* the 2 position in cyclopropylcarbinyl–allylcarbinyl rearrangements is *not* at all well understood at present.[15]
(15) (a) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 287. (b) Beckwith, A. L. J.; Moad, G. *Ibid.* **1980**, 1083.
(16) **11** was synthesized via CF_2: addition to 1,2-dimethylenecyclobutane. Spectral properties of **11**: IR (gas) ν_{max} 1475 cm^{-1}, $\nu_{C=C}$ 1690 cm^{-1}; NMR ($CDCl_3$) δ 4.8 (d of t, J = 0.8, 2.2 Hz, 1), 4.7 (p of t, J = 0.65, 2.7 Hz, 1) 3.0–2.6 (complex m, 2), 2.5–1.9 (complex m, 2), 1.7–1.3 (complex m, 2); ϕ 137.0 (midpoint) (AB with further splitting, J_{AB} = 151.9 Hz, $\Delta\nu_{AB}$ = 276.3 Hz). MS gave M^+ 130.05827 [standard deviation = 0.0042 (32 ppm)]. Calculated M^+ 130.05941 [deviation = −0.00114 (8.7 ppm)]. Base peak *m/e* = 115, M^+ 64.5% of base.
(17) Because of the structural demands of the cyclobutane ring, the methylene CH_2 group is *substantially* further removed from the cyclopropane ring bonds than in **1** and **4**, thus diminishing the potential for overlap in a concerted transition state.
(18) Intermediates **12** and **14** would not be expected to survive the conditions of the pyrolysis, but should rearrange rapidly to **13** and **15**, respectively.[19] Spectral properties of **13**: NMR ($CDCl_3$) δ 5.55 (complex m, 1), 5.05 (complex m, 1), 2.95 (t of t, J = 13.9, 1 Hz, 2); ϕ 98.7 (complex p, J = 13.9 Hz). GC/MS gave M^+ 130.0591; M^+ base peak. Spectral properties of **15**: NMR ($CDCl_3$) δ 5.66 (complex m, 1) 5.0 (complex m, 1) 2.7–2.34 (complex m, 2); ϕ 97.28 (t with further splitting, J = 12.65 Hz). GC/MS gave M^+ 130.0574. Base peak *m/e* = 39, M^+ 20.9% of base.
(19) Cocks, A. T.; Frey, H. M. *J. Chem. Soc. B* **1970**, 952.
(20) Tufariello, J. J.; Bayer, A. C. *Tetrahedron Lett.* **1972**, 3551.