about bond c. Finally, neat (6.4 *M*) *cis*-4-pentenal-5-d_1 was subjected to decarbonylation. The observed *cis*-1-butene-1-d_1:*trans*-1-butene-1-d_1 ratio was 1.42:1.00, indicating that **3** can be trapped in a manner analogous to the trapping of **1**. This lends additional support to the proposed rearrangement scheme, particularly the contention that **4** lies along the rearrangement reaction coordinate.

(8) National Institutes of Health Predoctoral Fellow, 1964–1967.

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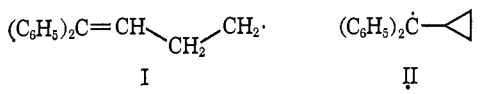
Evidence for Rapid and Reversible Equilibration of the γ,γ-Diphenylallylcarbinyl and Diphenylcyclopropylcarbinyl Free Radicals[1]

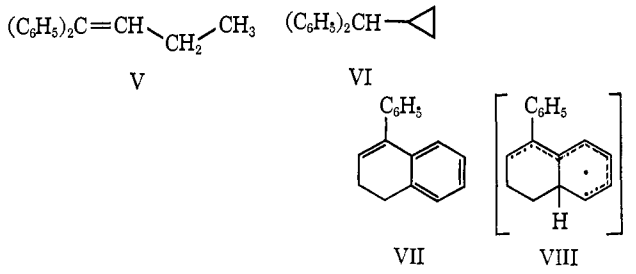
Sir:

We wish to report an example of an unusually facile and reversible free-radical rearrangement in which a substituted allylcarbinyl free radical is interconverted with the corresponding cyclopropylcarbinyl radical.[2] The investigation of the radical rearrangement complements previous studies on analogous carbanion[3] and similar carbonium ion[4] systems. Specifically, we have found that the γ,γ-diphenylallylcarbinyl radical (I) and the cyclopropyldiphenylcarbinyl radical (II) interconvert rapidly at 125° with respect to hydrogen abstraction by either from triethyltin hydride. Trialkyltin hydrides are known to be efficient hydrogen atom donors. For example, decarbonylation of the triphenylacetyl radical is competitive with hydrogen abstraction from tri-*n*-butyltin hydride only at low hydride concentrations.[5]



I II

In the present work, the radicals were generated by thermolysis of either *t*-butyl (γ,γ-diphenylallyl)-peracetate (III) or *t*-butyl cyclopropyldiphenylperacetate (IV). The amounts of the principal C_{16}-hydrocarbon products formed in the presence of several different hydrogen donors are listed in Table I. Of these, 1,1-diphenyl-1-butene (V) and cyclopropyldiphenylmethane (VI)[6] are assumed for our purposes here to arise from the radicals I and II, respectively, while 1-phenyl-3,4-dihydronaphthalene (VII) is considered to arise from an *ortho* ring cyclization[7] of I to VIII, followed by loss of a hydrogen atom.



V VI

VII VIII

The relative amounts of V and VII formed in 1,4-cyclohexadiene–cyclohexane mixtures as a function of the reaction temperature and of the cyclohexadiene concentration suggest that the *ortho* ring cyclization is irreversible and that VIII disappears mainly through disproportionation or dimerization, or through loss of a hydrogen atom to, or coupling with, a cyclohexadienyl radical. The conversion of VIII to VII appears to be fairly efficient, and one may write approximately

$$d(V)/d(VII) = k_a(I)(ZH)/k_r(I)$$

so that

$$k_a/k_r = (V)/(VII)(ZH)_{av}$$

where k_a is the rate constant for hydrogen abstraction by I from the hydrogen donor, ZH, and k_r is the rate constant for the isomerization of I to VIII. Values of k_a/k_r estimated for triethyltin hydride, 1,4-cyclohexadiene, and indene at 125–131° are about 17, 0.4, and 0.1, respectively.[8] All of the other solvents are much less active as hydrogen donors; in fact, the similarity in the yields of V for decomposition of III or IV in cyclohexane, ether, tetrahydrofuran, and cumene suggests that the active hydrogen donor in these cases is

Table I. Yields of C_{16}-Hydrocarbon Products in the Thermal Decomposition of *t*-Butyl (γ,γ-Diphenylallyl)peracetate and *t*-Butyl Diphenylcyclopropylperacetate in Various Solvents

Solvent	Perester[a]	Yield, % V	VI	VII
Triethyltin hydride, 0.14 *M* in *n*-octane	III[b]	23.5	1.63	10.0
1,4-Cyclohexadiene	III[d]	30.0	0.3[f]	11.9
Indene	III[c]	10.7	0.02[f]	16.0
Cyclohexane	III[d]	1.0	0.1[f]	26.5
Ether	III[d]	1.1	0.6[f]	31.5
Tetrahydrofuran	III[d]	1.0	0.05[f]	15.6
Cumene	III[d]	1.3	0.2[f]	*e*
1,4-Cyclohexadiene	IV[c]	45.0	14.6	11.0
Cyclohexane	IV[c]	1.1	7.5[f]	23.5
Ether	IV[c]	2.0	9.5[f]	28.5
Benzene	IV[c]	1.1	11.4	18.5

[a] The decomposition temperatures were 125–131° for III and 35° for IV. [b] 0.002 *M*. [c] 0.05 *M*. [d] 0.30 *M*. [e] Not determined. [f] As identification has been made by gas chromatographic retention time alone, this figure is an upper limit to the amount formed.

(1) Supported by the National Science Foundation. A preliminary account of the decomposition of *t*-butyl (γ,γ-diphenylallyl)peracetate and the theoretical problems posed thereby was presented at the Symposium on Small-Ring Compounds at the 142nd National Meeting of the American Chemical Society, Washington, D. C., March 22, 1962.

(2) For recent studies on related systems, see D. I. Schuster, Ph.D. Thesis, California Institute of Technology, 1961, and A. J. Rosen, Ph.D. Thesis, California Institute of Technology, 1964.

(3) A. Maercker and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1742 (1966).

(4) K. L. Servis and J. D. Roberts, *ibid.*, **87**, 1331 (1965).

(5) H. G. Kuivila and E. J. Walsh, Jr., *ibid.*, **88**, 571 (1966).

(6) The formation of VI is reasonable on the basis of the stabilization of the radical I by the phenyl groups. In the absence of these groups, no cyclopropanes may be formed; *cf.* L. K. Montgomery and J. W. Matt, *ibid.*, **89**, 3050 (1967).

(7) For a previously reported example of a rearrangement of this type, see S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956).

(8) (a) The concentration of hydrogen donor was taken to be 8.7 *M* for 1,4-cyclohexadiene and 7.4 *M* for indene. (b) The values of k_a/k_r may not be strictly comparable because recent rate studies have shown that the perester III mainly undergoes induced decomposition in the presence of triethyltin hydride. Formation of large amounts of triethyltin γ,γ-diphenylallylacetate (*ca.* 50%) and of hydrocarbon products (V, VI, etc.) under a variety of conditions can be rationalized in terms of attack of triethyltin radicals at either of the peroxy oxygens of III. The nature of the induced decomposition will be discussed more fully in a later publication.

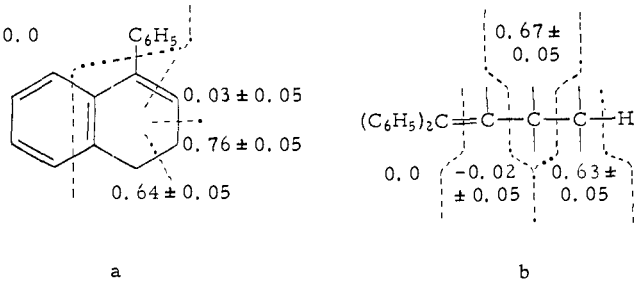


Figure 1. Distribution of the deuterium label as inferred by nmr spectroscopy in products from the decomposition of deuterium-labeled *t*-butyl (γ,γ-diphenylallyl)peracetate in (a) cyclohexane at 125°, and (b) 1.34 *M* triethyltin hydride in *n*-octane at 125°.

actually VII or a tetrahydronaphthalene believed to correspond to an as yet uncharacterized reaction product.

A detailed product analysis to be reported later indicates that relative yields of diphenylcyclopropylmethane and diphenylbutene formed from either perester in 1,4-cyclohexadiene as a function of initial perester and cyclohexadiene concentrations are compatible with VI being formed mainly through donation of hydrogen to II by cyclohexadienyl radicals while V arises similarly from I and 1,4-cyclohexadiene. In the solvents which are poor hydrogen donors, VI can be formed by hydrogen abstraction from VIII.[9]

For the decomposition of III in triethyltin hydride–*n*-octane mixtures, the ratio VI:V is independent of the tin hydride concentration. This observation indicates that the rearrangement of I to II is fast with respect to hydrogen abstraction by I from the hydride, or that there is a single "nonclassical" radical of intermediate structure which gives rise to both hydrocarbons. Thus, the degree of equivalence attained by the methylene groups in I before conversion to product is of special interest. To determine this, perester III was prepared with 1.40 g-atoms of deuterium in the α position. Following decomposition in cyclohexane at 125°, the distribution of the deuterium label in VII, the major reaction product, was determined by nmr spectroscopy. The results are summarized in Figure 1a.

It is clear that the rearrangement of I to II must be fast with respect to that of I to VIII. Here, the time during which the rearrangement may take place is limited only by the relatively slow rate at which the *ortho* ring cyclization occurs. Decomposition of III in the presence of 1.34 *M* triethyltin hydride made it possible to reduce this time by approximately a factor of 23, according to the value of k_a/k_r estimated for the tin hydride. Nonetheless, nmr analysis of the 1,1-diphenyl-1-butene (V) formed showed equilibration of the methylene groups to have occurred even in the presence of this active hydrogen donor (Figure 1b). Thus, the half-time for the isomerization of I to II must be short compared to that for the reaction of the former with the tin hydride.

At present there is no reason to postulate the existence of a "nonclassical" radical species to account for the experimental results and, on the whole, the radical system behaves more like the analogous carbanion system[3] than like similar carbonium ion systems.[4] Possible answers to the intriguing question[10] as to the magnitude of the equilibrium constant between I and II will be considered in detail later.

(9) The major difference in the amount of VI formed in the decomposition of the two peresters in cyclohexadiene (see Table I) can be understood essentially as follows. The half-life for decomposition of ring-opened perester, III, at 131° is about the same as that for IV at 35°. The steady-state cyclohexadienyl radical concentration goes roughly as the square root of the decomposition rate. Therefore, the cyclohexadienyl radical concentration will be about the same in the two cases. However, the steady-state concentration of the ring-closed radical, II, will be quite different. If, as we believe, II is energetically more stable than I, the ratio I:II will be greater at the higher temperature. The rates of hydrogen abstraction to give V and of conversion to ring-cyclized radical VIII will then be much faster at 131° due both to the temperature effect on k_a and on k_r and to the greater relative amount of I. As a result, the steady-state concentration of II will be much smaller at 131° than at 35°, and the amount of VI formed will be correspondingly less.

(10) D. Patel, C. H. Hamilton, and J. D. Roberts, *J. Am. Chem. Soc.*, 87, 5144 (1965).

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pH-Dependent Proton Absorption in Chymotrypsin Binding. Evidence for a pH-Dependent Conformation Change of the Enzyme[1]

Sir:

The second-order rate constant (k_{cat}/K_m(app)) of chymotrypsin-catalyzed reactions has long been known to decrease above pH 8, with an apparent dependence on a single ionizable group of p$K \sim 9$.[2] Recently this phenomenon has been identified as a pH-dependent binding by chymotrypsin, even for neutral substrates and inhibitors.[3-5] A pH-dependent binding of a neutral molecule implies that a pH-dependent proton change of the enzyme occurs on binding. In fact, a pH-dependent absorption of one proton per mole of enzyme has been observed upon acylation of chymotrypsin.[7] Is this proton phenomenon at high pH associated with the noncovalent binding of substrate to enzyme (K_s) or with the subsequent covalent acylation step (k_2)? Recent results with competitive inhibitors of chymotrypsin[4] and with derivatized chymotrypsins[8] favor the former possibility.

The binding of the competitive inhibitor, benzyl alcohol, to α-chymotrypsin was first investigated. This substance is particularly advantageous since it is endowed with both high solubility and partial resemblance to a natural chymotrypsin substrate; solutions with $[I]_0/K_i = 20$ can easily be prepared, leading to essentially complete saturation of the enzyme by the inhibitor even at high pH. The results of a series of experiments determining proton uptake by the enzyme upon binding of excess benzyl alcohol are shown in

(1) This research was supported by grants from the National Institutes of Health.
(2) H. Neurath and G. W. Schwert, *Chem. Rev.*, 46, 69 (1950).
(3) A. Himoe and G. P. Hess, *Biochem. Biophys. Res. Commun.*, 23, 234 (1966).
(4) M. L. Bender, M. J. Gibian, and D. J. Whelan, *Proc. Natl. Acad. Sci. U. S.*, 56, 833 (1966).
(5) Earlier erroneous reports associated this phenomenon with a subsequent rate step.[6]
(6) M. L. Bender, G. E. Clement, F. J. Kézdy, and H. d'A. Heck, *J. Am. Chem. Soc.*, 86, 3680 (1964).
(7) J. Keizer and S. A. Bernhard, *Biochemistry*, 5, 4127 (1966), and references therein.
(8) H. L. Oppenheimer, B. Labouesse, and G. P. Hess, *J. Biol. Chem.*, 241, 2720 (1966).