TABLE I
REACTIONS OF HEXAFLUOROACETONE WITH OLEFINS

$(CF_3)_2C{=}O + RCH_2CH{=}CH_2 \longrightarrow HO(CF_3)_2CCH_2CH{=}CHR$ (1, R = H; 2, R = CH_3) + $HO(CF_3)_2CCH{=}CHCH_2R$ (3, R = H; 4, R = CH_3)

$AlCl_3$-catalyzed reaction

R	Product, % conversion			
	1	*trans*-3	*cis*-3	
H	27	43	2	
	trans-2	*cis*-2	*trans*-4	*cis*-4
CH_3	26	6	47	0[a]

Thermal reaction

R	Product, % conversion			
	1	*trans*-3	*cis*-3	
H	82	0	0	
	trans-2	*cis*-2	*trans*-4	*cis*-4
CH_3	59	15	0	0[a]

[a] No standard was available, but there was no evidence for the presence of these compounds.

a free carbonium ion (or equivalent associated species). Electrophilic attack of the hexafluoroacetone–$AlCl_3$ complex on olefin yields an adduct as shown. This may lose a proton from either adjacent carbon to yield the mixtures of products observed.

$$(CF_3)_2\overset{+}{C}O\overset{-}{A}lCl_3 + CH_2{=}CHCH_3 \longrightarrow (CF_3)_2C(OAlCl_3)CH_2\overset{+}{C}HCH_3 \longrightarrow$$

$$HO(CF_3)_2CCH{=}CHCH_3 + HO(CF_3)_2CCH_2CH{=}CH_2 \quad (3)$$

Experimental Section[2]

$AlCl_3$-Catalyzed Reactions. Propylene.—The procedure is essentially the same as that in the literature.[1c] A cold (−30°) mixture of 166 g (1 mol) of hexafluoroacetone, 84 g (2 mol) of propylene, and 2 g of $AlCl_3$ in 1 l. of pentane was allowed to warm slowly. At *ca.* −15°, there was a gentle exotherm, after which the reaction mixture was stirred at 0° for 2 hr. Treatment with dilute (5%) hydrochloric acid and distillation yielded 150 g (72%) of product boiling at 97–100°. Glpc analysis showed the following product composition (yield, retention time): 1,1-bis(trifluoromethyl)-3-buten-1-ol (**1**) (37%, 9.0 min); *trans*-1,1-bis(trifluoromethyl)-2-buten-1-ol (*trans*-**3**)(60%, 13.2 min); and *cis*-1,1-bis(trifluoromethyl)-2-buten-1-ol (*cis*-**3**) (3%, 10.5 min). Compounds **1** and *trans*-**3** were isolated by preparative scale glpc techniques, but *cis*-**3** was not recoverable because of its low concentration.

Analytical Data. Compound 1 [$CH_{a2}{=}CH_bCH_{c2}C(CF_3)OH_d$].—Infrared spectrum: 1650 (C=C stretch) and 3500 cm^{-1} (OH stretch); ^1H nmr ($CDCl_3$) δ 5.8 (H_a, complex), 5.3 (H_b, complex), 2.70 (d, J_{cb} = 7 Hz H_c), and 3.35 (H_d). The ^{19}F nmr spectrum showed a single peak at 0.0 ppm.

Anal. Calcd for $C_6H_6F_6O$: C, 34.62; H, 2.90. Found: C, 34.82; H, 3.23.

Compound *trans*-**3** [$CH_{a3}CH_b{=}CH_cC(CF_3)_2OH_d$].—Infrared spectrum: 1680 (C=C stretch) and 3500 cm^{-1} (OH stretch); ^1H nmr δ 1.93 (d, J_{ab} = 7 Hz, H_a), 6.27 (q, 2, J_{ba} = 7 Hz, J_{bc} = 16 Hz, H_b), 5.58 (d, J_{cb} = 16 Hz, H_c), and 3.40 (H_d). The ^{19}F nmr spectrum showed a single peak at −0.1 ppm. The *trans* stereochemistry is dictated by the 16-Hz coupling constant for the vinyl protons. For the *cis* isomer, a value of *ca.* 11 Hz would be expected (see *cis*-**2**).

1-Butene.—The procedure is the same as that with propylene, using 166 g (1 mol) of hexafluoroacetone, 112 g (2 mol) of 1-butene, and 2 g of $AlCl_3$. Distillation yielded 175 g (79%) of product boiling at 114–117°. Glpc analysis showed the following product composition (yield, retention time): *trans*-1,1-bis(trifluoromethyl)-3-penten-1-ol (*trans*-**2**) (33%, 10.0 min); *cis*-1,1-bis(trifluoromethyl)-3-penten-1-ol (*cis*-**2**) (8%, 11.0 min); and *trans*-1,1-bis(trifluoromethyl)-2-penten-1-ol (*trans*-**4**) (59%, 13.0 min). Compounds were isolated by preparative scale glpc methods.

Analytical Data. Compound *trans*-**2** [$CH_{a3}CH_b{=}CH_cCH_{d2}C(CF_3)_2OH$] had ^1H nmr δ 1.70 (d, J_{ba} = 7 Hz, H_a); 5–6 (complex, H_b and H_c), and 2.60 (d, J_{cd} = 7 Hz, H_d). Spin decoupling shows H_b to be centered at 5.70 ppm and H_c to be at 5.35 ppm. Each shows a 16-Hz coupling constant, indicating the *trans* stereochemistry about the double bond. The ^{19}F nmr spectrum shows a single peak at −1.6 ppm.

Anal. Calcd for $C_7H_8F_6O$: C, 37.85; H, 3.62. Found: C, 38.39; H, 3.63.

Compound *cis*-**2** [$CH_{a3}CH_b{=}CH_cCH_{d2}C(CF_3)_2OH$] had nmr δ 1.64 (d, J_{ba} = 7 Hz, H_a), 5–6 (complex, H_b and H_c), and 2.70 (d, J_{cd} = 7 Hz, H_d). Spin decoupling showed H_b to be centered at 5.40 ppm and coupled with the *cis* vinyl proton showing an 11-Hz splitting constant.

Compound *trans*-**4** [$CH_{a3}CH_{b2}CH_c{=}CH_dC(CF_3)_2OH$] had ^1H nmr δ 0.97 (t, J_{ba} = 6 Hz, H_a), 2.1 (complex, H_b), 6.28 (t, 2, J_{cb} = 6 Hz, J_{cd} = 16 Hz, H_c), 5.60 (d, J_{cd} = 16 Hz, H_d). The ^{19}F nmr spectrum showed a single peak at 0.6 ppm.

Anal. Calcd for $C_7H_8F_6O$: C, 37.85; H, 3.62. Found: C, 37.78; H, 3.71.

Thermal Reactions. Propylene.—The procedure followed is essentially the same as that in the literature.[1c] A mixture of 21 g (0.5 mol) of propylene and 83 g (0.5 mol) of hexafluoroacetone was heated in a sealed tube at 150° for 16 hr. Distillation of the contents gave 85 g (82%) of **1**, bp 94–95° (lit.[1c] bp 95–98°). Glpc analysis showed no other isomer to be present.

1-Butene.—The reaction was carried out in the same manner as with propylene, using 2.8 g (0.05 mol) of 1-butene and 8.3 g (0.050 mol) of hexafluoroacetone. Distillation of the residue yielded 7.7 g (74%) of product boiling at 117–119°. Glpc analysis shows this to consist of 80% *trans*-**2** and 20% *cis*-**2**.

Treatment of Alkenols with Aluminum Chloride in Pentane.—The pure alcohol (0.25 g), 25 ml of pentane, and 0.050 g of $AlCl_3$ were stirred for 3 hr at room temperature. After washing with 5% hydrochloric acid, the reaction mixture was examined by glpc. With **1**, *trans*-**3**, and *trans*-**4**, only starting material was observed. With *trans*-**2**, however, the only product that was observed was a material with a retention time of 1.5 min. A sample obtained by preparative scale glpc methods was identified as 2,2-bis(trifluoromethyl)-5-methyltetrahydrofuran. The infrared spectrum shows no hydroxyl absorption, while the ^1H nmr spectrum may be described as follows: δ, 1.30 (d, J = 6 Hz, CH_3), 4.3 (complex, HCO), and 1.5–2.5 [complex, $(CH_2)_2$]. The ^{19}F nmr spectrum shows two quartets at −0.9 and 1.6 ppm (J = 9 Hz).

Anal. Calcd for $C_7H_8F_6O$: C, 37.85; H, 3.62. Found: C, 37.97; H, 3.65.

Registry No.—**1**, 646-97-9; *cis*-**2**, 16223-66-8; *trans*-**2**, 16203-00-2; *trans*-**3**, 21308-76-9; *trans*-**4**, 21308-77-0; 1,1-bis(trifluoromethyl)-4-methyltetrahydrofuran, 21297-53-0; hexafluoroacetone, 684-16-2.

(2) All boiling points are uncorrected. Infrared spectra were obtained as films using the Perkin-Elmer Model 337 spectrophotometer. Nmr spectra were obtained with a Varian Associates Model HA 100 spectrometer using chloroform as solvent and TMS as internal standard. For fluorine spectra, trifluoroacetic acid was used as an external standard. Spectra were run using field frequency lock at 94.1 MHz using a modification described by Douglas.[3] Spectra at both frequencies are accurate to ±0.02 ppm. Glpc analyses were run on an F & M Model 720 gas chromatograph using a 9-ft column filled with a 20% Carbowax 20M on Chromosorb P packing. Preparative work was done on an F & M Model 775 Prepmaster gas chromatograph using a similar column (column temp 110°, helium flow 100 ml/min). Elemental analyses were performed by Huffman Laboratories, Inc., Wheatridge, Col.

(3) A. W. Douglas, Abstracts of papers presented at the 7th Experimental Nmr Conference, Feb 1966.

1-Triptycyl Radical Stability

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1-Triptycyl radical should be destabilized both by its considerable angle strain (triptycene has about 63° of "total angle strain" compared with 75° for norbornane)

and by the inductive effect of the three phenyl groups (which are held parallel to the odd-electron orbital so there is no phenyl stabilization), as Bartlett and Greene[1] pointed out 15 years ago. They observed that about 66% of the thermal decomposition of triptoyl peroxide in benzene proceeds by O—O homolysis to carboxytriptycyl radicals, giving CO_2 and triptycene as the major products, along with some biphenyl. These findings have been interpreted[2] as indicating abstraction of hydrogen from benzene by triptycyl radical. We here report investigation of the decomposition of two other obvious sources of triptycyl radicals, the *t*-butyl perester and the aldehyde, undertaken to establish the energy of triptycyl radical relative to other radicals.

t-Butyl pertriptoate (**1**) decomposes in chlorobenzene with first-order kinetics, k (130.0°) $= 2.30, 2.35 \times 10^{-4}$ sec^{-1}. As expected,[3] this rate is close to the one-bond cleavage limit found for other peresters which give unstable radicals upon decarboxylation, such as *t*-butyl perbenzoate[4] and *t*-butyl 1-norbornylpercarboxylate.[5] Decomposition of **1** in benzene at 130° (sealed tube) gave 92% triptycene, and only a trace of materials with the vpc retention time of biphenyl. This is not surprising, since the alkyl hydrogens present in **1** and the decomposition products of *t*-butoxy radicals are better hydrogen donors than benzene. In chlorobenzene at 130°, 80% triptycene was isolated, along with a small amount of triptoic acid; no 1-chlorotriptycene was detectable.

We applied the chlorine abstraction/decarbonylation ratio technique of Applequist and Kaplan[6] to the triptycyl system to place triptycyl radical in the series of bridgehead radicals they studied. It is quite possible that this method makes errors in the D_{R-H} values derived from it, as the original authors discuss;[6] there is some evidence that it evaluates 1-adamanyl radical as being about 1 kcal/mol more stable than it actually is.[5,6] It remains, however, the only even semiquantitative method available for very unstable systems.[7] For triptycene-1-carboxaldehyde, the decarbonylation to abstraction ratio (k_1/k_2) observed was 0.048, 0.049, 0.054, and 0.060 in four separate runs. This figure is compared with literature values in Table I.

By the Applequist–Kaplan technique, 1-triptycyl is of about the same stability as 1-norbornyl radical. It is apparent that the inductive effect of the phenyl groups is not of overwhelming importance in destabilizing triptycyl radical; the latter should be closer to norbornyl than to bicyclooctyl radical in stability just on the basis of angle strain. Certainly the inductive destabilization cannot be greater than about 3 kcal/mol, and might be less.

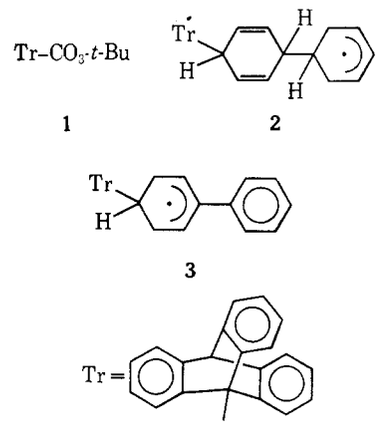
TABLE I

COMPARISON OF RADICAL STABILITIES BY THE APPLEQUIST–KAPLAN TECHNIQUE

R in RCHO	k_1/k_2	D_{R-H}[a]
1-Adamantyl	30	90.1
1-Bicyclo[2.2.2]octyl	15	91.0
1-Norbornyl	0.08	97.7
1-Triptycyl	0.05	98.3
Phenyl	0	

[a] See ref 6 for justification of these numbers.

No chlorobenzene could be detected from benzaldehyde upon treatment with the Applequist–Kaplan conditions. This is as expected, since the 112 kcal/mol value of D_{Ph-H}[8] should lead to a value of less than 10^{-6} for k_1/k_2. Since phenyl radical is at least 12 kcal/mol less stable than triptycyl, direct hydrogen abstraction from benzene would be prohibitively slow. We suggest that triptycyl radicals react with benzene by addition, as do less hindered radicals,[9] and that the addition product is too hindered to allow hydrogen abstraction. Addition to benzene would give **2**, which has hydrogens available for abstraction giving **3**, a reasonable source of the biphenyl observed by Bartlett and Greene.



Experimental Section

Materials.—1-Triptaldehyde,[10] 1-triptoic acid,[10] and 1-chlorotriptycene[11] were prepared by literature methods. *t*-Butyl 1-pertriptoate (**1**) was prepared[12] from the acid chloride[1] and sodium *t*-butyl hydroperoxide in 55% yield, and decomposed at 103–105°, ir 5.65 μ.

Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.05; H, 5.99; Found:[13] C, 81.20; H, 5.97.

Decomposition of 1.—Kinetics were determined by the ir method of Bartlett and Hiatt,[3] sealing 0.05 *M* aliquot of a chlorobenzene solution of **1** in ampoules after degassing, and heating at 130.00 ± 0.05° in an oil bath. Two seven-point runs were analyzed using a PE 421 spectrometer. From 100 mg of **1** in 2.3 ml of benzene heated to 130° for 24 hr, 66.0 mg (92%) of triptycene was isolated by chromatography with benzene–petroleum ether on 20 g of Fischer alumina. The triptycene contained a trace of material with the retention time of biphenyl (5 ft × 0.25 in. SE-30 column at 260°). Heating 88 mg of **1** in

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(7) The work of C. Rüchart, K. Herwig, and S. Eichler, *Tetrahedron Lett.*, 421 (1969), has shown that the remarkably low bromine to chlorine abstraction ratios for brigehead radicals do not reflect radical stabilities, and these facts can no longer be considered to be evidence against the Applequist–Kaplan dissociation energies. We also cannot consider the perester studies of ref 4 particularly damning for the bicyclo[2.2.2]octyl system number since important polar contributions to perester decomposition rates have been long known; see P. D. Bartlett and C. Ruchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960).
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(10) E. C. Kornfeld, P. Barney, J. Blankley, and W. Faul, *J. Med. Chem.*, **8**, 347 (1965).
(11) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **87**, 1332 (1965).
(12) P. D. Bartlett and J. M. McBride, *ibid.*, **87**, 1332 (1965).
(13) Spang Microanalytical Laboratories, Ann Arbor, Mich.

chlorobenzene (1.33 g) at 130° for 24 hr gave 48.3 mg (80%) of triptycene, and about 5 mg of triptoic acid.

Decarbonylation of Triptycene-1-carboxaldehyde.—Typically 63.0 mg of aldehyde, 59.5 mg of *t*-butyl peroxide, and 4.1815 g of carbon tetrachloride were degassed, sealed, and held at 130° for 24 hr, the volatile products removed by bulb-to-bulb distillation, 1 ml of methanol added, and the mixture let stand 48 hr before vpc analysis. Standard mixtures of chlorotriptycene and methyl triptoate were used to obtain the ratio of these two products; k_1/k_2 was calculated by the method of Applequist and Kaplan.

Attempted Decarbonylation of Benzaldehyde.—Using freshly distilled benzaldehyde, the product after the methanol treatment contained no chlorobenzene to the limits of vpc analysis. Methyl benzoate was formed in high yield.

Registry No.—1, 21343-33-9.

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The Use of Acetylenic Substrates in Enzyme Chemistry. Reaction of the Active Site of α-Chymotrypsin with N-Phenylpropioloylimidazole

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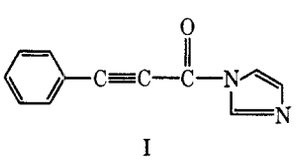
A new series of acetylenic substrates has been synthesized in this laboratory for the purpose of probing the reactions of a variety of enzymes. As an example of the wide applicability of the acetylenic substrates, the chromophoric compound N-phenylpropioloylimidazole (I) is introduced in the present note as a substrate for α-chymotrypsin, which can be employed for the direct spectrophotometric assay of this proteolytic enzyme.



I

We have found that I reacts very rapidly and stoichiometrically with chymotrypsin in an acylation step to give N-phenylpropioloyl-α-chymotrypsin. This reaction is followed by a deacylation step sufficiently slow to render I serviceable as an active site titrant.

Since there is no dearth of active site titrants for α-chymotrypsin,[2] the demonstration that N-propioloylimidazole rapidly acylates chymotrypsin is important, not only because it has allowed us to use I as an active site titrant, but also since it will permit us to delve further into the specificity of the active site. Considerable literature[3] exists on the reactions of olefinic substrates such as cinnamoylimidazole and cinnamate esters with chymotrypsin, and we can now embark on a thorough comparison of these reactions with those of acetylenic substrates, which obviously have a very different geometry. From such a comparison, a better picture of the stereochemistry of chymotrypsin's active site should emerge.[4]

Experimental Section

N-Phenylpropioloylimidazole (I) was synthesized by the reaction of N-phenylpropioloyl chloride with imidazole in benzene. After recrystallization from cyclohexane, I had mp 118–119° dec.

Anal. Calcd for $C_{12}H_8N_2O$: C, 53.63; H, 3.00. Found: C, 53.42; H, 3.14.

Titration of the Active Site of Chymotrypsin with I.—A wavelength of 310 mμ was determined to be most convenient for the spectrophotometric titration measurements. The stock solutions of N-propioloylimidazole were 1×10^{-2} *M* in this substrate and were prepared in acetonitrile which had been distilled over P_2O_5. Stock solutions of chymotrypsin in 0.05 *M* acetate buffer of pH 5.06 which were approximately 1×10^{-3} *M* in the enzyme were generally used.

In a typical experiment, 3 ml of 0.05 *M* acetate buffer was first placed in a 1-cm path-length spectrophotometer cell. After adjusting the base line of the spectrophotometer, 25 μl of the substrate stock solution was added and the absorbance of the resultant solution at 310 mμ was determined. Then 100 μl of the enzyme stock solution was added, and a sharp drop in the absorbance at 310 mμ was observed, which is ascribed to the consumption of the substrate by its reaction with the enzyme, leading to the formation of the acyl-enzyme, N-phenylpropioloyl-α-chymotrypsin. Finally, a slow further decrease in the absorption was seen due to the slow deacylation of the acyl-enzyme with attendant additional consumption of the substrate.

Using the above experimental procedure, the normality of enzyme-active sites in the reaction solution can be calculated from eq 1. In this equation, A_1 is the absorbance of the substrate solution at the time of addition of the enzyme. A_2 is the absorbance of the solution resulting after the addition of the enzyme, extrapolated back to the time of addition of the enzyme. A_3 is the absorbance of a solution prepared by adding 100 μl of the enzyme stock solution to 3.0 ml of 0.05 *M* acetate buffer at pH 5.06.

$$\text{normality} = \frac{0.968A_1 + 0.992A_3 - A_2}{250.2} \qquad (1)$$

Duplicate titrations with N-propioloylimidazole (I) agree to ±2%, a precision comparable to that obtained with the excellent chymotrypsin active site titrants, cinnamoylimidazole[5] and 5-nitro-1,2-benzoxathiole 2,2 dioxide.[6] Furthermore, excellent agreement was found between the normalities of chymotrypsin solutions determined by titration with I or with cinnamoylimidazole.

Registry No.—I, 21473-06-3.

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(1) Fellow of the Alfred P. Sloan Foundation.

(2) M. L. Bender, M. L. Begue-Canton, R. L. Blakely, L. J. Brubacher, J. Feder, C. R. Gunter, F. J. Kezdy, J. V. Kilheffer, Jr., T. H. Marshall, C. G. Miller, R. W. Roeske, and J. K. Stoops, *J. Amer. Chem. Soc.*, **88**, 5880 (1966).

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