repeatedly with boiling methanol to constant weight. The remaining solid (0.42 g, 42%[17]) was crystallized from dimethylformamide containing 1% formic acid to give I as colorless needles, 260 mg (26%[17]), mp 229–231°, $[\alpha]^{23}D$ −24.2° (*c* 2, dimethylformamide); lit.[3] mp 228–230°, $[\alpha]^{20.5}D$ −24.0° (*c* 2, dimethylformamide). A mixture melting point with authentic material[3,19] showed no depression. A sample for analysis was recrystallized from dimethylformamide–formic acid (99:1) with 95% recovery, mp 230–231°, $[\alpha]^{23}D$ −24.7° (*c* 2, dimethylformamide); lit.[3] mp 231–232°, $[\alpha]^{22}D$ −24.5° (*c* 2, dimethylformamide). *Anal.* Calcd for $C_{74}H_{91}O_{16}N_{13}S_4$ (mol wt 1546.8): C, 57.5; H, 5.93; N, 11.8. Found: C, 57.2; H, 5.80; N, 11.5. The infrared spectra of I and of authentic material were identical.

Amino acid analysis[20] of I gave the expected ratios of the constituent amino acids. Similar correct ratios were obtained from amino acid analyses of all fractions prior to crystallization, and even of the crude oil. This indicated that data obtained from amino acid analyses might be misleading if used by themselves as criteria of purity for peptides prepared by the solid phase method.

Conversion of I to [lysine]-vasopressin was carried out as described previously.[3] Thus treatment of I (50 mg) with sodium in liquid ammonia to remove all protecting groups, oxidative cyclization, desalting, and lyophilization gave a powder (37 mg, 95%) exhibiting approximately 250 units of pressor activity[21] per mg. Amino acid analysis of a sample which had been oxidized by performic acid[22] gave: $CySO_3H$, 1.90; Asp, 1.01; Glu, 1.00; Pro, 0.97; Gly, 1.00; Tyr, 0.95; Phe, 1.00; Lys, 1.03; NH_3, 3.01. Further purification[3] by ion-exchange chromatography afforded with 70% recovery [lysine]-vasopressin possessing a pressor activity of 308 ± 14 units/mg.

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(19) Kindly supplied by Dr. V. du Vigneaud.

(20) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, 30, 1190 (1958).

(21) Rat pressor assays were carried out by Miss M. Wahrenburg (Brookhaven National Laboratories) according to "The Pharmacopeia of the United States of America," 17th revised ed, Mack Printing Co., Easton, Pa., 1965, p 749.

(22) C. H. Li, *J. Biol. Chem.*, **229**, 157 (1957).

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Substituent Effects in the M − 42 Rearrangement of *n*-Butylbenzenes[1]

Sir:

The electron impact induced decomposition of *n*-butylbenzene requiring hydrogen transfer with benzylic cleavage yields an M − 42 fragment ion and competes with formal, simple benzylic cleavage for the major fraction of the fragment total ion current.[2–4] Earlier observations render doubtful the participation of a route which involves hydrogen transfer to benzylic carbon and support the McLafferty rearrangement.[3,5] Our data (Table I) also support these conclusions and argue against rearranged structures similar to those postulated to account for the behavior of substituted phenetoles, which have nearly identical Z/Z_0 values for *meta* and *para* isomers with the same substituent.[6,7]

Table I. Substituent Effects[a] on the Abundance of M − 42 Ions from $[XC_6H_4CH_2CH_2CH_2CH_3]\cdot^+$

X	Z/Z_0, 12 eV	Z/Z_0, 70 eV
H	1.00	1.00
p-NH_2	0.06	0.09
m-NH_2	0.47	1.15
p-OH	0.06	0.07
m-OH	0.84	1.15
p-OCH_3	0.03	0.05
m-OCH_3	0.76	1.15
p-F	0.15	0.19
m-F	1.05	1.24
p-I	0.09	0.05
m-I	0.52	0.27
p-CH_3	0.17	0.17
m-CH_3	0.73	0.81
p-$COOCH_3$	0.73	0.56
m-$COOCH_3$	0.90	0.73
p-COOH	1.02	0.64
m-COOH	1.22	0.94
p-CN	0.70[b]	1.75
m-CN	1.45	1.88
p-NO_2	1.05	0.94
m-NO_2	1.48	1.15

[a] $Z = [XC_7H_7]\cdot^+/[XC_6H_4CH_2CH_2CH_2CH_3]\cdot^+$. [b] Value at 14 eV is 1.32.

In the McLafferty rearrangement there are basically two processes which might be influenced by substituents: hydrogen transfer to the benzene ring and carbon–carbon bond cleavage.[8] If the carbon–carbon bond breaking here parallels the behavior observed in the M − 43 decomposition,[2] all *meta* substituents would be expected to exert a substantial effect in reducing Z/Z_0 ratios to similar small values, whereas *para* electron-donating groups (−X) should tend to enhance the relative rates of decomposition and give comparatively larger Z/Z_0 values. That these are not observed can be attributed to a considerable substituent effect on the transfer site or, without excluding this possibility, to a

(1) Financial assistance from the Research Corporation and from Eli Lilly and Company is gratefully acknowledged. The AEI MS-9 mass spectrometer used was purchased with funds made available by National Science Foundation Grant GP 3672.

(2) R. Nicoletti and D. A. Lightner, unpublished data.

(3) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 73–85 and references cited therein.

(4) H. M. Grubb and S. Meyerson in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 10.

(5) A third alternative which involves hydrogen transfer to the ring at the point of alkyl substitution would not be expected to show reduced transfer with substitution of one *ortho* methyl group (reduced ~50%) or two *ortho* methyl groups (zero transfer). See ref 3, p 82.

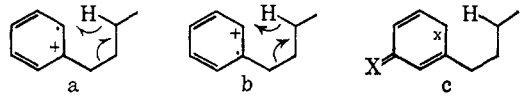
(6) F. W. McLafferty, M. M. Bursey, and S. M. Kimball, *J. Am. Chem. Soc.*, **88**, 5022 (1966).

(7) For a review of substituent effects in mass spectrometry see M. M. Bursey, *Org. Mass Spec.*, **1**, 31 (1968).

(8) The site, γ,[4] of carbon–hydrogen cleavage is probably too remote to be affected by the aromatic ring and its substituents.

very different substituent effect on carbon–carbon cleavage. For the hydrogen-transfer step alone, if it is dependent upon positive charge or radical character at the reaction sites on the ring,[9,10] *meta* isomers (which are *ortho* and *para* to the transfer sites) might be expected to exhibit more certain effects, through resonance, upon the reaction and the Z/Z_0 ratios than would *para* isomers. In fact, it can be seen in Table I that at 12-eV ionizing voltage electron-withdrawing (+X) *meta* substituents generally enhance the reaction rates relative to butylbenzene, whereas −X groups usually decrease the rates somewhat.

The McLafferty rearrangement in *n*-butylbenzene itself has been written as in **a** with hydrogen transfer to a radical site,[6] although in this formalism an alternative representation (**b**), in which hydrogen is transferred to a positively charged site, might also be considered. The relative importance of radical character or positive



charge at the transfer site should depend on the nature and position of a substituent; thus, in the resonance-structure formalism, the effect of a *m*-amino or *m*-nitro substituent would be depicted in **c** as X = $^{+}NH_2$, x = · or X = $\cdot NO_2$, x = +. Similar structures for *para* substituents do not appear to establish either radical character or positive charge at the transfer site. Accordingly, the observed difference in behavior of any pair of isomers is in qualitative agreement with the greater Z/Z_0 ratio being associated with greater radical character or positive charge at the transfer site.

However, interrelating the data of Table I using the above argument is not nearly so straightforward, and the relative importance of positive charge *vs.* radical character is difficult to assess from resonance structures. For, although +X groups do not induce the Z/Z_0 ratios to vary too far from unity, what differences are observed seem to be unrelated to the calculated π-electron positive charge (essentially zero) at the transfer site of the molecular ion.[11] At best, the larger Z/Z_0 value of a pair of isomers is in congruence with the lower π-electron density at the transfer site. Parallel correlations between +X and −X substituents are not obvious, except perhaps for *meta*-substituted compounds; *i.e.*, positive charge at the transfer site appears to decrease the probability of transfer.[11]

Whatever the implications of the above discussion, it may be shown that there is a reasonably good correlation with the Hammett equation[12] for the effect of *meta* substituents on the abundance of the M − 42 ions.[7] Plots of $\log Z/Z_0$ *vs.* σ^+ or σ for *meta* substituents treated as *para* (to the transfer site) give $\rho \approx +0.2$. Similar plots with *para* substituents show wide scattering.

(9) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 8.

(10) F. W. McLafferty and T. Wachs, *J. Am. Chem. Soc.*, **89**, 5043 (1967).

(11) D. A. Lightner, unpublished data. Calculated from LCAO–SCF wave functions of aniline and nitrobenzene, the respective radical-cation π-electron densities at C-4 are 0.876 and 0.968, at C-3 are 0.983 and 0.997, and at C-2 are 0.938 and 0.991. Similarly, the positive charge per cents at C-4 are 15.5 and 0.0, at C-3 are 1.5 and 0.5, and at C-2 are 10.0 and 0.2.

(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7.

(13) NATO Postdoctoral Fellow on leave from the University of Rome, 1966–1967.

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Additions of Difluorocarbene to an Ene–Yne System in a Steroid Molecule[1]

Sir:

We wish to report the first addition of difluorocarbene to an ene–yne systems[2] and to describe some chemical and spectral properties of the resulting adducts.

Addition of a large excess of difluorocarbene (generated by decomposition of the sodium salt of chlorodifluoroacetic acid in diglyme)[3] to **1**[4] afforded six new substances (separated by preparative silica gel thin layer chromatoplates) in addition to some recovered starting material.

The first three compounds were assigned structures **2a** [mp 237–238°; $[\alpha]D$ +161°; λ_{max} 224, 278, and 287 mμ (log ε 4.32, 3.30, and 3.26); ν_{max} 3430, 2225, and 1663 cm^{-1}; nmr 1.01 (poorly resolved d, $J \cong 1$ cps, 18-H), 2.05 (d, J = 1.5 cps, vinylic CH_3), and ~4.35 ppm (unresolved m, 16β-H); mass spectra 354 (M^+). *Anal.* Found: C, 78.08; H, 7.82; F, 4.76], **2b** [mp 169–170°; $[\alpha]D$ +136°; λ_{max} 226, 278, and 287 mμ (log ε 4.32, 3.32, and 3.29); ν_{max} 2220, 1662, and 1612 cm^{-1}; nmr 0.91 (unresolved d, 18-H), 2.04 (d, J = 1.5 cps, vinylic CH_3), and 5.01 ppm (d, $J_{HF} \cong 50$ cps, 16β-H); mass spectra 356 (M^+). *Anal.* Found: C, 77.80; H, 7.27; F, 10.82], and **3** [mp 177°; $[\alpha]D$ −100°; λ_{max} 288 mμ (log ε 4.05); ν_{max} 1640 cm^{-1}; nmr 0.91 (poorly resolved d, $J \cong 1$ cps, 18-H), 2.04 (d, J = 1.5 cps, vinylic CH_3), and 5.97, 6.08 ppm (15-, 16-H, J = 7 cps). *Anal.* Found: C, 81.64; H, 7.67; F, 5.14].

The formation of compounds **2a** and **2b**, characterized by their ultraviolet absorption in the 225-mμ region, can be rationalized as resulting from the attack of OH and F, respectively, at C-16 in **4**, followed by bond migration and fluorine loss, as depicted in **5**.[6] Structure **2a** was further confirmed by oxidation[7] to

(1) Publication No. 330 from the Syntex Institute of Steroid Chemistry.

(2) The addition of dichlorocarbene to an ene–yne system has been carried out; *cf.* (a) L. Vo-Quang and P. Cadiot, *Compt. Rend.*, **252**, 3827 (1961); (b) L. Vo-Quang and P. Cadiot, *Bull. Soc. Chim. France*, 1518 (1965); (c) I. A. D'yakonov and L. P. Danilkina, *Zh. Obshch. Khim.*, **32**, 1008 (1962); **34**, 738 (1964); (d) E. V. Dehmlow, *Tetrahedron Letters*, 3763 (1966), and references therein.

(3) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959); J. M. Birchall, G. W. Cross, and R. N. Hazeldine, *ibid.*, 81 (1960).

(4) Prepared by treatment of 3,17β-dihydroxy-17α-propionylestra-1,3,5(10)-triene 3-methyl ether with acetic anhydride in the presence of *p*-toluenesulfonic acid; mp 156–157°; $[\alpha]D$ +59°; λ_{max} 229–230, 278, 287 mμ (log ε 4.24, 3.37, and 3.31); ν_{max} 1608 and 1575 cm^{-1}; nmr 0.86 (18-H), 2.0 (acetylenic CH_3), and 5.95 ppm (16-vinylic H).[5] *Anal.* Found: C, 85.98; H, 8.33.

(5) Infrared spectra were determined in potassium bromide disks and the pmr spectra in deuteriochloroform solution containing tetramethylsilane as an internal reference; chemical shifts are reported in parts per million on the δ scale; d = doublet, t = triplet, m = multiplet. These determinations were made on a Varian A-60 spectrometer. We wish to thank Miss J. Tremble and Drs. T. Toube, L. Throop, and L. Tökes for the determination of the physical properties of compounds here reported.

(6) We wish to thank Professor G. Stork, Columbia University, and Dr. J. H. Fried, Syntex Laboratories, for helpful suggestions.

(7) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, 75, 422 (1953).