Reduction of 1-Substituted 7-Chloro-7-fluoronorcaranes with Tributyltin Hydride[1]

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The stereospecificity of the reduction of 1-fluoro- (1), 1-methoxy- (2), 1-(methoxycarbonyl)- (3), 1-(trimethylsilyl)- (4), 1-methyl- (5), and 1-unsubstituted 7-chloro-7-fluoronorcarane (6) with neat tributyltin hydride has been measured and found to decrease in the order $5 \approx 4 > 6 > 3 > 2 > 1$. This suggests that the configurational stability of the 7-fluoro-7-norcaryl radical is affected by the substituent situated at the position β to the radical center; the β-trimethylsilyl or β-methyl substituent stabilizes, whereas the β-fluoro, β-methoxy, or β-methoxycarbonyl substituent destabilizes, the pyramidal configuration of the cyclopropyl radical, relative to the β-hydrogen.

Many recent investigations on the stereochemistry of vinyl[2] and cyclopropyl radicals[3] have revealed that the nature of a substituent situated at the position α to the radical center has a profound effect on their configurational stability, or the energy barrier for their inversion of configuration. In contrast to this α-substituent effect, little or no attention has been paid to the possible effect of a β-substituent of increasing or decreasing the configurational stability of these radicals. In fact, no reports on this subject have appeared in the literature, except the proposal made by Bingham and Dewar[4] from the theoretical point of view.

We have now examined the stereochemistry of the reduction of some β-substituted α-fluorocyclopropyl chlorides with tributyltin hydride, which is believed to take place via α-fluorocyclopropyl radicals, in order to evaluate the β-substituent effect on their configurational stability.

Results and Discussion

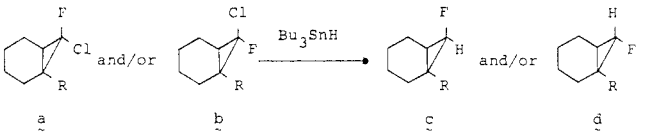
The halides used in the present study were 1-fluoro- (1), 1-methoxy- (2), 1-(methoxycarbonyl)- (3), 1-(trimethylsilyl)- (4), 1-methyl- (5), and 1-unsubstituted 7-chloro-7-fluoronorcarane (6). These compounds, except 3, were prepared as an isomeric mixture by the addition of chlorofluorocarbene, generated by the reaction of methyl dichlorofluoroacetate with sodium hydride and methanol,[5] to the corresponding cyclohexenes. 1-(Methoxycarbonyl)-7-chloro-7-fluoronorcarane (3) was obtained by chlorofluorocarbene addition to 1-[[(2-tetrahydropyranyl)oxy]methyl]cyclohexene followed by oxidation and esterification. The stereochemical assignment to the isomers a and b was made from their ^{19}F NMR spectra (Table I) based on the generalization that in fluorocyclopropanes the ring fluorine couples more strongly with the cis hydrogen than with the trans one[6] and that in alkyl- and aryl-substituted cyclopropanes the ring fluorine is shielded by cis and deshielded by trans substituents.[7] For compounds 1-3, 5, and 6, preparative GLC was used to sepa-

Table I. ^{19}F NMR Parameters for Starting Chlorides and Reduction Products

compd	δ_F (J, Hz)	compd	δ_F (J, Hz)
1a	88.5 (m), 77.5 (br s, 8.8[a])	7c	90.3 (m), 153.3 (dd, 9.2, 65.4)
1b	97.1 (m), 63.5 (d, 28.8)	7d	108.8 (m), 144.6 (dd, 28.4, 62.6)
2a	72.1 (br s, 11.9[a])	8c	149.4 (br d, 9.7,[a] 65.0)
2b	63.9 (d, 24.7)	8d	144.3 (dd, 28.5, 63.0)
3a	66.8 (br s, 13.0[a])	9c	143.4 (dd, 11.3, 66.9)
3b	52.3 (d, 20.3)	9d	132.7 (dd, 22.6, 63.8)
4a	55.8 (br s, 11.3[a])	10c	147.4 (dd, 6.8, 69.0)
4b	37.7 (d, 14.1)	10d	123.2 (dd, 16.6, 66.0)
5a	70.0 (br s, 9.8[a])	11c	147.8 (br d, 11.6,[a] 67.6)
5b	55.5 (d, 19.4)	11d	138.7 (dd, 22.7, 65.2)
6a	82.3 (br s, 5.2[a])	12c	156.0 (br d, 9.0,[a] 68.0)
6b	47.7 (d, 18.9)	12d	126.0 (dd, 18.0, 64.0)

[a] The value is the half-height width of resonance peak.

Scheme I



1, R = F
2, R = OMe
3, R = COOMe
4, R = $SiMe_3$
5, R = Me
6, R = H

7, R = F
8, R = OMe
9, R = COOMe
10, R = $SiMe_3$
11, R = Me
12, R = H

(1) (a) A portion of this work has been reported in a preliminary form: T. Ishihara, E. Ohtani, and T. Ando, *J. Chem. Soc., Chem. Commun.*, 367 (1975). (b) Presented at the 8th International Symposium on Fluorine Chemistry, Kyoto, Japan, Aug 1976, Abstract No. 0-21.

(2) (a) L. A. Singer and N. P. Kong, *Tetrahedron Lett.*, 2089 (1966); 643 (1967); *J. Am. Chem. Soc.*, 88, 5213 (1966); *ibid.*, 89, 5251 (1967). (b) L. A. Singer and J. Chen, *Tetrahedron Lett.*, 4849 (1969). (c) J. A. Kampmeier and R. M. Fantazier, *J. Am. Chem. Soc.*, 88, 1959 (1966). (d) R. M. Fantazier and J. A. Kampmeier, *ibid.*, 88, 5219 (1966). (e) M. S. Liu, S. Soloway, D. K. Wedegaertner, and J. A. Kampmeier, *ibid.*, 93, 3809 (1971).

(3) (a) T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Am. Chem. Soc.*, 89, 5719 (1967). (b) L. J. Altman and J. C. Vederas, *J. Chem. Soc., Chem. Commun.*, 895 (1969). (c) T. Ando, H. Yamanaka, F. Namigata, and W. Funasaka, *J. Org. Chem.*, 35, 33 (1970). (d) L. J. Altman and R. C. Baldwin, *Tetrahedron Lett.*, 2531 (1971). (e) L. A. Singer and J. Chen, *ibid.*, 939 (1971). (f) T. Ando, K. Wakabayashi, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jpn.*, 45, 1576 (1972). (g) H. Yamanaka, T. Shimamura, K. Teramura, and T. Ando, *Chem. Lett.*, 921 (1972). (h) J. Hatem and B. Waegell, *Tetrahedron Lett.*, 2019 (1973). (i) T. Ando, H. Hosaka, W. Funasaka, and H. Yamanaka, *Bull. Chem. Soc. Jpn.*, 46, 3513 (1973). (j) T. Ishihara, K. Hayashi, T. Ando, and H. Yamanaka, *J. Org. Chem.*, 40, 3264 (1975). (k) H. M. Walborsky and P. C. Collins, *ibid.*, 41, 940 (1976). (l) For studies based on physical methods, see T. Kawamura, M. Tsumura, Y. Yokomichi, and T. Yonezawa, *J. Am. Chem. Soc.*, 99, 8251 (1977), and references cited therein.

(4) R. C. Bingham and M. J. S. Dewar, *J. Am. Chem. Soc.*, 95, 7180, 7182 (1973).

(5) T. Ando, H. Yamanaka, S. Terabe, A. Horike, and W. Funasaka, *Tetrahedron Lett.*, 1123 (1967).

(6) K. L. Williamson, Y.-F. Li Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Am. Chem. Soc.*, 90, 6717 (1968).

(7) R. A. Moss and R. Gerstl, *Tetrahedron*, 23, 2549 (1967).

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Table II. Reduction of Chlorides with Tributyltin Hydride

compd	temp, °C	time, h	yield, %	isomer ratio, retn/invn
1a	80	6	78	89:11
1a	140	3	84	77:23
1b	80	6	80	79:21
1b	140	3	73	25:75
2a	80	4	74	94:6
2a	140	1.5	75	79:21
2b	80	4		88:12
2b	140	1.5		32:68
3a	80	5	83	97:3
3a	140	2		85:15
3b	80	5	77	96:4
3b	140	2		84:16
4[a]	80	8		(100:0)[b]
4[a]	140	2.5	87	(97:3)[c]
4[d]	140	2.5		(100:0)[e]
5a	80	10	70	100:0
5a	140	4	82	100:0
5b	80	10		100:0
5b	140	4		100:0
6a	80	8	76	100:0
6a	140	4	74	96:4
6b	80	8	78	98:2
6b	140	4	81	89:11

[a] An isomeric mixture was used, 4a/4b ratio of 17:83. [b] Ratio of 17:83 10c/10d. [c] Ratio of 19:81 10c/10d. [d] An isomeric mixture was used, 43:57 4a/4b. [e] Ratio of 43:57 10c/10d.

rate the isomers, **a** and **b**, the purity of the isomer obtained being higher than 99%. Each isomer was reduced under a nitrogen atmosphere with neat tributyltin hydride by adding the latter to the chloride (see Scheme I). Since separation of the isomers **4a** and **4b** could not be effected by either GLC or other methods,[8] isomeric mixtures were used for the reduction of **4**. Azobis(isobutyronitrile) (AIBN) and di-*tert*-butyl peroxide (DTBP) were used as initiators for the reduction at 80 and 140 °C, respectively. All reactions occurred smoothly to give reduction products in excellent yields and no other products such as a ring-opened one were detected. The yields of the reduction products were measured from their peak areas in gas chromatograms, calibrated against authentic sample solutions of known concentrations. Where only the isomer composition of the product was desired, no internal standard was added. The structures of the isomers **c** and **d** were determined from their ^1H and ^{19}F NMR spectra (Table I) on the basis of the relative magnitudes of the vicinal H–H[10] and H–F coupling constants.[6] The yields and the isomer compositions of the products are summarized in Table II, together with the reaction conditions.

The reduction of 1-methyl-7-chloro-7-fluoronorcarane (**5**) proceeded with complete retention of configuration, whereas those of 1-fluoro- (**1**), 1-methoxy- (**2**), and 1-(methoxycarbonyl)-7-chloro-7-fluoronorcarane (**3**) occurred with partial stereospecificity to give a mixture of two possible geometrical isomers. The complete stereospecificity observed with **5** means that the intermediary 1-methyl-7-fluoro-7-norcaryl radical has an extremely high configurational stability and inverts its configuration much more slowly than it abstracts a hydrogen from the tin hydride. On the other hand, the configurational stability of the 1-fluoro-, 1-methoxy-, and 1-(methoxycarbonyl)-7-fluoro-7-norcaryl radical is not so high as that of the 1-methyl-7-fluoro-7-norcaryl radical, and their inversion between the two pyramidal structures takes place at a rate comparable to their hydrogen abstraction.

In the case of 1-(trimethylsilyl)-7-chloro-7-fluoronorcarane (**4**), the isomer composition of the reduction product was nearly identical with that of the starting chloride, irrespective of the latter. Though the reduction of the pure isomer was not examined, this fact strongly suggests that the reaction of **4** proceeds stereospecifically, i.e., the intermediate 1-(trimethylsilyl)-7-fluoro-7-norcaryl radical is configurationally as stable as the methyl-carrying 7-fluoro-7-norcaryl radical.

Table II also shows that the ratio of retention to inversion decreases as the reaction temperature increases and that the degree of stereospecificity of the reduction decreases in the order **5** ≈ **4** > **6** > **3** > **2** > **1**. In the reaction of chloride **1** at 140 °C, in particular, the isomer distributions in the products were essentially equal irrespective of the stereochemistry of the starting chloride. This finding indicates that under these conditions the inversion of configuration of the 1,7-difluoro-7-norcaryl radical occurs more rapidly than its hydrogen abstraction. The behavior of this radical is in striking contrast with that of the 1-unsubstituted 7-fluoro-7-norcaryl radical, which is known as one of the configurationally most stable radicals.[3a,c,j,k] This provides strong evidence for a novel type of substituent effect caused by β-substituents.

Comparison of the retention data given for *endo*-F (**a**) and *exo*-F (**b**) isomers reveals that the *endo*-F isomer generally has a greater tendency to retain its configuration than does the corresponding *exo*-F isomer, suggesting that the hydrogen abstraction of the *endo*-F radical proceeds more rapidly than that of the *exo*-F radical, probably for steric reasons. This interpretation is supported by the preferential formation of the *endo*-F isomer (*endo*-F/*exo*-F ratio of 77:23 from the *endo*-F isomer and 75:25 from the *exo*-F isomer) observed in the reaction of **1a** or **1b** at 140 °C, where an equilibrating mixture of the *endo*-F and the *exo*-F radicals reacts with the hydride. The *endo*-F radical is conceivably of higher energy than the *exo*-F radical, and so its concentration in an equilibrating mixture must be lower than that of the *exo*-F radical, but, nevertheless, the product contains a larger amount of the *endo*-F isomer.

To be noted is that in the above discussion the term "configurational stability" is used to mean the ratio of the rate of hydrogen abstraction (k_a[R·][Bu_3SnH]) to that of inversion (k_i[R·]), because the isomer distribution listed in Table II only reflects the competition between the two reactions of the pertaining radical R·.

The configurational stability in this sense should be dependent on the molar concentration of tin hydride, as well as on the ratio of k_a to k_i. To get rid of the effect of the molar concentration of tin hydride, which varied (though only slightly) from experiment to experiment in obtaining the data of Table II, we competitively reduced two chlorides, **1b** and **3b**, with a twofold excess of tributyltin hydride in one vessel. The results (see the Experimental Section) show that the two chlorides were reduced at similar rates; i.e., radicals were formed at similar rates from **1b** and **3b** and were consumed at similar rates at the same concentration of the hydride. In this case, therefore, the degree of stereospecificity of the reaction can be regarded as reflecting the ratio of k_a to k_i alone. The

(8) Preparative GLC separation of the isomers **4a** and **4b** was unsuccessful by use of various liquid phases such as Apiezon L, silicon grease, tricresyl phosphate, and polyethylene glycol. An attempt to isolate **4a** by the selective decomposition of isomer **4b** in hot quinoline[9] was also not satisfactory.

(9) T. Ando, H. Hosaka, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jpn.*, **42**, 2013 (1969).

(10) (a) J. D. Graham and H. T. Rogers, *J. Am. Chem. Soc.*, **84**, 2249 (1962). (b) W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967).

ratio of retention to inversion observed for **3b** was again much higher than that for **1b**, though both of them were a little higher than those found in separate experiments because of a higher concentration of tin hydride being used.

Though only one competitive experiment was done, it is very probable that similar situations prevail for other substrates; one may regard the ratio of retention to inversion observed in separate experiments as a reflection of the ratio of k_a to k_i for each radical.

It is very unlikely, though possible, that k_a varies appreciably with the 1-substituent; it would rather be more reasonable to assume that k_a's are constant irrespective of the 1-substituent or at least that the variation in k_a with the 1-substituent would be much smaller than that in k_i. If this assumption is valid, the ratio of retention to inversion, or the stereospecificity of the reaction, can be directly related to k_i, or the configurational stability of the radical in the sense of the energy barrier for inversion.

On the basis of this assumption and the stereochemical results described herein, it can be concluded that in comparison with the 1-unsubstituted 7-fluoro-7-norcaryl radical, the fluoro, the methoxy, and the methoxycarbonyl substituents which are located β to the radical center have the effect of decreasing the configurational stability of the radical. The fluorine has the strongest influence in magnitude, followed by the methoxy group, and the methoxycarbonyl has the weakest one. The trimethylsilyl and the methyl substituents, on the other hand, have the effect of increasing the configurational stability of the radical, relative to the hydrogen. Of most significance is that the order of the *destabilizing* effect of this type observed for β substituents, F > MeO > MeOCO > H > $Me_3Si \approx Me$, is in good agreement with the order of the electronegativities of the substituents;[11] the more electron withdrawing the β substituent is, the lower is the configurational stability of the radical. Moreover, this order is the opposite of the *destabilizing* effect of α substituents; the more electron withdrawing the α substituent is, the higher is the configurational stability of the radical.[3]

Bingham and Dewar[4] have argued that the β-substituent effect can be due to an antibonding interaction between the nonbonding electrons of an α substituent and the MO's arising from hyperconjugative interactions between the singly occupied carbon AO and the MO's of adjacent carbon bonds. They showed that this antibonding interaction serves to destabilize the planar configuration of cyclopropyl radicals, or the transition state for their inversion, relative to the pyramidal one. It was predicted, on the basis of MINDO/3 calculations, that the effect of a β substituent of decreasing the configurational stability of cyclopropyl radicals should follow the order Cl > H > CH_3.

The order of the destabilizing effect of β substituents reported herein agrees with this prediction.[12] This fact seems to render support for the above-described assumption that the stereospecificity observed in the present study is directly related to the configurational stability of the intervening radical, although more detailed work would be necessary to draw any decisive conclusions.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were obtained on a Shimadzu IR-400 infrared spectrometer. A Varian EM-360 (60 MHz) or EM-390 (90 MHz) spectrometer was used to measure ^1H NMR spectra for solutions in CCl_4 with tetramethylsilane (Me_4Si) as an internal standard. ^{19}F NMR spectra were recorded on a Hitachi H-60 (56.4 MHz) or R-20BK (56.45 MHz) or on a Varian EM-390 (84.67 MHz) spectrometer in CCl_4 with trifluoroacetic acid (TFA) as an external reference. The proton and fluorine chemical shifts are expressed in parts per million (ppm) downfield from Me_4Si and in parts per million upfield from TFA, respectively. Mass spectra were taken on a Hitachi RMS-4 instrument operating at 70 eV. Analytical and preparative gas chromatography (GLC) was performed with a Shimadzu GC-2C or GC-6A or with a JEOLCO JGC-20KT gas chromatograph. Preparative GLC separations were done on a 2 m × 10 mm column with 25% tricresyl phosphate at 120 °C for **1**, 10% Triton X-305 at 100 °C for **2**, 30% silicon DC 550 at 160 °C for **3**, or 15% tricresyl phosphate at 80 °C for **5** and **6**. For analytical purposes, a 3 m × 3 mm column was used with 7% Apiezon L at 70 °C for **7**, 7% tricresyl phosphate at 120 °C for **8**, 5% silicon DC 550 at 140 °C for **9**, 7% tricresyl phosphate at 80 °C for **11**, or 7% Apiezon L at 50 °C for **12**. Though isomer ratios of **4** and **10** were determined from their ^{19}F NMR spectra, those of the others were calculated from the peak areas in gas chromatograms. The accuracy for the values of the isomer ratios listed in Table II is within ±2%.

Materials. All chemicals were of reagent grade and used without further purification. Solvents were distilled or vacuum distilled through a 25-cm Vigreux column and, if necessary, were purified in the conventional manner.

1-Methoxy-,[13] 1-(hydroxymethyl)-,[14] 1-(trimethylsilyl)-,[15] and 1-methylcyclohexene[16] were prepared according to the reported methods.

1-Fluorocyclohexene. In a 1-L four-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser with a drying tube were placed cyclohexene oxide (0.98 mol), potassium bifluoride (1.47 mol), and diethylene glycol (190 g). This mixture was maintained at 170–175 °C with stirring for 1 h, followed by vacuum distillation. The crude product was redistilled under reduced pressure to give *trans*-2-fluorocyclohexanol: 64% yield; bp 77.0–78.0 °C (22 mm) [lit.[17] bp 68–69 °C (14 mm)]; n^{21}_D 1.4495; IR (film) 3400–3260, 2970, 1452, 1385, 1355, 1233, 1075, 1031, 925, 905, 856 cm^{-1}; ^1H NMR δ 0.6–2.4 (m, 8 H), 3.33 (s, 1 H), 3.2–4.8 (series of m, 2 H). To a suspension of phosphorus tribromide (1.0 mol) and dry NaBr (0.8 mol) was added *trans*-2-fluorocyclohexanol (1.0 mol) with stirring at 150 °C. After being kept at the same temperature for 3 h, the reaction mixture was poured into ice–water and was worked up as usual. Distillation of the crude product gave *cis*-1-bromo-2-fluorocyclohexane as a pale yellow liquid in 56% yield: bp 68.0–70.0 °C (14 mm) [lit.[17] bp 78 °C (16 mm)]; $n^{19.5}_D$ 1.4869; IR (film) 2950, 2875, 1452, 1375, 1260, 1210, 1183, 1146, 1105, 1055, 962, 855, 810, 705 cm^{-1}; ^1H NMR δ 1.0–2.6 (m, 8 H), 3.8–5.1 (series of m, 2 H). To a mixture of sodium methoxide (0.55 mol) in anhydrous dimethyl sulfoxide (200 mL) was added *cis*-1-bromo-2-fluorocyclohexane (0.5 mol) at room temperature over a period of 1.5 h. This mixture was stirred for several hours, was heated at 70 °C for 1 h, and then was poured into water. The resulting solution was extracted four times with pentane. The combined extracts were washed with water, dried over anhydrous calcium chloride, and distilled on a 20-cm Widmer-type column to give 1-fluorocyclohexene: 62% yield; bp 95–96 °C (lit.[17] bp 96 °C); $n^{17.5}_D$ 1.4299 (lit.[17] n^{20}_D 1.4269); IR (film) 2938, 2858, 1702, 1447, 1374, 1341, 1134, 974, 922, 858, 800, 781 cm^{-1}; ^1H NMR δ 1.66 (m, 4 H), 2.11 (m, 4 H), 5.07 (br d, J = 16.8 Hz, 1 H); mass spectrum, m/e (relative intensity) 100 (M^+, 46), 85 (44), 80 (11), 72 (100), 59 (17).

Preparation of 1-Substituted 7-Chloro-7-fluoronorcaranes 1–6. In a 300-mL four-necked flask with a condenser, a mechanical

(11) P. R. Wells, *Prog. Phys. Org. Chem.*, 6, 111 (1968), and references cited therein.

(12) Reduction of 1,7-dichloro-7-fluoronorcarane with tributyltin hydride was conducted to obtain some information of the β-chlorine effect. Unfortunately, the 7-chlorine atom in this compound was not reduced at all, but 1-chlorine was reduced selectively to give 7-chloro-7-fluoronorcarane.

(13) R. A. Wohl, *Synthesis*, 38 (1974).

(14) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

(15) A. D. Petrov, V. F. Mironov, and V. G. Glukhovtsev, *Zh. Obshch. Khim.*, **27**, 1535 (1957).

(16) R. T. Arnold, G. G. Smith, and R. M. Dodson, *J. Org. Chem.*, **15**, 1256 (1950).

(17) G. Wittig and U. Mayer, *Chem. Ber.*, **96**, 329 (1963); D. R. Strobach and G. A. Boswell, Jr., *J. Org. Chem.*, **36**, 818 (1971).

stirrer, a thermometer, a dropping funnel, and an inlet tube for nitrogen was placed a mixture of sodium hydride (0.3 mol), methyl dichlorofluoroacetate (0.3 mol), anhydrous ether (70 mL), and the corresponding cyclohexene (0.3 mol). To this mixture was added slowly absolute methanol (0.3 mol) under a nitrogen atmosphere at 25–30 °C. After the reaction mixture was stirred overnight at 30 °C, a small amount of methanol and subsequently 100 mL of water were added to it. The organic layer was separated, and the aqueous layer was extracted three times with ether. The ethereal extracts were washed with aqueous $NaHCO_3$ and with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual oil was distilled under reduced pressure to afford a colorless liquid.

7-Chloro-1,7-difluoronorcarane (1a,b): 43% yield (**1a/1b**, 23:77); bp 52.5–53.5 °C (15 mm); n^{18}_D 1.4418; IR (film) 2954, 2882, 1452, 1420, 1340, 1195, 1162, 1130, 1111, 1065, 1019, 935, 885 cm^{-1}; ^1H NMR for **1a** δ 0.8–2.5 (m, 9 H); for **1b** δ 0.7–2.6 (m, 9 H); mass spectrum, m/e (relative intensity) 168 (M + 2, 3), 166 (M^+, 9), 139 (13), 137 (37), 131 (59), 126 (35), 124 (100), 111 (25), 89 (26), 85 (24), 77 (10).

Anal. Calcd for $C_7H_9ClF_2$: C, 50.47; H, 5.44; F, 22.81. Found: C, 50.61; H, 5.53; F, 22.74.

7-Chloro-7-fluoro-1-methoxynorcarane (2a,b): 59% yield (**2a/2b**, 43:57); bp 88.0–89.0 °C (21 mm); n^{18}_D 1.4637; IR (film) 2950, 2860, 1455 1250, 1185, 1135, 1090, 1080, 1000, 955 cm^{-1}; ^1H NMR for **2a** δ 1.1–2.3 (m, 9 H), 3.32 (s, 3 H); for **2b** δ 1.0–2.3 (m, 9 H), 3.32 (s, 3 H); mass spectrum, *m/e* (relative intensity) 180 (M + 2, 0.7), 178 (M^+, 2), 151 (10), 143 (100), 111 (34), 109 (13), 93 (21), 85 (13), 71 (14).

Anal. Calcd for $C_8H_{12}OClF$: C, 53.79; H, 6.77; F, 10.63. Found: C, 53.86; H, 6.85; F, 10.49.

7-Chloro-7-fluoro-1-(trimethylsilyl)norcarane (4a,b): 23% yield (**4a/4b**, 17:83); bp 59.0–60.0 °C (4.0 mm); $n^{14.5}_D$ 1.4723; IR (film) 2944, 2874, 1444, 1392, 1284, 1250, 1178, 1140, 1060, 1022, 1000, 893, 835, 752 cm^{-1}; ^1H NMR δ 0.07 (s, 9 H), 0.7–2.8 (m, 9 H); mass spectrum, *m/e* (relative intensity) no parent peak to 220, 128 (7), 113 (12), 97 (20), 93 (28), 77 (44), 73 (100).

Anal. Calcd for $C_{10}H_{18}ClFSi$: C, 54.40; H, 8.22. Found: C, 54.52; H, 8.14.

7-Chloro-7-fluoro-1-methylnorcarane (5a,b): 48% yield (**5a/5b**, 25:75); bp 60.5–61.5 °C (20 mm); n^{20}_D 1.4581; IR (film) 2945, 2880, 1452, 1344, 1221, 1211, 1188, 1143, 1099, 1064, 1034, 990, 965, 890, 842 cm^{-1}; ^1H NMR for **5a** δ 0.8–2.3 (m, 9 H), 1.25 (d, J = 1.8 Hz, 3 H); for **5b** δ 0.8–2.4 (m, 9 H), 1.25 (d, J = 1.8 Hz, 3 H); mass spectrum, *m/e* (relative intensity) 164 (M + 2, 5), 162 (M^+, 15), 149 (11), 147 (26), 135 (4), 133 (16), 127 (100), 122 (11), 120 (32), 111 (22), 109 (12), 108 (12), 107 (33), 106 (33), 95 (17), 85 (55), 79 (24).

Anal. Calcd for $C_8H_{12}ClF$: C, 59.08; H, 7.44; F, 11.68. Found: C, 59.18; H, 7.49; F, 11.63.

7-Chloro-7-fluoronorcarane (6a,b): 51% yield (**6a/6b**, 34:66); bp 47.5–49.0 °C (14 mm); n^{28}_D 1.4565; IR (film) 2935, 2870, 1450, 1232, 1090, 1020, 872 cm^{-1}.

1-(Methoxycarbonyl)-7-chloro-7-fluoronorcarane (**3**) was obtained from 1-[[(2-tetrahydropyranyl)oxy]methyl]-7-chloro-7-fluoronorcarane in the following manner. 1-[[(2-Tetrahydropyranyl)oxy]methyl]-7-chloro-7-fluoronorcarane was deprotected with 10 N HCl in 80% aqueous ethanol to give quantitatively 1-(hydroxymethyl)-7-chloro-7-fluoronorcarane: IR (film) 3340, 2944, 2874, 1445, 1414, 1214, 1128, 1080, 1067, 1026, 967, 891 cm^{-1}; ^1H NMR δ 0.5–2.4 (m, 9 H), 2.70 (s, 1 H), 3.58 (m, 2 H). This compound was used without further purification. In a 500-mL four-necked flask were placed 1-(hydroxymethyl)-7-chloro-7-fluoronorcarane (0.14 mol), concentrated H_2SO_4 (45 mL), and water (360 mL). To this mixture was added potassium permanganate (0.28 mol) with stirring at such a rate that the temperature was maintained below 20 °C. The mixture was stirred at 50 °C for 2 h, treated with $NaHSO_4$, and filtered. The filtrate was made basic by adding 30% aqueous KOH and then was extracted with ether. The aqueous layer was acidified with 10 N HCl, followed by extraction with ether. The ethereal extracts were combined, washed with water, dried over anhydrous $MgSO_4$, and concentrated under vacuum to give 7-chloro-7-fluoronorcarane-1-carboxylic acid: 40% yield; bp 116.0–118.0 °C (3.0 mm); IR (film) 3150–2540, 1670, 1444, 1414, 1290, 1246, 1187, 1097, 967, 905 cm^{-1}; ^1H NMR δ 0.8–3.1 (m, 9 H), 12.28 (s, 1 H). This carboxylic acid was converted quantitatively to methyl ester **3** by using diazomethane.

7-Chloro-7-fluoro-1-(methoxycarbonyl)norcarane (3a,b): bp 82.5–84.0 °C (5 mm), **3a/3b**, 25:75; n^{16}_D 1.4737; IR (film) 2955, 2875, 1738, 1443, 1283, 1265, 1245, 1196, 1175, 1093, 1030, 962, 898 cm^{-1}; ^1H NMR for **3a** δ 0.9–2.6 (m, 9 H), 3.70 (s, 3 H); for **3b** δ 1.0–2.5 (m, 9 H), 3.70 (s, 3 H); mass spectrum, *m/e* (relative intensity) 208 (M + 2, 8), 206 (M^+, 24), 177 (8), 175 (23), 171 (25), 149 (24), 147 (71), 111 (50), 109 (100), 91 (33), 81 (29).

Anal. Calcd for $C_9H_{12}O_2ClF$: C, 52.31; H, 5.85; F, 9.19. Found: C, 52.09; H, 5.80; F, 9.15.

Reduction of 1-Substituted 7-Chloro-7-fluoronorcaranes 1–6 with Tributyltin Hydride. In a 5-mL flask fitted with a magnetic stirrer bar, a microthermometer, and a rubber septum were placed the chloride (0.6–30 mmol) and a small amount of AIBN (at 80 °C) or DTBP (at 140 °C) under a nitrogen atmosphere. To this mixture, which had been maintained at a specified temperature, was added 1.2 equiv of tributyltin hydride by use of a syringe. After the reaction mixture was stirred for several hours, CCl_4 (ca. 0.5 mL) was added to it. The reduction products were isolated by vacuum distillation. The isomer distributions in the products were determined by means of GLC or ^{19}F NMR before distillation and are given in Table II.

1,7-Difluoronorcarane (7c,d): bp 64–71 °C (65 mm); $n^{18.5}_D$ 1.4255; IR (film) 2949, 2874, 1455, 1435, 1363, 1345, 1265, 1195, 1175, 1124, 1095, 1062, 977, 935, 912, 895, 845, 694 cm^{-1}; ^1H NMR for **7c** δ 0.5–2.6 (m, 9 H), 4.62 (ddd, J = 8.0, 13.0, 65.4 Hz, 1 H); for **7d** δ 0.5–2.6 (m, 9 H), 3.99 (br d, J = 62.6 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 132 (M^+, 10), 112 (7), 104 (22), 103 (29), 99 (40), 97 (12), 90 (100), 85 (16), 79 (15), 77 (12).

Anal. Calcd for $C_7H_{10}F_2$: C, 63.62; H, 7.63; F, 28.75. Found: C, 63.51; H, 7.56; F, 28.73.

7-Fluoro-1-methoxynorcarane (8c,d): bp 56.0–57.0 °C (17 mm); n^{18}_D 1.4449; IR (film) 2940, 1458, 1417, 1343, 1265, 1208, 1184, 1160, 1120, 1088, 1077, 1023 cm^{-1}; ^1H NMR for **8c** δ 0.7–2.4 (m, 9 H), 3.14 (s, 3 H), 4.36 (dd, J = 8.0, 65.0 Hz, 1 H), for **8d** δ 0.8–2.3 (m, 9 H), 3.29 (s, 3 H), 4.04 (dd, J = 3.0, 63.0 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 144 (M^+, 18), 143 (13), 129 (13), 116 (50), 115 (100), 112 (25), 111 (48), 102 (13), 97 (23), 85 (33), 79 (18), 72 (33).

Anal. Calcd for $C_8H_{13}OF$: C, 66.64; H, 9.09; F, 13.18. Found: C, 66.56; H, 8.98; F, 13.26.

7-Fluoro-1-(methoxycarbonyl)norcarane (9c,d): bp 104–110 °C (13 mm); n^{18}_D 1.4667; IR (film) 2940, 2865, 1725, 1453, 1438, 1359, 1280, 1238, 1188, 1166, 1141, 1087, 1053, 1040, 906 cm^{-1}; ^1H NMR for **9c** δ 0.8–2.5 (m, 9 H), 3.55 (s, 3 H), 4.64 (dd, J = 6.2, 66.9 Hz, 1 H); for **9d** δ 0.8–2.5 (m, 9 H), 3.60 (s, 3 H), 4.30 (dd, J = 3.5, 63.8 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 172 (M^+, 42), 152 (13), 141 (35), 113 (84), 109 (29), 97 (16), 93 (100), 92 (39), 91 (32), 81 (26), 79 (26), 77 (29).

Anal. Calcd for $C_9H_{13}O_2F$: C, 62.78; H, 7.61; F, 11.03. Found: C, 62.66; H, 7.57; F, 10.94.

7-Fluoro-1-(trimethylsilyl)norcarane (10c,d): bp 82.0–86.0 °C (26 mm); mp 76.0–78.0 °C; ^1H NMR for **10c** δ 0.10 (s, 9 H), 0.7–2.1 (m, 9 H), 4.28 (dd, J = 5.7, 69.0 Hz, 1 H); for **10d** δ 0.10 (s, 9 H), 0.7–2.1 (m, 9 H), 4.36 (dd, J = 2.3, 66.0 Hz, 1 H); mass spectrum, *m/e* (relative intensity) no parent peak to 186, 96 (19), 95 (22), 81 (100), 79 (37), 75 (63).

Anal. Calcd for $C_{10}H_{19}FSi$: C, 64.46; H, 10.28. Found: C, 64.58; H, 10.31.

7-Fluoro-1-methylnorcarane (11c,d): bp 65.0–66.0 °C (55 mm); n^{20}_D 1.4383; IR (film) 2937, 2862, 1452, 1421, 1184, 1165, 1133, 1093, 1063, 960 cm^{-1}; ^1H NMR for **11c** δ 0.5–2.3 (m, 9 H), 0.97 (d, J = 2.4 Hz, 3 H), 4.01 (dd, J = 7.6, 67.6 Hz, 1 H); for **11d** δ 0.6–2.2 (m, 9 H), 1.16 (d, J = 1.8 Hz, 3 H), 4.11 (dd, J = 2.0, 65.2 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 128 (M^+, 60), 113 (52), 108 (6), 99 (58), 95 (100), 93 (29), 86 (87), 85 (78), 81 (42), 79 (22), 77 (19), 73 (20).

Anal. Calcd for $C_8H_{13}F$: C, 74.96; H, 10.22; F, 14.82. Found: C, 75.13; H, 10.29; F, 14.80.

7-Fluoronorcarane (12c,d): bp 68.0–69.0 °C (107 mm); n^{28}_D 1.4376; IR (film) 2940, 2865, 1453, 1435, 1222, 1168, 1077, 1048, 1015, 850 cm^{-1}; ^1H NMR for **12c** δ 0.5–2.3 (m, 10 H), 4.39 (dt, J = 6.2, 68.0 Hz, 1 H); for **12d** δ 0.6–2.1 (m, 10 H), 4.13 (dt, J = 1.8, 64.0 Hz, 1 H).

Competitive Reduction of 1b and 3b with Tributyltin Hydride. Into a 5-mm NMR sample tube were placed 77 mg (0.462 mmol) of **1b**, 99 mg (0.480 mmol) of **3b**, 571 mg (1.962 mmol) of tributyltin hydride, and a catalytic amount of AIBN under a nitrogen atmosphere. Before the sample tube was sealed, 12 mg of benzotrifluoride and a capillary containing TFA were introduced to it as a reference for determination of the products and for NMR analysis, respectively. This mixture was heated and kept at 80 °C with occasional shaking, and ^{19}F NMR analyses were made every hour. The reduction occurred very cleanly, no byproducts such as a ring-opened compound being formed. The amounts of the reduction products **7c**, **7d**, and **9d** were determined from their resonance peak areas due to the 7-fluorine atom relative to that due to benzotrifluoride in ^{19}F NMR spectra. The yields of the reduction products from **1b** and **3b** were 58.9% and 59.2% after 1 h, 76.8% and 76.9% after 2 h, 89.8% and 90.4% after 3 h, and 96.8% and 97.3% after 4 h, respectively. The complete stereospecificity was observed throughout the reduction of **3b** while the stereospecificity of the reduction of **1b** was as follows: 84% after 1 h, 83% after 2 h, 84% after 3 h, 84% after 4 h.

Registry No. 1a, 78986-62-6; **1b**, 79081-95-1; **2a**, 56620-30-5; **2b**, 56650-00-1; **3a**, 78986-63-7; **3b**, 79081-96-2; **4a**, 78986-64-8; **4b**, 79081-97-3; **5a**, 56620-29-2; **5b**, 56649-99-1; **6a**, 16646-94-9; **6b**, 16646-93-8; **7c**, 78986-65-9; **7d**, 79081-98-4; **8c**, 56620-32-7; **8d**, 56650-02-3; **9c**, 78986-66-0; **9d**, 79081-99-5; **10c**, 78986-67-1; **10d**, 79082-00-1; **11c**, 56620-31-6; **11d**, 56650-01-2; **12c**, 16646-97-2; **12d**, 16646-98-3; Bu_3SnH, 688-73-3; 1-methoxycyclohexene, 931-57-7; 1-(hydroxymethyl)cyclohexene, 4845-04-9; 1-(trimethylsilyl)cyclohexene, 17874-17-8; 1-methylcyclohexene, 591-49-1; 1-fluorocyclohexene, 694-51-9; *trans*-2-fluorocyclohexanol, 14365-32-3; *cis*-1-bromo-2-fluorocyclohexane, 51422-74-3; 1-[[(2-tetrahydropyranyl)oxy]methyl]-7-chloro-7-fluoronorcarane, 78986-68-2; 1-(hydroxymethyl)-7-chloro-7-fluoronorcarane, 78986-69-3; 7-chloro-7-fluoronorcarane-1-carboxylic acid, 78986-70-6.

Reaction Mechanisms of Gaseous Organic Cations. 20.[1] Reactivity of Ionized 3-Phenylisoxazol-5(4*H*)-one

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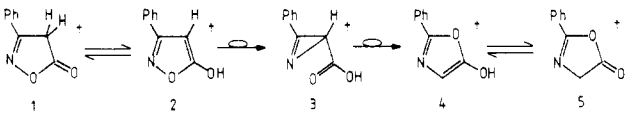
The chemistry of ionized 3-phenylisoxazol-5(4*H*)-one, which is relatively slow reacting in the gas phase, has been investigated by analysis of the mass-analyzed ion kinetic energy spectrum (MIKES), kinetic energy release, appearance energy, exact mass measurements and D, ^{15}N, and ^{13}C labeling. Appropriate experiments show that the N,O-heterocyclic radical cations under study undergo unimolecular dissociations leading to the formation of benzoyl and formanilinium cations through pathways which involve phenyl migration. $PhCO^+$ fragment ion formation must occur through a reaction channel akin to a thermochemical process. This implies a deep skeletal reorganization similar to an electrophilic substitution onto the aromatic ring and excludes the occurrence of photochemical-like activation giving rise to isoxazole–oxazole ring isomerization. The decomposing ions possess, therefore, only a small excess energy, and have to follow only low-lying reaction channels.

Information about the chemistry of organic ions in a noninteracting environment can be acquired by investigating the behavior of a beam of positive ions reacting via unimolecular processes in a mass spectrometer. The chemical reactivity of the molecular ion of a given precursor has already been exploited to predict the primary products of photolysis or thermolysis of the same molecule[2a] and to project synthetic approaches to complex natural products by the analysis of some retro mass spectral processes.[2b] The relationship between chemical reactions occurring in a mass spectrometer and those taking place as a result of thermal and photochemical activations has been the subject of several recent investigations.[2a,3a] Since the energy of the conventional colliding particle used during the ionization process is fairly spread out,[4] some excitation energy is generally transferred to the reacting ions. This means that the excess energy available to the gaseous organic ions can reduce selectivity between the competing dissociation paths accessible to the reacting species. Thus, the major difference between the photochemical and thermochemical processes of neutrals in the condensed phase may be less evident in ionic dissociation reactions in the gas phase, because at the energies available both the ground and excited electronic states can be populated, giving rise to a different electronically controlled reactivity of the ions. However, during a mass spectrometric experiment, isolated organic ions can either undergo unimolecular degradation closely similar to[2,3a,b] or strictly analogous with[5] that of thermochemical processes, or else they can follow competing fragmentation paths involving bond breaking and formation in conformity with a high-energy reaction channel. If the chemistry of ionic processes in different systems is to be correlated and used for the purpose mentioned above, it must be concerned with ionic reactions that can be thoroughly investigated as, for example, for those occurring when metastable ions are sampled.[4]

Scheme I



The chemical behavior of ionized 3-phenylisoxazol-5-(4*H*)-one (**1**)[5,7-9] and related systems[10-12] has attracted

(1) Part 19: Sindona, G.; Uccella, N. *Ann. Chim. (Rome)* **1980**, *70*, 405.
(2) (a) Dougherty, R. C. *Fortschr. Chem. Forsch.* **1974**, *45*, 93. (b) Kametani, T.; Fukumoto, K. *Acc. Chem. Res.* **1976**, *9*, 319.
(3) (a) Bentley, T. W. In *Mass Spectrom.* **1975**, *3*, 74; **1977**, *4*, 58. (b) Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 722.
(4) Levsen, K. "Fundamental Aspects of Organic Mass Spectrometry"; Verlag Chemie: Weinheim Bergstr., Germany, 1978.
(5) Cum, G.; Giannetto, P.; Uccella, N. *J. Chem. Soc., Perkin Trans. 2* **1973**, 2038.
(6) Schwarz, H.; Williams, D. H.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1978**, *100*, 7052.
(7) Nishiwaki, T. *Tetrahedron* **1969**, *25*, 747.
(8) Bowie, J. H.; Kallury, R. K. M. R.; Cooks, R. G. *Aust. J. Chem.* **1969**, *22*, 563.

0022-3263/81/1946-4450$01.25/0