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Fluorination with Xenon Difluoride. Stereochemistry of Fluorine Addition to Phenyl-Substituted Cycloalkenes

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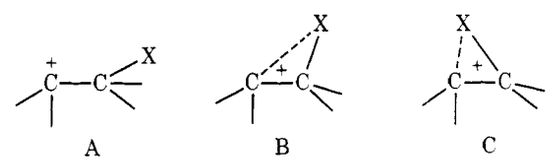
Acid-catalyzed liquid-phase fluorine addition with xenon difluoride to some phenyl-substituted cycloalkenes, i.e., 1-phenylcyclopentene, 1-phenylcyclohexene, and 1-phenylcycloheptene, results in the formation of vincinal difluorides in high yield. The ratio of syn and anti addition depends on ring magnitude. The stereochemistry of fluorine addition to aryl-substituted cyclohexenes also depends on the substituent in the phenyl ring.

The mechanisms of electrophilic addition of halogens have been widely investigated, both from the kinetic and stereochemical points of view.[1] Apart from the relative importance of the various kinetically significant processes, it is now known that the nature of the intermediates of the addition depends on the structure of the substrate, on the halogen, and on the reaction medium, ranging from strongly bridged ions (type C), to weakly bridged species (type B), or to open ions like A (Scheme I). If the cation is of the open structure A (X = F), a mixture of cis and trans adducts is generally expected. However, ion-pairing phenomena can cause preferential formation of the cis adduct and electronic, steric, or conformational effects can cause attack at one or the other side of the carbonium p orbital of A to be favored. On the other hand, the intermediate can have a bridged structure (C, X = Br), which will be presumably opened stereospecifically to form a trans adduct.

Recently we have observed that xenon difluoride readily adds fluorine to phenyl-substituted olefins to give the corresponding 1,2-difluorophenylalkanes in high yield and under mild conditions.[2] The ratios of *dl*-erythro and *dl*-threo difluorides formed by fluorination of alkyl- or phenyl-substituted olefins are nearly independent of the starting olefin, and in the trans series anti addition of fluorine predominates. We have suggested the formation of an open β-fluorocarbonium ion intermediate.[3] The intermediate from the trans olefin collapses preferentially to an anti adduct, while the cis olefin intermediate can freely rotate about the newly formed single bond, thus assuming a sterically more favorable conformation identical with that of the trans intermediate. As an extension

Scheme I



of our research, we therefore chose some phenyl-substituted cycloalkenes, i.e., 1-phenylcyclopentene, 1-phenylcyclohexene, and 1-phenylcycloheptene, as substrates in the acid-catalyzed liquid-phase fluorination reaction with xenon difluoride. We extended our studies to cycloolefins so as to eliminate a complexity which exists in an acyclic system, in which there is a possibility of rotation about the carbon–carbon single bond in the β-fluorocarbonium ion, depending on its lifetime and the energy barrier resisting free rotation about the newly formed single bond. From the data obtained it should be possible to get information about the influence of the ring magnitude on the stereochemistry of the fluorine addition. The variation of the substituent on the phenyl ring (X = H, *p*-OCH_3, *m*-Cl) in 1-phenylcyclohexene will give us further information about the effect of the stability of β-fluorocarbonium ions on the stereochemistry of fluorine addition.

Results and Discussion

The preparation of fluoroalkanes presents a different problem from that of other haloalkanes and necessitates a specific method of fluorination.[4] The acid-catalyzed liquid-phase fluorination of organic substrates with XeF_2 avoids some experimental difficulties, e.g., low temperature, high-

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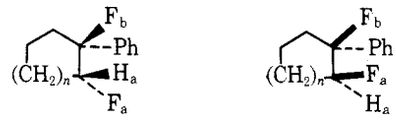
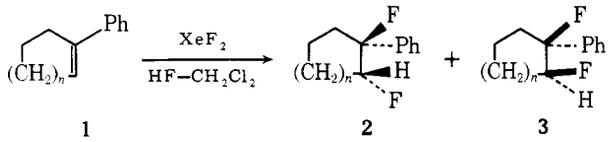
Table I



2 3

	2			3		
	$n = 1$	$n = 2$	$n = 3$	$n = 1$	$n = 2$	$n = 3$
δ_{F_b}	−157.9	−178.4	−159.4	−172.5	−197.5	181.1
δ_{F_a}	−186.4	−212.0	−189.4	−207.0	−205.5	
δ_{H_a}	4.8	4.81	4.63	4.8	4.9	4.63
$^2J_{F_aH_a}$	52	49.5	45	54	48	45
$^3J_{F_bH_a}$	7.5	<1	6	18	25	27
$^3J_{H_bH}$	5	<1	6	7.5	7.5	9

Scheme II



1 2 3

relative yields, %

n	2	3
1	79	21
2	50	50
3	35	65

pressure equipment, only a catalytic amount of hydrogen fluoride, which prevents the polymerization of alkenes and products.

We now report the reaction of xenon difluoride with some phenyl-substituted cycloalkenes. In a typical experiment, we dissolved 1 mmol of compound in methylene chloride; anhydrous hydrogen fluoride (1 mmol) was introduced into the reaction mixture and, under stirring, 1 mmol of xenon difluoride was added at room temperature. The colorless solution turned dark blue and xenon gas quickly evolved. After 10–40 min, when gas evolution has ceased, the crude, reaction mixture was isolated by the usual work-up procedure, analyzed by NMR, and separated by preparative GLC and TLC. The crude reaction mixture formed by fluorination of 1-phenylcyclopentene (1) (Scheme II) showed four multiplets in its ^{19}F NMR spectrum corresponding to two products in relative yields of 79:21% (2:3). Products were separated by preparative TLC. The major product formed (2) showed two multiplets in its ^{19}F NMR at δ −157.9 and −186.4 and in its ^1H NMR a ddd signal at δ 4.8, corresponding to one proton with coupling constants of J = 52, 7.5, and 5 Hz, while the minor product formed (3) showed two multiplets in its ^{19}F NMR at δ −172.5 and −207.0 and in its ^1H NMR a ddd signal at δ 4.8, corresponding to one proton with coupling constants of J = 54, 18, and 7.5 Hz. On the basis of the differences in NMR data, we have established that the major product was formed after trans addition of fluorine and that the minor product corresponds to cis addition. The results are parallel to those observed by fluorination of indene with xenon difluoride.[3]

The fluorination of 1-phenylcyclohexene resulted in the formation of two products in equal amounts (Scheme II). The products were separated by preparative GLC and their NMR spectra are presented in Figure 1. On the basis of the differences in NMR spectra, which are listed in Table I, and on the basis of the fact that the coupling constant between fluorine and the proton ($^3J_{F_bH_a}$) is greater when the atoms are in a diaxial position (J = 25 Hz) than in the case of an axial–equatorial position (J < 1 Hz), we have established that syn and anti addition took place in equal proportions.

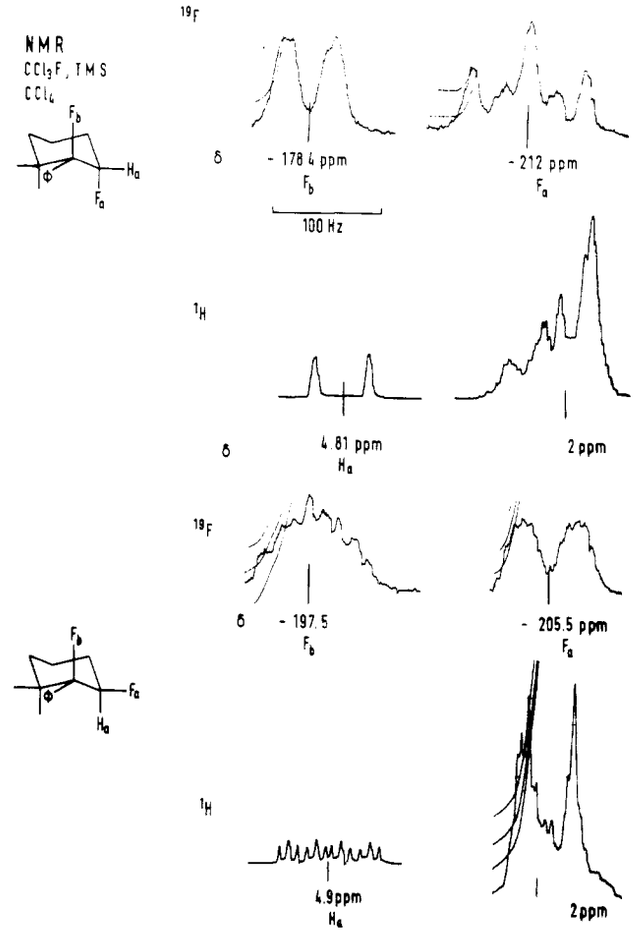
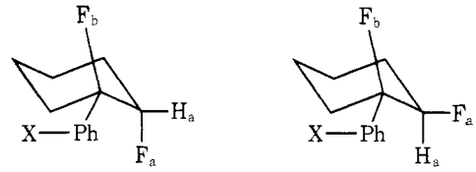


Figure 1. NMR spectra of compounds 2 and 3.

The acid-catalyzed liquid-phase fluorination of 1-phenylcycloheptene (Scheme II) also resulted in the formation of two products. The crude reaction mixture showed only three multiplets in its ^{19}F NMR spectrum. By separation using preparative TLC we have isolated two products. The major product formed showed one multiplet signal at δ −181.1 in its ^{19}F NMR and in ^1H NMR a ddd signal at δ 4.63 with coupling constants of J = 45, 27, and 9 Hz, while the minor product formed showed two multiplets in its ^{19}F NMR at δ −159.4 and −189.4 and in ^1H NMR a ddd signal at δ 4.63 with coupling constants of J = 45, 6, and 6 Hz. A comparison of the NMR data to those of the products formed by fluorination of 1-phenylcyclopentene and 1-phenylcyclohexene (Table I) enabled us to establish that the major product formed (3) arose from syn addition of fluorine, while the minor product formed (2) corresponded to anti addition.

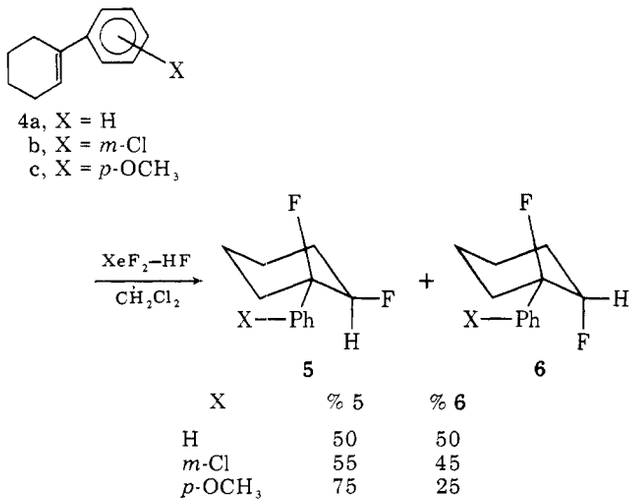
Table II



6 5

	6			5		
	X = H	X = *m*-Cl	X = *p*-OCH_3	X = H	X = *m*-Cl	X = *p*-OCH_3
δ_{F_a}	−212	−211	−211	−205.5	−204	−205
δ_{F_b}	−178.4	−178.5	−178	−197.5	−198	−197
δ_{H_a}	4.81	4.8	4.8	4.9	4.9	4.9
$^2J_{F_aH_a}$	49.5	48	48	48	48	48
$^3J_{F_bH_a}$	<1	<1	<1	25	25	24.5
$^3J_{H_aH}$	<1	<1	<1	7.5	7	8

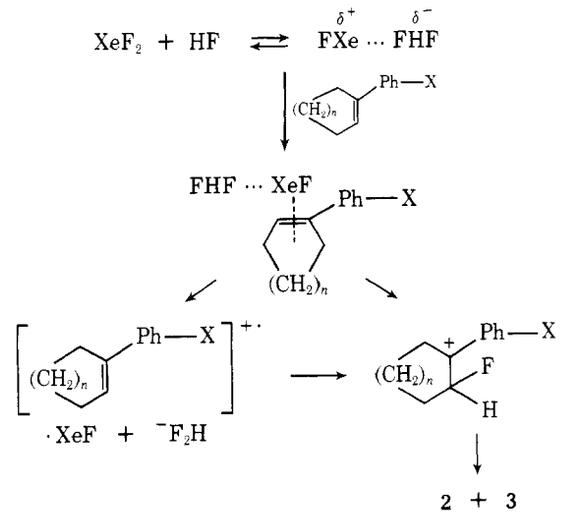
Scheme III



4a, X = H
b, X = *m*-Cl
c, X = *p*-OCH_3

X	% 5	% 6
H	50	50
m-Cl	55	45
p-OCH_3	75	25

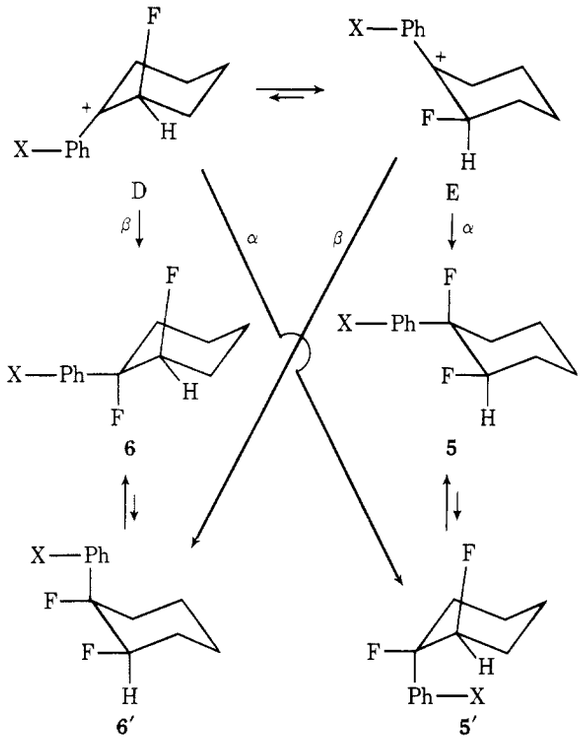
Scheme IV



Dependence of the steric course of fluorine addition to phenyl-substituted cycloalkenes on ring magnitude, which could be ascribed to flexibility of the intermediates, stimulated us to study the effect of the group bonded to the phenyl ring on the stereochemistry of fluorine addition to the cyclohexene ring. The addition of fluorine with xenon difluoride to 1-phenylcyclohexene yielded equal amounts of syn and anti adducts as already mentioned above, while the fluorination of the *m*-chlorophenyl derivative **4b** resulted in the formation of 55% of **5** and 45% of **6** (Scheme III). The NMR data of the adducts are very similar to those observed by fluorination of 1-phenylcyclohexene and are listed in Table II. The fluorination of the *p*-methoxyphenyl derivative **4c** also resulted in the formation of two products with the cis adduct being the major product (the NMR data are very similar to those observed for products resulting from fluorination of unsubstituted 1-phenylcyclohexene). The acid-catalyzed liquid-phase fluorination of 1-phenylcyclohexene with xenon difluoride in the presence of a free-radical inhibitor (oxygen) had no significant effect on the product distribution.

On the basis of earlier observations of the addition of fluorine with xenon difluoride in the liquid-phase acid-catalyzed reaction to phenyl-substituted olefins,[3] and the observations already made in this paper, the following reaction mechanism (Scheme IV) could be suggested. The mechanism must involve catalysis by hydrogen fluoride, since the reaction proved to be very slow without it. It might be expected that in the presence of hydrogen fluoride xenon difluoride behaves as an electrophile. Previously this has been suggested by Filler et al.[5] for the fluorination of aromatic compounds. In the next step a π complex is probably formed between this electrophilic species and the olefin, which could be transformed by a heterolytic Xe–F bond cleavage into an open β-fluorocarbonium ion intermediate, which then, after fluoride ion attack, results in the formation of cis and trans difluorides. Furthermore, another possibility is the formation of an ion radical which has already been observed in the fluorination of benzene and its derivatives,[5] transforming in the next step by XeF· or XeF_2 into an open carbonium ion. The lower oxidation potentials of olefins (in comparison to those of benzo derivatives) make the suggested path quite reasonable. It is very interesting that the stereochemistry of addition depends on ring magnitude. The situation resembles that already observed in the fluorination of various 1-phenyl-2-alkyl-substituted ethenes, where the ratios of *dl*-erythro and *dl*-threo difluorides are independent of the starting olefin and trans addition of fluorine predominates.[3] The higher amounts of syn adducts formed by fluorination of cis alkenes were explained by rotation about the newly formed C–C single bond in the β-fluorocarbonium ion. The stereochemistry of fluorine addition to 1-phenylcyclopentene is very similar to that of indene.[3] The addition is preferentially anti. The lower anti stereoselectivity in the case of 1-phenylcyclohexene could be explained by isomerization of the initially formed ion D (Scheme V), in which fluorine is in an axial position, into the more stable ion E, in which fluorine is in an equatorial position. Ion E is more stable, because there are smaller interactions between the fluorine atom and the p orbital of the carbocation than in the primarily formed ion D, while the steric interactions become

Scheme V[a]



[a] α = syn attack; β = anti attack.

less important than in substituted cyclohexanes. Initially formed ion D could undergo preferential anti attack by a fluoride ion, thus forming difluoride **6**, or the less favored syn attack, thus resulting in the nonstable conformation of cis difluoride **5′** with the phenyl group in an axial position, which then transformed into preferential conformation **5** with the phenyl group in the equatorial position.[6] The more stable ion E could undergo preferential syn fluoride ion attack, thus forming defluoride **5**, or anti attack, thus forming the unfavored conformation **6′**, which transforms into the more stable conformation **6**. On the basis of the literature data,[6] conformations **5′** and **6′** could be practically excluded. Isomerization of initially formed ion D into ion E becomes more important in the case of the *p*-methoxy (*p*-OCH_3) substituent, which is then reflected in the preferential formation of difluoride **5**. The formation of greater amounts of syn adduct in the fluorination of 1-phenylcycloheptene could also be ascribed to the secondary isomerization of the primarily formed β-fluorocarbonium ion, in which interaction between the p orbital of the carbocation and fluorine atom becomes smaller, and also to the high flexibility of the cycloheptane ring. However, limited data are available about the conformation of the β-halonium ions of cycloheptanes.

Experimental Section

IR spectra were recorded using a Perkin-Elmer 257 spectrometer and ^1H and ^{19}F NMR spectra by a Jeol JNM-PS-100 from CCl_4 solution with Me_4Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph Model 1800 and TLC on Merck PSC-Fertigplatten silica gel F-254 (activated for 3 h at 120 °C before use).

Materials. Pure samples of olefins were prepared by known methods: 1-phenylcyclopentene,[7] 1-phenylcyclohexene,[7] 1-phenylcycloheptene,[7] 1-(3-chlorophenyl)cyclohexene,[7] and 1-(4′-methoxyphenyl)cyclohexene.[7] Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride was purified[8] and stored over molecular sieves. Xenon difluoride was prepared by a photosynthetic method[9] and its purity was better than 99.5%.

Addition and Isolation Procedures. To a solution of 1 mmol of olefin in methylene chloride (5 mL) in a Kel-F vessel, 1 mmol of xenon difluoride was added at T = 25 °C and under stirring anhydrous hydrogen fluoride (trace amounts) was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was evolved. After 10–40 min xenon gas evolution ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 mL), washed with 10 mL of 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The crude reaction mixture was separated by preparative TLC or GLC.

Fluorination of 1-phenylcyclopentene: yield, 94% of crude products; separation by preparative TLC.

1-Fluoro-1-phenyl-*trans*-2-fluorocyclopentane (2): yield, 54% of liquid product; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{11}H_{12}F_2$, 182.0920; found, 182.0920) *m/e* 182 (M^+, 77), 161 (12), 150 (12), 147 (18), 142 (22), 136 (24), 135 (100), 133 (22), 122 (25), 121 (26), 115 (30), 109 (32), 105 (15), 91 (15), 77 (15), 51 (14).

1-Fluoro-1-phenyl-*cis*-2-fluorocyclopentane (3): yield, 13% of liquid product; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{11}H_{12}F_2$, 182.0920; found, 182.0912) *m/e* 182 (M^+, 31), 142 (23), 141 (13), 136 (10), 135 (77), 133 (8), 123 (10), 121 (100), 109 (13).

Fluorination of 1-phenylcyclohexene: yield, 81% of crude products; separation by preparative GLC [Carbowax 20M/Varaport 30 (70:80), 10%, T = 250 °C].

1-Fluoro-1-phenyl-*trans*-2-fluorocyclohexane (2): yield, 27% of oily products; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{12}H_{14}F_2$, 196.1064; found, 196.1062) *m/e* 196 (M^+, 40), 135 (100), 122 (21).

1-Fluoro-1-phenyl-*cis*-2-fluorocyclohexane (3): yield, 30% of liquid products; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{12}H_{14}F_2$, 196.1064; found, 196.1054) *m/e* 196 (M^+, 39), 135 (100), 122 (20).

Fluorination of 1-phenylcycloheptene: yield, 91% of crude products; separation by preparative TLC.

1-Fluoro-1-phenyl-*trans*-2-fluorocycloheptane (2): yield, 20% of solid product; mp 55–57 °C; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{13}H_{16}F_2$, 210.1238; found, 210.1236) *m/e* 210 (M^+, 77), 136 (19), 135 (100), 122 (77), 115 (19), 109 (28), 91 (15).

1-Fluoro-1-phenyl-*cis*-2-fluorocycloheptane (3): yield, 51% of solid product; mp 49–51 °C; NMR data are stated in Table I; mass spectra (mol wt calcd for $C_{13}H_{16}F_2$, 210.1238; found, 210.1238) *m/e* 210 (M^+, 79), 136 (23), 135 (100), 122 (78), 115 (15), 109 (30), 91 (10).

Fluorination of 1-(3′-chlorophenyl)cyclohexene: yield, 79% of crude products; separation by prepative TLC.

1-fluoro-1-(3′-chlorophenyl)-*trans*-2-fluorocyclohexane (6b): yield, 22% of oily product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{12}H_{13}F_2Cl$, 230.0674; found, 230.0667) *m/e* 230 (M^+, 31), 169 (58), 86 (61), 28 (100).

1-Fluoro-1-(3′-chlorophenyl)-*cis*-2-fluorocyclohexane (5b): yield, 31% of oily product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{12}H_{13}F_2Cl$, 230.0674; found, 230.0678) *m/e* 230 (M^+, 29), 169 (59), 86 (63), 28 (100).

Fluorination of 1-(4′-methoxyphenyl)cyclohexene: yield, 94% of crude products; separation by preparative TLC.

1-Fluoro-1-(4′-methoxyphenyl)-*trans*-2-fluorocyclohexane (6c): yield, 15% of oily product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{13}H_{16}OF_2$, 226.1169; found, 226.1159) *m/e* 226 (M^+, 42), 165 (100), 84 (28), 66 (36).

1-Fluoro-1-(4′-methoxyphenyl)-*cis*-2-fluorocyclohexane (5c): yield, 37% of oil product; NMR data are stated in Table II; mass spectra (mol wt calcd for $C_{13}H_{16}OF_2$, 226.1169; found, 226.1162) *m/e* 226 (M^+, 40), 165 (100, 84 (30), 66 (35).

Fluorination in the Presence of Oxygen. 1-Phenylcyclohexene (1 mmol) was dissolved in 5 mL of methylene chloride, 1 mmol of xenon difluoride was added at 25 °C, and, under stirring, a mixture of anhydrous hydrogen fluoride and oxygen was introduced into the reaction mixture for 30 min. After workup, the residue was analyzed by NMR spectroscopy; the product distribution was 50% of **2** and 50% of **3**. It can be seen that the free-radical inhibitor had no effect on the product distribution.

Acknowledgments. We thank Professor J. Slivnik for xenon fluoride. The financial assistance of the Boris Kidrič Foundation is acknowledged.

Registry No.—**1** (n = 1), 825-54-7; **1** (n = 2), 771-98-2; **1** (n = 3), 25308-75-2; **2** (n = 1), 64332-84-9; **2** (n = 2), 64332-83-8; **2** (n = 3), 64332-82-7; **3** (n = 1), 64332-81-6; **3** (n = 2), 64332-80-5; **3** (n = 3),

64332-79-2; **4b**, 27163-65-1; **4c**, 20758-60-5; **5** (X = *m*-Cl), 64332-78-1; **5** (X = *p*-OCH_3), 64332-77-0; **6** (X = *m*-Cl), 64332-76-9; **6** (X = *p*-OCH_3), 64332-75-8; xenon difluoride, 13709-36-9.

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Chemistry of Carbanions. 31. Cyclization of the Metal Enolates from ω-Bromo Ketones[1]

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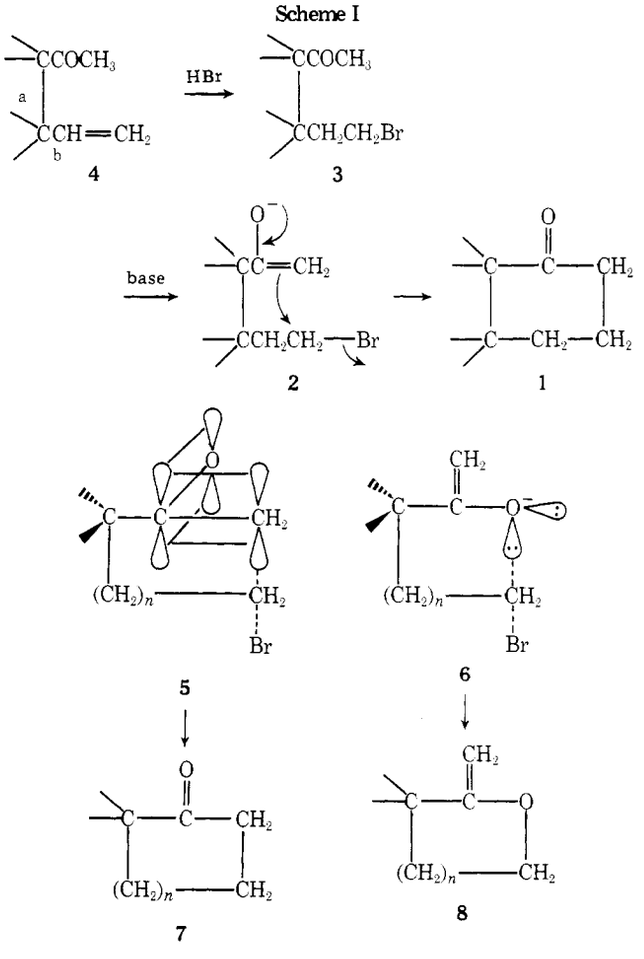
Utilizing *stable solutions* of *i*-Pr_2NLi in hexane, a convenient procedure is described for the conversion of methyl ω-bromoalkyl ketones **9–12**, **32**, **42**, **50**, and **67** to mixtures of Li^+ enolates containing predominantly the terminal enolates. Although solutions of these Li^+ enolates in Et_2O–hexane mixtures are stable at 0 °C, when activating ligands such as 4 molar equiv of HMP [$(Me_2N)_3PO$], 1 molar equiv of triglyme (**15**) or the 14-crown-4 ether **16**, or excess DME are added these Li^+ enolates undergo intramolecular cyclization reactions. In the absence of serious geometrical constraints (cf. bromo ketone **32**), the enolates of bromo ketones **9–12** underwent intramolecular C-alkylation to form the corresponding cyclohexanone derivatives in 60–80% yield. Similar intramolecular cyclization by bromo ketone **67** produced a mixture of five-membered and seven-membered C-alkylated products, but intramolecular cyclization of the bromo ketone **42** yielded only the five-membered O-alkylated product **43**. The Li^+ enolate of bromo ketone **50** underwent a very slow intramolecular cyclization to produce a mixture of O-alkylated and C-alkylated four-membered ring products. Thus, the method described constitutes a useful synthetic route to cyclohexanone derivatives and, with limitations, is also applicable to the synthesis of cycloheptanone derivatives.

The most common synthetic routes to cyclohexane derivatives involve the reduction of benzene derivatives, use of the Diels–Alder reaction to form intermediate cyclohexenes, or use of the Robinson annulation technique (or related procedures) to form intermediate cyclohexenones. It seemed to us that another rather general synthetic route to cyclohexanone derivatives **1** (Scheme I) could be based on the cyclization of a regiospecifically generated metal enolate **2** derived from an ω-bromo ketone **3**. We have noted elsewhere[2] that the requisite ω-bromo ketones **3** can readily be obtained by addition of HBr to the vinyl ketones **4** in a free-radical chain process. The vinyl ketone precursors **4** can generally be assembled either by addition of a $(vinyl)_2CuLi$ reagent to an enone to form bond b in **4** or by allylation of a regiospecifically generated metal enolate to form bond a in **4**.

Superficially the intramolecular C-alkylation reaction (arrows in structure **2**) would appear to be straightforward. However, when one imposes the geometrical constraints that the nucleophile (the enolate α-carbon atom) attack along a path collinear with the C–Br bond[3] and that the electron density at the α carbon of the enolate is concentrated in orbitals perpendicular to the plane of the enolate anion, then the transition state required for this intramolecular C-alkylation is represented by structure **5**. In this transition state **5** three of the carbon atoms lie in a plane perpendicular to the forming C–C bond. Study of molecular models indicates that this transition state **5** can be attained without excessive distortion of normal carbon bond angles when *n* has values of two or larger to form cyclic ketones **7** with six or more ring members. However, substantial distortion of normal carbon bond angles is required to attain the transition state **5** when *n* has values one or zero. In such cases an alternative transition state **6** in which the forming C–O bond lies in the plane of the enolate anion with a nonbonded electron pair on the oxygen atom

Scheme I



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