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Effect of cycloalkene structure on fluorination with 1-chloromethyl-4-fluoro-1,4-diazonia[2.2.2]octane bis(tetrafluoroborate) (F-TEDA)

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Abstract—Liquid phase fluorination of norbornene with 1-chloromethyl-4-fluoro-1,4-diazonia[2.2.2]octane bis(tetrafluoroborate)—F-TEDA resulted in the formation of two rearranged Ritter type products: 2-*exo*-acetamido-7-*syn*-fluoro norbornane and 2-*exo*-acetamido-7-*anti*-fluoro norbornane in 1:1 ratio in acetonitrile, while the presence of an external nucleophile, e.g. water or methanol resulted in formation of two additional rearranged products: 2-*exo*-hydroxy or methoxy -7-*syn*-fluoro norbornane and 2-*exo*-hydroxy or methoxy-7-*anti*-fluoro norbornane. Fluorination of cycloalkenes obeys a simple second order rate equation, relative rates close to unity were found for norbornene/cyclohexene and cyclopentene/cyclohexene pairs. Activation parameters were determined for cycloalkenes in acetonitrile–water ($\Delta H^{\ddagger}$=14 kcal mol^{-1} and $\Delta S^{\ddagger}$=−20 cal mol^{-1}K^{-1} for norbornene), while the Winstein–Grunwald solvent polarity variation had negligible effect.

1. Introduction

Bicyclo[2.2.1]heptene (norbornene) is one of the most versatile model olefins for studying the role of the structure of electron acceptor type E–L reagents in determining the course of addition reactions.[1–4] From these studies, two types of information can be obtained. Firstly, the structures of the products and their distributions inform us about the type of electron shift from the π electron system to the acceptor E–L reagent.[5,6] Secondly, the relative rate of functionalisation of norbornene compared with cyclohexene appears to be very dependent on the geometry of the rate determining transition state:[2] close to unity in the case of a three-centred intermediate (mercuric acetate[7] and perbenzoic acid[8]), while a ratio of up to 8000 was observed in four-centred or larger intermediates (picryl azide[9]).

The reactivities of almost all F–L reagents for mild fluorine introduction into organic molecules have been tested on norbornene. The type of products and their distribution depend strongly on the reagent and on the reaction conditions. In the reaction with caesium fluoroxysulphate the initially formed fluorocarbonium ion underwent proton loss to yield fluoro nortricyclane and Meerwein–Wagner rearrangement resulted in 7-*syn*-fluoro-norbornenene in nearly equal amounts at room temperature in dichloromethane[10] while low temperature reaction with fluorine gave only rearranged 7-*syn*-fluoro-norbornenene.[11] Introduction of fluorine with xenon difluoride however is very sensitive to solvent (CH_2Cl_2, CCl_4, CH_3CN), the catalyst used (HF, BF_3OEt, C_6F_5SH) and photochemical initialisation, and up to six products were isolated.[12–17]

The N–F class of reagents are easy to handle and commercially available, while their reactivity depends on their type, which might be of R^1R^2NF type, *N*-fluoropyridinum and related salts or $FN^+R^1R^2R^3$ type.[18–22]

Kinetic evaluation of fluorine transfer from F–L type reagents is rather scarce, due mainly to their high reactivity and the high sensitivity to the reaction conditions. Many of these difficulties can be overcome by using some N–F reagents whose reactions could be followed by iodometric titration and reproducible data have been obtained.[23–25] We report here our studies of mild fluorine introduction to norbornene, cyclopentene and cyclohexene with F-TEDA in acetonitrile in the presence of water or methanol.

2. Results and discussion

In a typical experiment, 1 mmol of norbornene (**1**) was dissolved in 5 ml of acetonitrile, 1.2 mmol F-TEDA (**2**) was added and stirred at room temperature for 4 h. The crude reaction mixture showed two signals in the ^{19}F NMR spectrum (δ=−207, −201 ppm) and after GC

Keywords: bicyclic aliphatic compounds; cycloalkenes; halogenation; kinetics.

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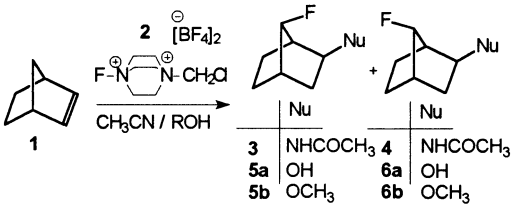


Scheme 1.

Table 1. Effect of reaction conditions on product distribution of the reaction of norbornene with F-TEDA in acetonitrile at 20°C

NuH	(% mass)	3	4	5	6	5+6
	None	50	50			
H_2O	5	32	25	18	25	43
	10	25	20	21	34	55
	20	22	17	25	36	61
	40	16	12	31	42	73
	60	12	9	38	41	79
CH_3OH	5	31	30	20	19	39
	10	15	25	26	34	59
	20	7	13	33	45	78
	40	11	7	33	49	82

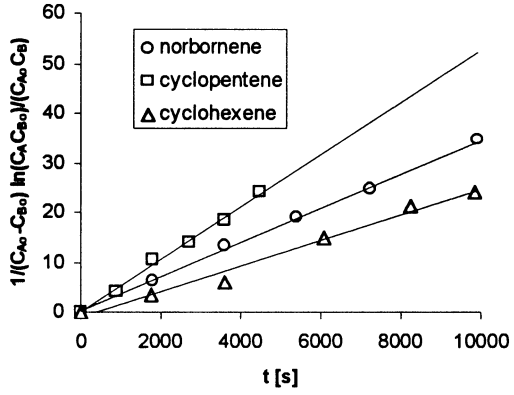


Figure 1. Effect of alkene structure on the fluorination with F-TEDA in acetonitrile–water mixture (5:1) at 20°C.

separation two products were isolated, 2-*exo*-acetamido-7-*syn*-fluoro norbornane (**3**) and 2-*exo*-acetamido-7-*anti*-fluoro norbornane (**4**) with both products having very similar mass spectra. The products were formed in equal amounts with acetonitrile acting as nucleophile indicating a Ritter type of fluorofunctionalisation. It is evident that the course of this reaction differs markedly from other fluorinations and for this reason we further studied the effect of the structure of the external nucleophile (water, methanol) and its amount on the course of fluorination. In the presence of 5% (by mass) of external nucleophile in acetonitrile, two additional products in each case were formed in up to 43% in the case of water and 39% in the case of methanol. Products were isolated and characterised on the basis of their spectroscopic data (Scheme 1, Table 1). In the presence of nucleophile, only 2,7-disubstituted norbornane derivatives are formed, the 7-*anti* isomer (**6a** Nu=OH, **6b** Nu=OCH_3) in excess of the *syn* isomer (**5a** Nu=OH, **5b** Nu=OCH_3). Although as seen in Table 1, further increase of external nucleophile increased the proportion of fluoro-hydroxy and fluoro-methoxy products, Ritter type products are still present even in the presence of 60% (by mass) of nucleophile.

We studied the kinetics of fluorine transfer from F-TEDA to norbornene. The progress of reaction of norbornene with F-TEDA in an acetonitrile–water mixture (5:1) was monitored by iodometric titration and clearly indicated that the course of reaction obeys a simple second order rate equation.

$$v = \mathrm{d[F\text{-}TEDA]}/\mathrm{d}t = k_2[\mathrm{F\text{-}TEDA}]\,[\mathrm{alkene}]$$

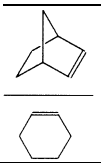
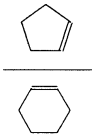
Typical progress of norbornene fluorofunctionalisation at 20°C is presented in Fig. 1 and a value of $k_2 = 3.4\times10^{-3}\ \mathrm{M^{-1}\,s^{-1}}$ was determined. Next we studied the effect of solvent polarity on the rate of fluorofunctionalisation of norbornene. Due to its sensitivity to solvent the reactions are restricted to acetonitrile–water or acetonitrile–methanol mixtures. As is evident from Table 2, the Winstein–Grunwald[26] variation over 2.5 units (from 20 to 60% water in acetonitrile) had a negligible effect ($m=-0.03$). Insensitivity of the rate of fluorofunctionalisation to solvent polarity indicates that the difference in polarity between the reactants and the rate determining transition step is minimal. Similar insensitivity was also observed for fluorine transfer from 1-fluoro-4-hydroxy-1,4-diazonia-[2.2.2]octane bis(tetrafluoroborate)—NFTh to phenyl substituted alkenes ($m=-0.2$).[25]

The activation parameters for fluorine transfer to norbornene

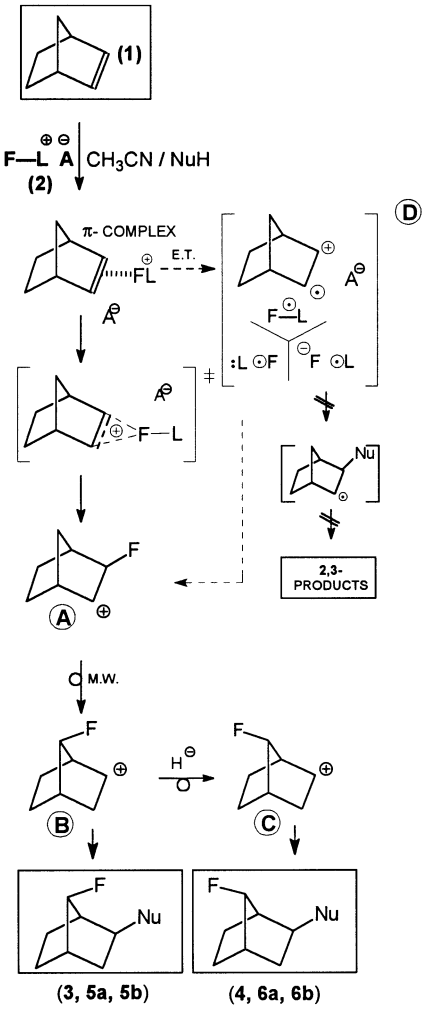
Table 2. Effect of reaction conditions on second order rate constants for functionalisation of norbornene with F-TEDA in acetonitrile

Reaction conditions		$k_2\times10^{-3}$ ($\mathrm{l\,mol^{-1}\,s^{-1}}$)	
NuH	T (°C)		
H_2O (20%)	20	3.5±0.1	$\ln k/k_0 = mY$, $m=-0.03$
(30%)	20	3.8±0.3	
(40%)	20	4.0±0.1	
(50%)	20	4.0±0.1	
(60%)	20	2.8±0.5	
H_2O (17%)	15	2.3±0.2	$\Delta H^{\ddagger} = 14.3 \pm 0.7$, (kcal $\mathrm{mol^{-1}}$)
	20	3.4±0.1	$\Delta S^{\ddagger} = -20 \pm 2$, (cal $\mathrm{mol^{-1}K^{-1}}$)
	25	6.0±0.2	
	30	8.2±1.0	
MeOH (17%)	20	4.5±0.3	$\Delta H^{\ddagger} = 14.5 \pm 0.4$, (kcal $\mathrm{mol^{-1}}$)
	25	7.3±0.6	$\Delta S^{\ddagger} = -19 \pm 0.9$, (cal $\mathrm{mol^{-1}K^{-1}}$)
	30	10.9±0.2	
	35	16.5±0.3	

Table 3. Effect of reagent structure on the norbornene/cyclohexene and cyclopentene/cyclohexene reactivity ratios

Reagent	Relative rate	
		
FTEDA	1.3	1.9
$Hg(OAc)_2$[7]	1	0.7
RCOOOH[8]	1.3	1.5
ICH_2ZnI[28]	1.7	1.6
O_3[7]	10	4.5
Br_2[7]	13	3.5
CrO_2Cl_2[29]	511	4.1
NOCl[7]	660	88
ArN_3[9]	8000	42

in an acetonitrile–water mixture (5:1) are presented in Table 2. The found values $\Delta H^{\ddagger}=14$ kcal mol^{-1}, $\Delta S^{\ddagger}=-20$ cal mol^{-1} K^{-1} are comparable to activation profiles determined for other functionalisations of norbornene (phenylazide under similar conditions[9] $\Delta H^{\ddagger}=13.9$ kcal mol^{-1}, $\Delta S^{\ddagger}=-33.1$ cal mol^{-1} K^{-1}). Methanol as the external nucleophile results in similar reaction rates and activation parameters.



Scheme 2.

The effect of the ring size of cycloalkenes on the rate of fluorofunctionalisation was studied. Similar second order rate behaviour was established for cyclopentene and cyclohexene, with constants determined at 20°C: $k_2=4.9\times10^{-3}$ M^{-1} s^{-1} and $k_2=2.4\times10^{-3}$ M^{-1} s^{-1}, respectively. As evident from Fig. 1, cyclopentene is more reactive than norbornene which is more reactive than cyclohexene. The activation parameters for fluorofunctionalisation of these cycloalkenes in acetonitrile–water (5:1) were determined: $\Delta H^{\ddagger}=12.3$ kcal mol^{-1}, $\Delta S^{\ddagger}=-26.6$ cal mol^{-1} K^{-1} for cyclopentene and $\Delta H^{\ddagger}=14.5$ kcal mol^{-1}, $\Delta S^{\ddagger}=-20.6$ cal mol^{-1} K^{1} for cyclohexene. It is known that the relative rates of the norbornene/cyclohexene pair are much more dependent on the nature of the reagent, and therefore on the type of the intermediate (three-centred, four-centred, etc.) than in the case of the cyclopentene/cyclohexene pair. Table 3 summarises various reagents and it is clear that fluorofunctionalisation with F-TEDA in acetonitrile–water solution is a very similar process to those transformations which occur through the three-centred intermediate which is common to functionalisation with mercuric acetate[7] and peroxy acids.[8] Larger ratios are observed for four or even five-centred cyclic intermediates with nitrosyl chloride[7] and picryl azide,[9] respectively.

On the basis of our experimental results, we propose the mechanism presented in Scheme 2. In the first step a π complex is probably formed capable of being transformed through a three-centred transition state to β-fluorocarbonium ion A, Meerwein–Wagner rearrangement then gives ion B and reaction with acetonitrile results in the formation of 2-*exo*-acetamido-7-*syn*-fluoro norbornane (**3**) and in the presence of water or methanol, 7-*syn*-fluoro-2-*exo*-hydroxy norbornane (**5a**) and 7-*syn*-fluoro-2-*exo*-methoxy norbornane (**5b**). The rearranged fluorocarbonium ion B undergoes hydride shift forming ion C which reacts with acetonitrile giving 2-*exo*-acetamido-7-*anti*-fluoro norbornane (**4**) and in the presence of external nucleophile hydroxy (**6a**) and methoxy (**6b**) product. The possibility of an electron transfer process is diminished because ion radical D photochemically generated from norbornene and acceptor sensitiser collapsed with nucleophile, forming radical species which do not rearrange and only 2,3-disubstituted products were formed.[27] However, the conversion of ion radical D to fluorocarbonium ion A can not be completely excluded, because the situation in the proposed intimated pair D (norbornene cation radical–radical species formed from the reagent) differs from cation radicals generated under photochemical conditions.[27]

The present results confirm that the main intermediates in the mild fluorination of cycloalkenes with F-TEDA have an ionic nature and are probably formed through three-centred transition states.

3. Experimental

1-Chloromethy-4-fluoro-1,4-diazoniabicyclo[2.2.2] octane bis-(tetrafluoroborate) (F-TEDA) (crystallised from acetonitrile),

norbornene (sublimed), cyclopentene and cyclohexene (distilled) and solvents (distilled) were obtained from commercial sources. KI and a standard solution of sodium thiosulphate were used as received.

3.1. Fluorination of alkenes with F-TEDA

F-TEDA (1.3 mmol) was added to a solution of 1 mmol of alkene (norbornene, cyclohexene, cyclopentene) in 10 ml acetonitrile–water or acetonitrile–methanol solutions (Table 1), and the reaction mixture stirred at room temperature. The solvent was partially removed under reduced pressure and extracted with dichloromethane. The solution was washed with water and dried over sodium sulphate. The crude reaction mixture, after careful evaporation of solvent, was analysed by ^{1}H and ^{19}F NMR spectroscopy and GC–MS (HP-1 column). Product distributions were analysed by ^{19}F NMR spectroscopy and data are presented in Table 1. Product distributions in the crude reaction mixture as determined by GC are in good agreement with NMR. Norbornene: four products were isolated in case of each external nucleophile, by preparative GC on a FFAP column and their structures determined on the basis of their spectroscopic data or by comparison to the literature.

3.1.1. 7-*syn*-Fluoro-2-*exo*-acetamido norbornane (3). White volatile crystals, mp: 87–88°C; [found: C, 63.03; H, 8.67; N, 8.11, $C_9H_{14}NOF$ requires: C, 63.14; H, 8.24; N, 8.18]; δ_F (54.6 MHz $CDCl_3$) −201 (dm, J=58 Hz); δ_H (60 MHz $CDCl_3$) 1–2.5 (8H, m), 4.15 (1H, m, H_2), 4.90 (1H d, J=58 Hz, H_7); ν_{max} (KBr) 3260 (br), 2940, 1630, 1540, 1370, 1280, 1160, 1050, 990 cm^{-1}; m/z=171, 109, 92, 86, 67.

3.1.2. 7-*anti*-Fluoro-2-*exo*-acetamido norbornane (4). White volatile crystals, mp: 129–131°C; [found: C, 62.76; H, 8.38; N, 8.05. $C_9H_{14}NOF$ requires C, 63.14; H, 8.24; N, 8.18]; δ_F (54.6 MHz $CDCl_3$) −207 (ddd, J=58, 6, 6 Hz); δ_H (60 MHz $CDCl_3$) 1–2.5 (8H, m), 3.73 (1H, m, H_2), 4.90 (1H, d J=58 Hz, H_7); ν_{max} (KBr) 3280 (br), 2960, 1640, 1545, 1370, 1290, 1055, 1025 cm^{-1}; m/z 171, 109, 92, 86, 67.

3.1.3. 7-*syn*-Fluoro-2-*exo*-hydroxy norbornane (5a).[30] White volatile crystals, mp 115–119°C (lit.: 132–134°C),[30] δ_F (54.6 MHz $CDCl_3$) −201.5 (dm, J=57.2 Hz); δ_H (300 MHz $CDCl_3$) 1–2.6 (8H, m)), 3.85 (1H, m, H_2), 4.90 (1H, d, J=57.2 Hz, H_7).

3.1.4. 7-*anti*-Fluoro-2-*exo*-hydroxy norbornane (6a).[30] White volatile crystals, mp 108–112°C (lit.: 126–129°C),[30] δ_F (54.6 MHz $CDCl_3$) −209 (ddd, J=57.4, 6, 6 Hz); δ_H (300 MHz $CDCl_3$) 1–2.6 (8H, m), 3.77 (1H, m, H_2), 5.11 (1H, d, J=57.4 Hz, H_7).

3.1.5. 7-*syn*-Fluoro-2-*exo*-methoxy norbornane (5b).[16] Colourless volatile oil, δ_F (54.6 MHz $CDCl_3$) −201.3 (dm, J=56.5 Hz); δ_H (300 MHz $CDCl_3$) 1–2.5 (8H, m), 3.32 (3H, s, OCH_3), 3.47 (1H, m, H_2), 4.77 (1H, d, J=56.5 Hz, H_7).

3.1.6. 7-*anti*-Fluoro-2-*exo*-methoxy norbornane (6b).[16] Colourless volatile oil, δ_F (54.6 MHz $CDCl_3$) −209 (ddd, J=57.5, 5.5, 5.5 Hz); δ_H (300 MHz $CDCl_3$) 1–2.5 (8H, m), 3.22 (1H, m, H_2), 3.29(3H, s, OCH_3), 4.95 (1H, d, J=57.5 Hz, H_7); cycloalkenes: NMR confirmed formation of fluoro hydroxy[31] as well as fluoro acetamido cycloalkanes.

3.2. Determination of kinetic data for reaction of alkenes with F-TEDA

Alkene (norbornene, cyclohexene, cyclopentene) (0.6 mmol) was dissolved in a thermostatted mixture of 30 ml acetonitrile and 10 ml water, then 20 ml of a thermostatted acetonitrile solution of F-TEDA was added (0.3 mmol) and the reaction mixture further stirred at 20°C. F-TEDA consumption was monitored by iodometric titration. After various times 10 ml aliquots of reaction mixture were mixed with 20 ml of cold 0.02 M KI and the liberated iodine was titrated with 0.05 M $Na_2S_2O_3$. Second order rate constants were calculated from the equation: $1/(C_{Ao}-C_{Bo})\ln(C_{Bo}C_A)/(C_BC_{Ao}) = k_2t$. Measurements were made at different alkene concentration to confirm second order rate behaviour and repeated in at least 3 runs; average data is presented in Table 2. Kinetic measurements were repeated at various temperatures (Table 2) to determine the activation parameters of studied reactions. Linear correlation was observed between $\log k_2$ and reciprocal temperature and activation parameters were calculated from the equation: $\ln(k_2/T) = \ln(k_B/h) + (\Delta S^{\ddagger}/R) - (\Delta H^{\ddagger}/RT)$. The same procedures at 20°C, with the exception that ratios of acetonitrile–water mixtures ranged from 10% v/v water to 40% v/v, were performed to evaluate the influence of solvent polarity on second order rate constants for reactions of norbornene with F-TEDA. The second order rate constants are shown in Table 2 and were plotted according to the Winstein–Gruenwald equation (YtBuCl values[26]): $\log k_2 = mY + log\ k_0$ showing no effect.

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