Destabilized Carbocations: C_2F_5 Substituent Effects on Ground and Transition States in 2-Bicyclo[2.2.1]heptyl Brosylates

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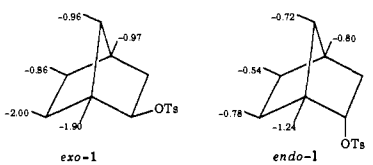
Abstract: The solvolyses of the *exo*- and *endo*-2-C_2F_5-2-norbornyl brosylates (**11**) and *exo*- and *endo*-1-C_2F_5-2-norbornyl brosylates (**12**) give $k_{exo}/k_{endo} = 10^3$ for the 2-C_2F_5 substituent and $k_H/k_{C_2F_5} = 1100$ (exo) and 340 (endo), while the 1-substituted derivative gives $k_{exo}/k_{endo} = 42$ (81.8 °C in TFA), with $k_H/k_{C_2F_5} = 8.0 \times 10^4$ (exo) and 2.1×10^4 (endo). Solvolysis of *exo*-**11** occurs with rearrangement and ion pair return to *exo*-**12**, which is 150 times less reactive than *exo*-**11**. Ionization with participation occurs in *exo*-**11**, but the exo/endo rate ratio is not enhanced by the increased electron demand in the destabilized substrate. This is attributed to the almost fully developed participation already present in the unsubstituted parent. The greater reactivity of the 2-C_2F_5 versus the 1-C_2F_5 derivatives is indicative of enhanced reactivity due to ground-state destabilization in the former.

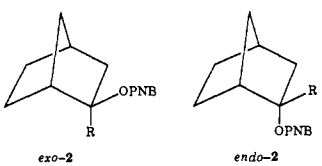
The influence of electron-withdrawing substituents on the generation of carbocations has been of continuing interest.[1] The major effects of groups such as CF_3, cyano, carbonyl, and others in affecting carbocation formation and reactions have been well-documented,[1,2] but fundamental question remain. These questions regard the contribution of ground-state destabilization[3] to the observed reactivities and the degree to which electron donation by neighboring groups[1,2] can be enhanced by destabilizing substituents.

We have chosen the 2-substituted bicyclo[2.2.1]heptyl (norbornyl) system **1** as a substrate to test for these effects for per-



fluoroalkyl substituents. This system has been extensively studied,[4,5] and the effects of substituents on the solvolytic reactivity[6,7] can be summarized by the ρ_I values compiled by Grob.[6d]

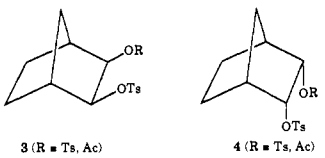
There are also major effects of substituents at the 2-position on the solvolytic reactivity of norbornyl derivatives,[2,4a,7] with a rate difference of 5×10^7 for **2** (R = Ar) as the aryl group varies.



However, the exo/endo rate ratio was essentially constant between 127 and 284 with no systematic effect of the substituent,[7a] and even with the 3,5-bis(trifluoromethyl)phenyl substituent these derivatives were still 10^5 times more reactive than the parent secondary norbornyl system.[7a]

Steric effects are significant but are evidently of approximately equal magnitude in both the exo- and endo-2-substituted norbornyl derivatives. Thus for **2** (R = *t*-Bu) the rates are accelerated by more than 10^4 relative to R = Me and the exo/endo rate ratio is 470.[8]

The norbornyl system has been utilized previously in investigations of strongly electron-withdrawing substituents. The derivatives **3** and **4** gave ratios of di-exo/di-endo = 50 (R = Ts) and 11 (R = Ac).[4c] This decrease in the exo/endo rate ratio is clearly



3 (R = Ts, Ac) 4 (R = Ts, Ac)

in the opposite direction of that expected for inductive enhancement of neighboring group participation. The possible importance of steric factors in masking an enhanced k_{exo}/k_{endo} ratio was

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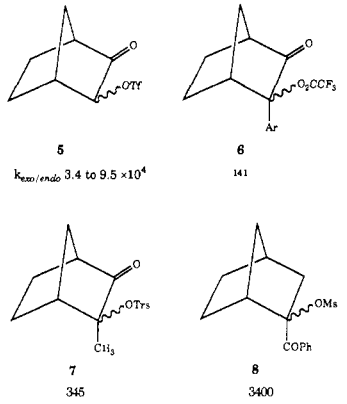
Table I. Solvolytic Rate Constants for $PhC(C_2F_5)(CH_3)OTs$ (9)

solvent (Y_{OTs} or [salt])	t (°C)	k_{obs} (s^{-1})[a]	$k_{C_2F_5}/k_{CF_3}$
TFA (0.200)	25.0	2.20×10^{-1}	4.3
TFA (4.57)	25.0	2.25×10^{-2}	4.2
97 HFIP (3.61)	25.0	1.60×10^{-2}	5.4
HCO_2H (3.04)	25.0	1.44×10^{-3}	3.7
97 TFE (1.83)	25.0	1.83×10^{-4}	3.1
80 EtOH (0.00)	25.0[b,c]	9.31×10^{-7}	1.1
100 EtOH (−1.75)	25.0[b,d]	9.59×10^{-8}	2.2

[a] Measured by observing the decrease in the UV absorption with at least duplicate runs at each temperature, ±5% unless noted. [b] Extrapolated from data at higher temperatures. [c] k (s^{-1}, t) 6.44×10^{-4} (77.1), 1.73×10^{-4} (65.4), 2.50×10^{-5} (49.4); $\Delta H^{\ddagger} = 25.6$ kcal/mol, $\Delta S^{\ddagger} = 0.3$ eu. [d] k (s^{-1}, t) 8.39×10^{-4} (109.2), 1.72×10^{-4} (91.1), 5.89×10^{-5} (77.1), 1.06×10^{-5} (65.4); $\Delta H^{\ddagger} = 24.0$ kcal/mol, $\Delta S^{\ddagger} = -10.3$ eu.

discussed at some length,[4c] but no clear evidence of such an effect was apparent. Solvent participation in **4** has been suggested as a possible factor which increases k_{endo} and thereby decreases the exo/endo rate ratio.[4a]

The α-keto triflates **5** give values of k_{exo}/k_{endo} of (3.4–9.5) × 10^4 in TFE, HFIP, and HCO_2H,[2a,b] whereas **6** gave values of 141 (Ar = 4-$CH_3C_6H_4$) and 126 (Ar = Ph),[2b] **7** gave 345,[2c] and **8** gave 3400.[2d] The greater rate ratio in **5** was argued[2b] to indicate that

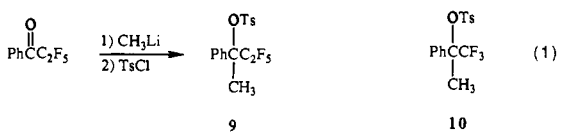


exo-**5** was accelerated relative to the endo isomer by σ-participation of the 1,6-bond and that this participation was enhanced by the electron-withdrawing carbonyl group. The reduced effect in **6–8** evidently results from lower electron demand in these tertiary substrates.

The importance of ground-state destabilization in affecting solvolytic reactivity has recently been recognized[3a–c] but has not been tested utilizing substituents that are strongly destabilizing but are not π-donors. The expectation of a significant effect of a 2-perfluoroalkyl group on carbocation stability in tertiary norbornyl derivatives has been pointed out,[4c] but suitable substrates have not been available. The destabilizing effect of perfluoroalkyl groups on carbocation formation is well-established,[1] and the effect of the 1- and 2-pentafluoroethyl (C_2F_5) substituent on the solvolysis of 2-norbornyl 4-bromobenzenesulfonates is now reported.

Results

To determine the effect of the C_2F_5 substituent on carbocation formation,[9a] the tosylate **9** was prepared as shown in eq 1, and



(1)

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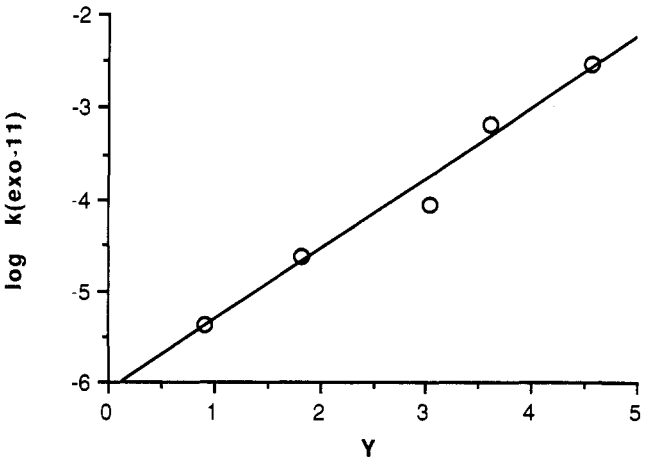

Figure 1. Correlation of log k (*exo*-**11**) versus Y_{OTs}.

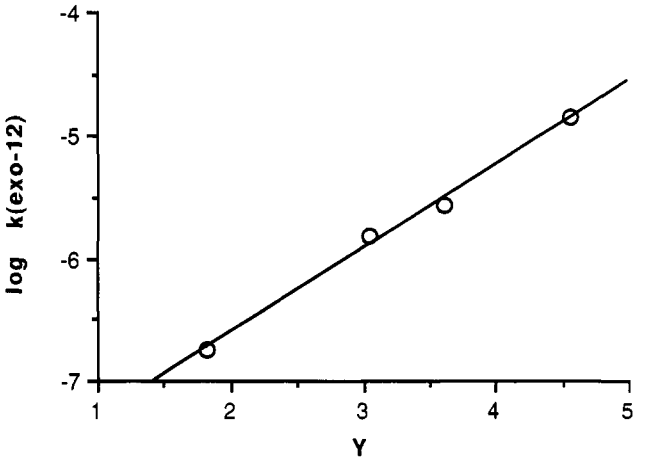

Figure 2. Correlation of log k (*exo*-**12**) versus Y_{OTs}.

its reactivity relative to the corresponding CF_3 compound **10**[9b] was measured in seven different solvents as reported in Table I. This gave a correlation of log $k(C_2F_5)$ = 1.08 (±0.03) log $k(CF_3)$ + 0.796, r = 0.998, and an average value of $k_{C_2F_5}/k_{CF_3}$ = 3.4. Studies of the large salt effects observed in trifluoroacetolysis of **9** and **10** are reported elsewhere.[9c]

The syntheses of the substrates *exo*- and *endo*-**11** and *exo*- and *endo*-**12** as well as authentic materials for the product studies were carried out as shown in Scheme I. The products of the substrates under solvolytic conditions were determined as listed in Table II.

Solvolytic rate constants for **11** and **12** as a function of solvent were measured by monitoring the change in the absorption by UV spectroscopy as we have done previously,[11] and the results are presented in Table III. The dependences of the rates on the solvent ionizing power parameter Y_{OTs}, expressed as the slope m, are *exo*-**11**, 0.78 (Figure 1), *endo*-**11**, 0.60 (two points), and *exo*-**12**, 0.69 (Figure 2). These values are similar to those reported for the parent norbornyl tosylates (exo, 0.81; endo, 0.69)[12b] and provide evidence that the reactions occur through carbocationic transition states.

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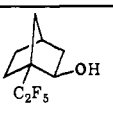
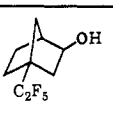
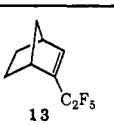
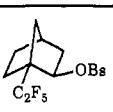
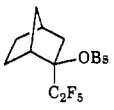
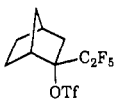
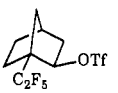
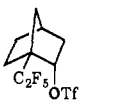
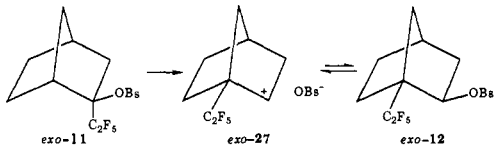
Table II. Products from Solvolyses

substrate	conditions	 19	 18	 26	 24	 13	 exo-12
 *exo*-**11**	H_2O, acetone, 1 h, 70 °C	3.4[c]	6.8	5.9		16.6	67.3
endo-**11**	TFA-d_1, 75 °C, 1 h	37[a,b]	63[a]				
 **17**	H_2O, acetone,[c] 2 h, 80 °C	28.7	56.4	7.5	0.8	6.6	
	TFA, CF_3CO_2K,[d] 1 h, 0 °C	42.2	53.5	1.6	2.7		
 *exo*-**25**-OTf	H_2O, acetone,[c] 15 min, 60 °C	16.5[e]	70.8	10.0	1.6		
	TFA, CF_3CO_2K,[d] 15 min, rt[g]	32.9[f]	55.2	4.8	6.6		
 *endo*-**25**-OTf	H_2O, acetone,[c] 1 h, 80 °C	43.8[e]	40.9	14.1	1.1		
	TFA, CF_3CO_2K,[d] 1 h, rt[g]	32.5	62.9	1.4	3.2		

[a] By ^{1}H-NMR. [b] **19**-OTFA. [c] Containing 2,6-lutidine. [d] Trifluoroacetate products converted to alcohols for GC analysis. [e] *endo*-OH:1.1. [f] Trace *endo*-OH. [g] Room temperature.

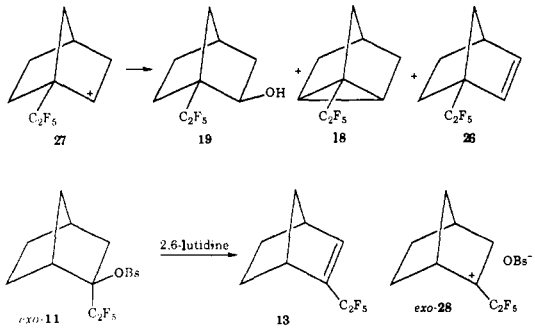
Discussion

Solvolysis of *exo*-**11** occurs with extensive formation of the rearranged isomer *exo*-**12**, and this evidently occurs by ionization with participation to the rearranged ion pair **27** which undergoes



extensive ion pair return to *exo*-**12**. The formation of *exo*-**12** is demonstrated by product isolation (Table II). In the solvolysis of *exo*-**11**, the slower reaction of *exo*-**12** is observed after the reaction of *exo*-**11** is complete.

Reaction of *exo*-**11** in aqueous acetone gave 67.3% of the rearranged brosylate *exo*-**12** and also the products **13**, **18**, **19**, and **26** (Table II). The formation of **18**, **19**, and **26** is readily understood from substitution or elimination of the rearranged carbocation **27**, but the unrearranged alkene **13** is evidently formed by reaction of the 2,6-lutidine present with *exo*-**11**. The unrearranged ion pair corresponding to **28** would rearrange with essentially no barrier to **27** and is not expected to be an energy minimum, and thus **28** cannot be a precursor to the unrearranged alkene **13**.



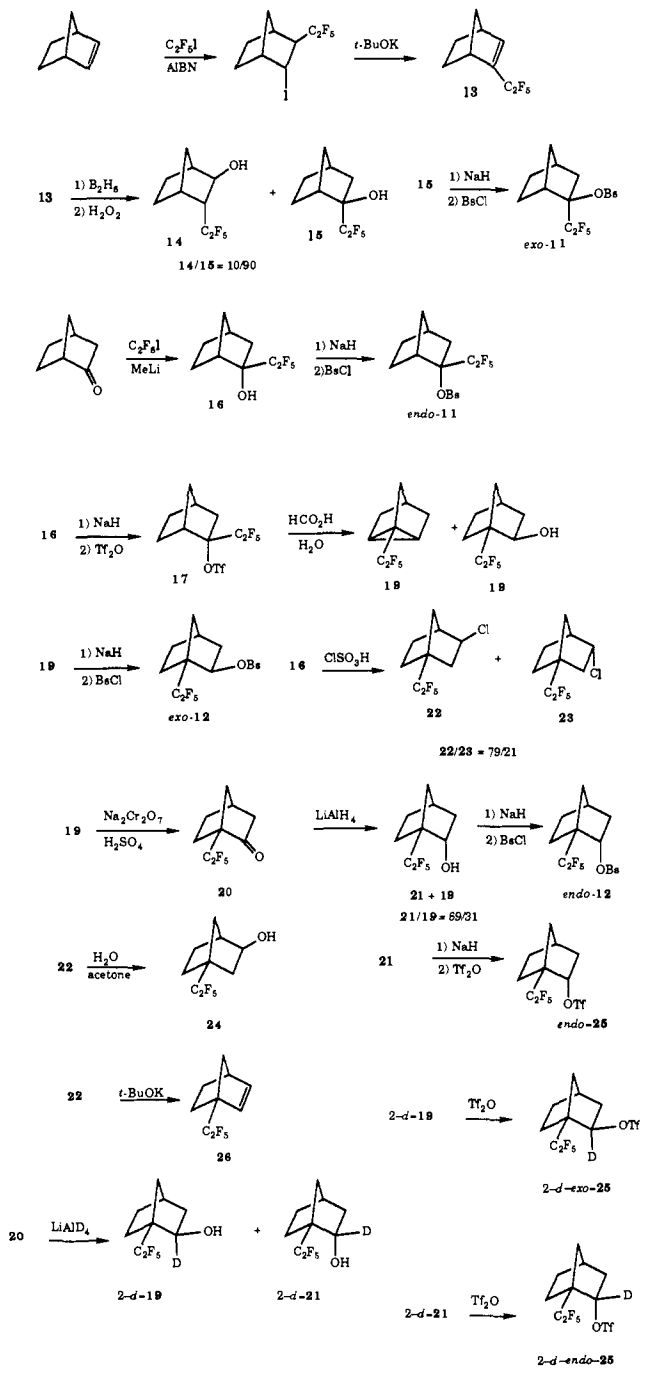
The solvolysis rate of *endo*-**11** is less than that of *exo*-**11** by factors of 824, 1240, and 1040 in TFA (0.20 M NaO_2CCF_3), TFA, and HFIP, respectively. These exo/endo rate ratios are not larger but smaller than the largest value, 1750, reported for the parent norbornyl system.[6a] It had been anticipated[4c] that strong inductive electron withdrawal at C_2 would increase the electron demand at this position and result in enhanced participation by the C_1C_6 bond in *exo*-**11**, leading to an enhanced exo/endo rate

Table III. Solvolytic Rate Constants for (Pentafluoroethyl)norbornyl Brosylates at 25 °C

substrate	solvent (Y_{OTs})	k_{obs} (s^{-1})[a]	$k(H)/k(C_2F_5)$[o]
exo-**11**[b]	TFA (NaO_2CCF_3)	3.04×10^{-3}	4.6×10^2
	TFA (4.57)	3.05×10^{-3}	
	97 HFIP (3.61)	6.79×10^{-4}	5.8×10^2
	HCO_2H (3.04)	8.62×10^{-5}	1.77×10^3
	97 TFE (1.83)	2.40×10^{-5}	5.9×10^2
	60 EtOH (0.92)[c,d]	4.29×10^{-6}	1.93×10^3
endo-**11**[e]	TFA (NaO_2CCF_3)[c,f]	3.69×10^{-6}	3.4×10^2
	TFA[c,g]	2.46×10^{-6}	
	97 HFIP[c,h]	6.53×10^{-7}	3.4×10^2
exo-**12**[i]	TFA (NaO_2CCF_3)	2.46×10^{-5}	5.7×10^4
	TFA[j]	1.48×10^{-5}	
	HFIP[c,k]	2.73×10^{-6}	1.43×10^5
	HCO_2H[c,l]	1.53×10^{-6}	1.00×10^5
	97 TFE[c,m]	1.78×10^{-7}	8.0×10^4
endo-**12**	TFA[c,n]	5.83×10^{-8}	2.14×10^4

[a] Rates measured by monitoring the decrease in UV absorption at 262 nm for RCO_2H solvents and at 242 nm for others with at least duplicate runs at each temperature. [b] log k_{obs} = 0.78 (±0.07) Y_{OTs} − 6.11 (±0.21), r = 0.988. [c] Extrapolated from data at other temperatures; measured rates (×10^5), t (°C). [d] 101 (70.5), 24.0 (56.6), 3.42 (41.2); $\Delta H^{\ddagger}$ = 24.2 kcal/mol, $\Delta S^{\ddagger}$ = −2.1 eu. [e] log k_{obs} = 0.60 Y_{OTs} − 8.35. [f] 76.5 (74.3), 28.8 (63.5), 5.26 (48.0); $\Delta H^{\ddagger}$ = 21.9 kcal/mol, $\Delta S^{\ddagger}$ = −10.0 eu. [g] 35.3 (74.6), 14.0 (63.1), 2.27 (45.6); $\Delta H^{\ddagger}$ = 20.4 kcal/mol, $\Delta S^{\ddagger}$ = −15.9 eu. [h] 5.27 (74.8), 2.58 (63.1), 0.769 (51.6); $\Delta H^{\ddagger}$ = 18.1 kcal/mol, $\Delta S^{\ddagger}$ = −26.3. [i] log k_{obs} = 0.69 (±0.04) Y_{OTs} − 7.99 (±0.12), r = 0.997. [j] 461 (extrapolated, 81.8), 55.4 (58.9), 14.2 (44.4); $\Delta H^{\ddagger}$ = 20.5 kcal/mol, $\Delta S^{\ddagger}$ = −11.8 eu. [k] 9.46 (58.9), 4.06 (50.6), 0.795 (34.7); $\Delta H^{\ddagger}$ = 20.1 kcal/mol, $\Delta S^{\ddagger}$ = −16.5 eu. [l] 78.0 (74.6), 15.7 (60.6), 2.79 (46.4); $\Delta H^{\ddagger}$ = 25.4 kcal/mol, $\Delta S^{\ddagger}$ = 0.1 eu. [m] 22.7 (90.1), 6.85 (75.1), 1.19 (60.4); $\Delta H^{\ddagger}$ = 23.4 kcal, $\Delta S^{\ddagger}$ = −10.9. [n] 45.6 (96.5), 11.0 (81.8), 1.58 (66.4); $\Delta H^{\ddagger}$ = 27.1 kcal/mol, $\Delta S^{\ddagger}$ = −0.8 eu. [o] Rates for **1**-OBs from ref 12b, using the conversion factor $k_{OBs} = k_{OTs} \times 3$, and ref 6k (HFIP).

Scheme I



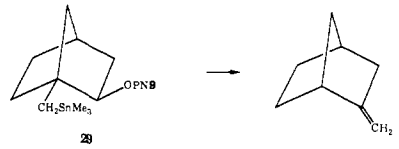
ratio. However, the decelerating effect of the C_2F_5 substituent is almost equally strong on both the exo and endo isomers.

A plausible explanation for the absence of the anticipated electron-demand induced enhancement of the exo/endo rate ratio in **11** is that the ability of the 1,6-bond to enhance the exo reactivity is near its maximum in the parent 2-norbornyl system, and the increase in the electron demand by the C_2F_5 group is not sufficient to further enhance the electron supply. It is known that such carbocation-forming reactions have late transition states,[10] as demonstrated by the correlation with slope 0.89 of solvolytic reactivity with the thermodynamic heats of ionization, and evidently the participation of the 1,6-bond is almost fully developed in the unsubstituted system.

The only case in which there is good evidence for an enhanced exo/endo rate ratio due to increased electron demand at C_2 is the secondary 3-keto system **5**,[2b] which gives k_{exo}/k_{endo} of (3.4–9.5) $\times 10^4$. In contrast to **11** this substrate has no electron-donating CH_2 group adjacent to the leaving group, and conversions based on 2-AdOTf/2-AdOTs rate ratios for different solvents[12f,g] give rate ratios of $k_{CH_2}/k_{C=O}$ or $k(\mathbf{1})/k(exo\text{-}\mathbf{5}\text{-OTs})$ from 7×10^5 (HOAc) to 1.9×10^8 (HFIP) and $k(endo\text{-}\mathbf{1})/k(endo\text{-}\mathbf{5}\text{-OTs})$ from 5.0×10^8 (HCO_2H) to 7.0×10^8 (TFE). Thus the electron demand in the α-keto substrate **5** is significantly greater than in the C_2F_5-substituted *exo*-**11**, and this increased demand is manifested in an enhanced exo/endo rate ratio. As discussed below, the keto tosylates **5** are less reactive than the corresponding C_2F_5-substituted tosylates by factors of from 5.0×10^3 (HCO_2H) to 3.2×10^5 (HFIP) for the exo isomers, and by 1.7×10^6 (HFIP) for the endo isomers. Thus the electron demand in **5** is so extreme as to induce extra σ-donation and fragmentation despite any π-donation by the carbonyl oxygen.[1a,2]

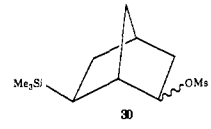
There appears to be general agreement[4a] that participation with rearrangement as is proposed in *exo*-**11** is to be expected in systems in which there is a strong driving force for rearrangement to a more stable carbocation upon ionization. It has been possible to achieve accelerations of *exo*-2-norbornyl solvolyses by various electron-donating 1-substituents (Me, 51.2; Et, 77.8; 1-c-C_6H_{11}, 150; 1-Ph, 3.91; 1-*p*-Anis, 7.7; 1-MeO, 1.28).[4a] These factors and the ρ_1 value for the 1-position of Grob[4b] show that electron donors at this position can modestly enhance participation, although a steric factor is also apparent.

These accelerations by 1-substituents also give some increase in the exo/endo rate ratio in norbornyl derivatives by enhancing the donor ability of the C_1–C_6-bond. Thus for 1-methyl-2-norbornyl tosylate the ratio is 4090 (in 80% EtOH)[6d] or 1.4×10^4 (in HOAc),[6g] while a 1-MeO group gives a ratio of 6200.[6f] The solvolysis rate of the tin-substituted derivatives **29** is accelerated



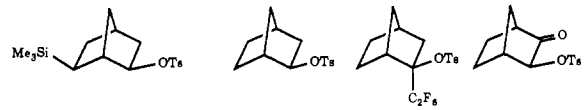
by 6×10^5,[6h] but the endo compound was not studied, and the exo/endo rate ratio was estimated to be 10^9 or 10^7.[6i] This reaction proceeds exclusively with rearrangement and loss of tin.

The solvolysis of the *exo*-6-trimethylsilyl-2-norbornyl mesylates **30** gave exo/endo rate ratios of 2.1×10^6 (EtOH) and 5.0×10^6 (80% EtOH) and an acceleration $k(6\text{-}Me_3Si)/k(H)$ of 3.3×10^4



(EtOH) for the *exo*-2-mesylate.[6i] Thus these results provide clear evidence for a significant enhancement of the exo/endo rate ratio by increasing electron supply to the 1,6-bond.

The largest variations in the exo/endo rate ratios of 2-norbornyl solvolyses due to increased electron demand at the 2-position (*pulling*) or increased electron supply in the 1,6-bond (*pushing*) are summarized below. The influence of the 2-C_2F_5 group is



k^{exo}_{rel}	3.3×10^4	1.0	10^{-3}	10^{-7}
exo/endo	2.1×10^6	10^3	10^3	10^5

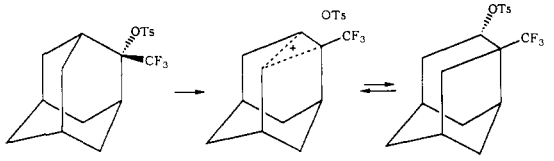
evidently not great enough to cause a significant change in this ratio.

The rate ratio $k(H)/k(C_2F_5)$ for *exo*-**11** ranges from 4.6×10^2 to 1.9×10^3 in different solvents, with no apparent dependence on solvent ionizing power (Table III). For *endo*-**11** this ratio is 3.4×10^2 in both TFA and HFIP. These values are lower than those observed for the system $PhCR(CH_3)OTs$, where $k(H)/k(C_2F_5)$ may be estimated to be between 1.5×10^4 (in TFA) and 1.2×10^6 (in 100% EtOH).[9b] The ratio for the latter substrate

increases with the solvent nucleophilicity, and the larger values may be enhanced because of a nucleophilic component in the rates for $PhCH(OTs)CH_3$.

Thus the $k(H)/k(C_2F_5)$ ratios are attenuated for both the *exo*- and *endo*-2-norbornyl brosylates relative to an acyclic model. Diminution of $k(H)/k(CF_3)$ ratios in some other cases has been attributed to the presence of strong π-donor groups which delocalize the positive charge,[1,11a] but such a donation due to the 1,6-bond is not relevant here as the effect is seen in both the exo and endo brosylates. Steric acceleration of both the rates may contribute to this effect. Thus for 2-*tert*-butyl-2-norbornyl derivatives both the exo and endo rates were accelerated relative to the 2-methyl-2-norbornyl derivatives by similar amounts of 2.1×10^4 and 4.0×10^4, respectively.[8]

It is interesting to compare the effect of 2-C_2F_5 on the 2-norbornyl system to the reported effect of 2-CF_3 on the 2-adamantyl system.[1e] In the case of adamantyl tosylate, $k(H)/k(CF_3)$ averaged 0.5 (four solvents), and this was attributed to a combination of steric acceleration and σ-delocalization to accelerate the rate of the 2-CF_3 derivative.[1e] The reaction of 2-CF_3-2-AdOTs (**31**) was interpreted as proceeding via an ion pair (**32**) which returned to a less reactive rearranged structure (**33**).



31 32 33

The appearance of enhanced participation in the 2-adamantyl system upon substitution of the CF_3 group is plausible because participation is small in the unsubstituted derivative, so this system has the capacity to respond to increased demand by enhanced donation, and thereby the destabilizing effect of the CF_3 group is partially attenuated. Steric effects in the 2-adamantyl system are only a little greater than in 2-norbornyl, as judged by the larger $k(t\text{-Bu})/k(Me)$ ratio in the former, 2.4×10^5.[13b]

Reactivity of 12. Based on previous studies of norbornyl derivatives with strongly electron-withdrawing 1-substituents, *exo*-**12** is not expected to react with any significant participation by the 1,6-bond.[6a,d,i-k] The exo/endo rate ratio for **12** is 42 at 81.8 °C in TFA (Table III), and thus is significantly reduced from the parent system.

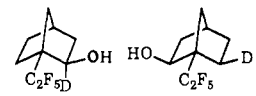
For the 1-substituted *exo*-norbornyl structure the ratio $k(H)/k(C_2F_5)$ averages 9.5×10^4 for four solvents (Table III), whereas for the endo series this ratio is estimated as 2.14×10^4 for TFA. The lower ratio for the endo derivative is predicted from the lower dependence of the endo rates on the σ_1 value of the substituent,[6d] and this leads to the reduced exo/endo rate ratio.

The $k(H)/k(C_2F_5)$ ratios for *exo*-**12** may be compared to the corresponding $k(H)/k(CF_3)$ ratio of 2.5×10^5 reported in 20% EtOH.[6j] The σ_1 values of CF_3 and C_2F_5 are almost identical (0.42 and 0.41, respectively),[1b] and for the substrate $PhC(OTs)(CH_3)R$ the ratio $k(C_2F_5)/k(CF_3)$ averages 3.4 for seven different solvents, so the slightly smaller $k(H)/k(C_2F_5)$ relative to $k(H)/k(CF_3)$ ratio appears normal.

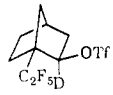
In their study of 1-substituted *exo*-2-norbornyl tosylates in 80% EtOH, Grob et al. reported that the substituents gave two separate correlations.[6d] The 1-H, CO_2Me, and CN derivatives fell on one line, with slope $\rho_I = -1.86$, whereas the substituents Me, CH_2OAc, CH_2Cl, CH_2OTs, $COCH_3$, OAc, and Br gave a separate parallel correlation line with $\rho_I = -1.90$. The 1-CN derivative was less reactive by a factor of 17 than predicted by the latter correlation of $k_H/k_{CN} = 4.5 \times 10^5$.[6d]

A rate for 1-C_2F_5-2-*exo*-norbornyl tosylate in 80% EtOH at 25 °C may be calculated from the *mY* plot for *exo*-**12** (Table III) and the conversion factor $k_{OBs} = 3k_{OTs}$[12b] $= 3 \times 10^{-9}$ s^{-1}. Extrapolation of the data for 1-cyano-2-*exo*-norbornyl tosylate in 80% EtOH to 25 °C gives a rate of 2.5×10^{-10} s^{-1} for a $k(C_2F_5)/k(CN)$ ratio of 12. The σ_1 values of CN range from 0.51 to 0.63,[14] whereas the value for C_2F_5 is 0.41.[1b] Thus the ρ_1 value predicts a rate ratio $k(C_2F_5)/k(CN)$ of 10^2–10^3, and, while this is somewhat larger than that obtained from the experimental values, the ratios agree rather well if one considers the large extrapolations made.

Table IV. Deuterium Distributions from Solvolysis of 2-*d*-**25**



2-d-19 *exo*-6-d-19

	H_2O, acetone, 30 min, 60 °C	59	41
	TFA, CF_3CO_2K, 45 min, rt[a]	56	44
	H_2O, acetone, 1 h, 60 °C	92	8
	TFA, CF_3CO_2K, 2.5 h, rt[a]	61	39

[a] Room temperature.

It is striking that the 2-C_2F_5-2-norbornyl brosylates are consistently more reactive than the 1-C_2F_5 isomers by an average factor of 150 for the exo compounds (five solvents) and 42 for the endo (in TFA). The origin of the greater reactivity for the compounds with α-C_2F_5 substituents compared to the β-substituted isomers is plausibly assigned to ground-state destabilization of the geminally substituted compounds.[3a-c]

It has also been found that β-CN substituents are more rate-retarding than α-CN groups in solvolyses of 2-substituted bicyclo[2.1.1]hexyl systems by factors of 10^2–10^3.[3a-c] In this case it was also argued that this effect is due to ground-state destabilization of the α-CN reactant and not necessarily due to stabilization of α-CN carbocations.[3a-c] In the case of α-CF_3 compounds it has been concluded[1] that there is no evidence for significant electron donation from CF_3 and so the greater reactivity of the 2-C_2F_5-substituted norbornyl brosylates relative to the 1-C_2F_5 isomers provides strong evidence for the importance of acceleration due to ground-state destabilization when geminal electronegative groups are present.

The products (Table II) obtained for *exo*-**25** in H_2O/acetone show a much higher proportion of tricyclene **18** relative to the alcohol **19** compared to the endo isomer, indicating that hydride loss from C_6 is facile for the initial exo ion pair in this medium. In TFA the **18**/**19** product ratios are more similar, suggesting the ion pairs are longer-lived and equilibrate in this medium. In all cases there is a little more of the hydride-shifted alcohol **24** in TFA, also suggesting a longer-lived ion. The enhanced yield of substitution product **19** relative to the tricyclene **18** from *endo*-**25** in H_2O suggests enhanced nucleophilic displacement from the exo direction occurs either in the covalent substrate or an ion pair in this medium.

Hydride Shifts. 2-Norbornyl cations are known to undergo 6,2- and 3,2-hydride shifts. Under stable ion conditions, the activation barriers of these processes have been estimated by dynamic NMR spectroscopy to be 5.9 and 10.8 kcal/mol, respectively.[15] For solvolytic systems, the ^{14}C data of Roberts and co-workers[16] and the ^3H data of Lee and Lam[17] have been subjected to detailed

(13) (a) Allen, A. D.; Kangasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513–4519. (b) Fry, J. L.; Engler, E. M.; Schleyer, P. v. R. *Ibid.* **1972**, *94*, 4628–4634.

(14) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

(15) (a) Olah, G. A.; White, A. M.; De Member, J. R.; Commeyras, A.; Lui, C. Y. *J. Am. Chem. Soc.* **1970**, *92*, 4627–4640. (b) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M.; Anet, F. A. L. *J. Am. Chem. Soc.* **1982**, *104*, 7105–7108.

(16) (a) Roberts, J. D.; Lee, C. C. *J. Am. Chem. Soc.* **1951**, *73*, 5009–5010. (b) Roberts, J. D.; Lee, C. C.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 4501–4510.

(17) Lee, C. C.; Lam, L. K. M. *J. Am. Chem. Soc.* **1966**, *88*, 2831–2834, 5355–5356.

and sophisticated analysis.[18] Only in the formolysis of 2-norbornyl brosylate does there appear to be definitive evidence for a minor contribution of the 2,3-H shift ($k_s/k_r > 30$ at 25 °C), while 6,2-H shifts, on the other hand, compete efficiently with solvent capture. The k_s/k_r ratio was found to be ca. 1 in formic acid, ca. 2 in acetic acid, and ca. 6 in aqueous acetone.[18,19]

The influence of electron-withdrawing groups on the relative rates of hydride shifts has not received much attention. In the case of **27**, the 3,2-H shift should be exoergic, due to further separation of the positive charge from C_2F_5. Nevertheless, the formation of **24** remains a minor process even in TFA. The degenerate 6,2-H shift in **27** was examined in solvolyses of the deuterated triflates [2-^{2}H]-**25**. With the exo precursor, scrambling of the label in **19** was substantial (Table IV), the k_s/k_r ratios being 0.22 in aqueous acetone and 0.14 in TFA. The data indicate that the C_2F_5 group in **27** accelerates the 6,2-H shift, as compared with the parent 2-norbornyl cation **2**.

The following rationale is offered: the 2-norbornyl cation may be viewed as a corner-protonated cyclopropane, with positive charge on C_1, C_2, and hydrogen. The transition state of the 6,2-H shift is reasonably described as an edge-protonated cyclopropane, with positive charge on C_2, C_6, and hydrogen. Electron-withdrawing groups at C_1 will destabilize **27** more strongly through direct interaction with a positively charged carbon than the transition state of the 6,2-H shift. Therefore we anticipate a smaller barrier for rearrangement in **27** than in **2**.

The solvolysis of 2-*d*-*endo*-**25** in aqueous acetone proceeded with only 16% scrambling of the label, as compared with 82% for the exo isomer (Table IV). These findings point to inverting nucleophilic displacement as a major reaction path of *endo*-**25** in aqueous acetone. The results obtained with 2-*d*-*endo*-**25** in TFA/CF_3CO_2K approach those reported for the exo isomer (Table IV), suggesting that the displacement reaction is minimized in a weakly nucleophilic solvent.

Salt Effects. The lower exo/endo rate ratio in TFA containing 0.2 M NaO_2CCF_3 arises from the fact that the rate of *exo*-**11** is unaffected by the salt, while *endo*-**11** is 1.5 times more reactive with added salt at 25.0 °C and even more at higher temperatures. The absence of a salt effect in *exo*-**11** is consistent with rearrangement in this system which precludes ion-pair return to starting material, which is the process usually affected by salts. However, the mechanism by which added salt accelerates the reaction of *endo*-**11** is not established. Formation of the ion-pair *endo*-**28** which in the absence of salt can return to *endo*-**11** appears very unlikely, as no such return from an ion pair has been detected in the parent *endo*-norbornyl system.[4h] Backside nucleophilic participation by the salt to assist the departure of the leaving group is also unlikely, as nucleophilic participation in such tertiary fluorinated systems has not been documented.[1b] The response of *exo*- and *endo*-**11** to solvent ionizing power is similar and so both would be expected to respond similarly if the effect of the salt is just to increase the ionizing power of the solvent.

Thus the ion-pair *endo*-**28** rearranges to ion **27**, which then forms product. The reactivity of *endo*-**11** is less than that of *exo*-**12** so it cannot be demonstrated whether *endo*-**11** is converted to *exo*-**12** via return. The product distributions from the two substrates show some differences (Table II) and so even though the reactions were done at different temperatures it appears that some of the product from *endo*-**11** forms without return to *exo*-**12**.

The absence of an effect of the addition of NaO_2CCF_3 on the rate of reaction of *exo*-**11** in CF_3CO_2H is consistent with a mechanism for salt acceleration in TFA by reaction with the ion pairs so as to prevent ion–pair return, since if no ion pair **28** is formed from *exo*-**11**, then there is no mechanism available for salt to increase the rate. The role of ion pairs is pervasive in norbornyl cations, and even upon rearrangement ion-pair return is preferred to the original oxygen of the leaving group.[3d]

(18) (a) Berson, J. A.; Bergman, R. G.; Hammons, J. H.; McRowe, A. W. *J. Am. Chem. Soc.* **1967**, *89*, 2581–2589. (b) Collins, C. J.; Lietzke, M. H. *J. Am. Chem. Soc.* **1967**, *89*, 6565–6572.

(19) Murr, B. L.; Conkling, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 3462–3464, 3464–3466.

Conclusions

The chemistry of the 2-norbornyl cation is strongly influenced by the electron-withdrawing C_2F_5 group. The 2-C_2F_5-2-norbornyl cation escapes nucleophilic capture by rapid rearrangement to the 1-C_2F_5-2-norbornyl cation, i.e., α-C_2F_5 is more destabilizing than β-C_2F_5. The relative stabilities of the carbocations are not reflected by the reaction rates of their precursors, with 2-C_2F_5-2-norbornyl brosylates solvolyzing faster than 1-C_2F_5-2-norbornyl brosylates. Destabilization of the 2-C_2F_5-2-norbornyl sulfonates by the synergistic effect of geminal electron-withdrawing groups appears to be a major rate-determining factor. Judging from exo/endo rate ratios, the σ participation in *endo*-2-C_2F_5-*exo*-2-norbornyl brosylate solvolyses is not enhanced over that in the parent 2-norbornyl system. Several lines of evidence point to solvent participation (k_s) in the solvolyses of 1-C_2F_5-*endo*-2-norbornyl sulfonates. The ratio of 6,2-hydride shift to solvent capture for the 1-C_2F_5-2-norbornyl cations exceeds that for the 2-norbornyl cation by an order of magnitude. The data suggest that the relative stabilities of edge- and corner-protonated nortricyclenes are reversed by C_2F_5 substitution.

Experimental Section

General Procedures. All reactions were carried out with dry glassware under dry N_2 or Ar. Many of the (pentafluoroethyl)norbornyl derivatives were quite volatile, and so reaction products to be used in subsequent preparative reactions were frequently obtained as concentrated solutions in ether after workup and used directly in the next step. All new liquid products were obtained in at least 99% purity except as noted as evidenced by analytical GC. ^{1}H NMR signals are often assigned as s (syn), a (anti), x (exo), or n (endo).

2-(Pentafluoroethyl)-2-norbornene (13). Norbornene (18.8 g, 0.2 mol) and AIBN (0.400 g, 2.44 mmol) were cooled to −10 °C in an autoclave, and C_2F_5I (51.2 g, 0.20 mol) condensed at −78 °C was added. The sealed autoclave was heated with shaking for 3 h at 80 °C and 1 h at 90 °C, and after cooling to −20 °C more AIBN (0.150 g, 0.91 mmol) was added followed by heating with shaking 3 h more at 80 °C. After being cooled to room temperature the product was distilled to give *endo*-2-iodo-*exo*-3-(pentafluoroethyl)norbornane (57 g, 84%, 98.7% pure by GC) which was purified to >99% purity by GC: bp (15 Torr) 90–92 °C; ^{19}F NMR ($CDCl_3$) δ −83.9 (3, s), −122.0 and −122.2 (2, d, $J_{F,H\text{-}3n}$ = 16.6 Hz); ^{1}H NMR ($CDCl_3$) 1.30 (1, d, J = 10 Hz, H-7a), 1.34 (1, m, H-5n), 1.63 (1, tt, J = 12, 4.5 Hz, H-5x), 1.65–1.74 (2, m, H-7s,6x), 1.90 (1, m, H-6n), 2.27 (1, td, J = 16.5, 6 Hz, H-3n), 2.42 (1, br s, H-4), 2.49 (1, br s, H-1), 4.27 (1, ddd, J = 6, 3, 2 Hz, H-2x). Anal. C, H.

The above iodide (1 g, 2.94 mmol) and *t*-BuOK (1 g, 8.9 mmol) were heated up to 400 °C under vacuum in a flask with a short-path distillation head and receiver cooled in liquid N_2. After cooling, the apparatus was washed with pentane, which was then extracted with H_2O, and dried over $MgSO_4$. The pentane was distilled, and the product **13** (0.55 g, 88%) was collected by preparative GC: ^{19}F NMR ($CDCl_3$) δ −85.0 (3, t, J = 3 Hz), −114.8 and −115.0 (2, inner lines of AB system); ^{1}H NMR ($CDCl_3$) δ 1.03–1.20 (2, m, H-5n,6n), 1.23 (1, br d, J = 8.5 Hz, H-7a), 1.56 (1, dquintet, 1, J = 8.5, 2 Hz, H-7s), 1.69–1.80 (2, m, H-5x,6x), 3.01 (1, br d, J = 1.5 Hz, H-4), 3.13 (1, br s, H-1), 6.55 (1, q, J = 3 Hz, H-3); IR (film) 1621 cm^{-1} (C=C). Anal. C, H.

***endo*-2-(Pentafluoroethyl)-*exo*-2-norbornanol (15).** The crude alkene **13** in 20 mL of ether obtained from *endo*-2-iodo-*exo*-3-(pentafluoroethyl)norbornane (10 g, 29.4 mmol, reacted in 1-g portions) was added to diborane at 0 °C, generated from $NaBH_4$ (2.27 g, 60 mmol) and BF_3 etherate (10 mL, 80 mmol) in 45 mL of diglyme at 0 °C and collected in 200 mL of ether. The solution was warmed to 25 °C, stirred overnight, and then cooled to 0 °C. Water was added followed by 45 mL of 3 N NaOH and 30 mL of 37% H_2O_2. The solution was stirred for 4 h at room temperature, the layers were separated, and NaCl was added to the aqueous phase which was extracted twice with ether. The combined ether layers were washed with ferrous sulfate solution and with H_2O and dried over magnesium sulfate. The solvent was distilled and the product purified by low-pressure liquid chromatography using 7/3 petroleum ether/ethyl acetate to give **15** (3.51 g, 52%) as colorless needles: mp 39 °C; ^{19}F NMR ($CDCl_3$) δ −80.7 (3, s), −114.8/−118.5, −121.3/−125.0 (2, AB, $J_{F,F}$ = 281 Hz); ^{1}H NMR ($CDCl_3$) δ 1.15 (1, m, H-5n), 1.28 (1, dm, $J_{7a,7s}$ = 10 Hz, H-7a), 1.42 (1, m, H-6x), 1.49–1.61 (2, m, H-3x,5x), 1.68 (1, br t, $J_{5n,6s}$ = 11 Hz, H-6n), 1.77 (1, s, OH), 1.85 (1, dt, J = 13.5, 2.5 Hz, H-3n), 1.91 (1, dm, $J_{7a,7s}$ = 10 Hz, H-7s), 2.38 (2, m, H-1,4); IR (CCl_4) 3602, 3550–3350 cm^{-1} (OH). Anal. C, H.

***endo*-3-(Pentafluoroetbyl)-*exo*-2-norbornanol (14)**: colorless liquid; ^{19}F NMR ($CDCl_3$) δ −85.8 (3, s), −113.2/−113.5; −116.8/−117.1 (2, AB

system, $J_{F,F}$ = 275 Hz; $J_{F,H-3}$ = 21, 17 Hz); ^{1}H NMR ($CDCl_3$) δ 1.13 (1, m, H-6n), 1.43 (1, dquintet, J = 10, 1.5 Hz, H-7a), 1.45 (1, m, H-5n), 1.52–1.63 (2, m, H-5x,6x), 1.76 (1, d, J = 4 Hz, OH), 1.78 (1, dquintet, J = 10, 2 Hz, H-7s), 2.20–2.33 (2, m, H-3,4), 2.54 (1, br s, H-1), 3.90 (1, br s, H-2); IR (CCl_4) 3627, 3600–3050 cm^{-1} (OH). Anal. C, H.

***endo*-2-(Pentafluoroethyl)-2-*exo*-norbornyl Brosylate (*exo*-11).** Using the published procedure,[9b] reaction of **15** (690 mg, 0.3 mmol) with NaH (700 mg, 55%, 16 mmol) was followed by addition of brosyl chloride (920 mg, 3.6 mmol) in ether. After being stirred for 16 h, the solution was shaken 3 h with 20 mL of 2 N NaOH, washed with H_2O, dried over $MgSO_4$, evaporated, and separated by HPLC (silica, 6/4 petroleum ether/ether) to give **15** (600 mg, 45%) as white crystals: mp 90–91 °C; ^{19}F NMR ($CDCl_3$) δ −80.8 (3, s), −110.8/−114.5; −118.7/−122.4 (2, AB system, $J_{F,F}$ = 283 Hz); ^{1}H NMR ($CDCl_3$) δ 1.17 (1, dddd, J = 12, 10, 5, 2.5 Hz, H-5n), 1.40 (1, dm, $J_{7a,7s}$ = 10.5, H-7a), 1.46–1.64 (2, m, H-5x,6x), 1.69 (1, br t, J = 11 Hz, H-6n), 1.97 (1, dt, J = 15, 2, H-3n), 2.02 (1, dm, J = 10.5 Hz, H-7s), 2.49 (1, br s, H-4), 2.52 (1, br d, J = 15, H-3x), 3.02 (1, br d, J = 3 Hz, H-1), 7.66 and 7.74 (4, each dm, J = 8.5, Ar). Anal. C, H.

***exo*-2-(Pentafluoroethyl)-*endo*-2-norbornanol (16).** Following the general procedure of Gassman and O'Reilly,[20a] reaction of norcamphor (10 g, 91 mmol) with 26.6 g (108 mmol) of C_2F_5I and 85 mL of 1.3 M MeLi/LiBr solution in ether (111 mmol) at −78 °C was followed by extraction with H_2O, drying over $MgSO_4$, and distillation (13 Torr, 72–74 °C) to give **16** (18.9 g, 90%) as colorless needles: mp 30–32 °C; ^{19}F NMR ($CDCl_3$) δ −79.0 (3, s), −122.1/−122.2 (2, AB); ^{1}H NMR ($CDCl_3$) δ 0.87 (1, dm, J = 13 Hz, H-3n), 0.92–1.02 (2, m, H-7a,6x), 1.06 (1, ddd, J = 11, 5.5, 2 Hz, H-5n), 1.24 (1, s, OH), 1.27 (1, m, H-5x), 1.52 (1, dm, J = 10.5, H-7s), 1.62 (1, m, H-6n), 1.83 (1, m, H-4), 1.86 (1, br d, J = 13 Hz, H-3x), 2.36 (1, br s, H-1); IR (CCl_4) 3580, 3540–3300 cm^{-1} (OH).

***exo*-2-(Pentafluoroethyl)-*endo*-2-norbornyl Brosylate (*endo*-11).** Reaction of **16** (500 mg, 2.2 mmol) with NaH (300 mg, 55%, 6.9 mmol) was followed by addition of brosyl chloride (720 mg, 2.8 mmol) in ether. Workup and isolation as for *exo*-**11** gave *endo*-**11** (230 mg, 24%) as white crystals: mp 56–57 °C; ^{19}F NMR ($CDCl_3$) δ −79.2 (3, s), −115.0/−118.8, −119.3/−123.1 (2, AB system, $J_{F,F}$ = 282 Hz); ^{1}H NMR ($CDCl_3$) δ 1.35 (1, dm, J = 10.5 Hz, H-7a), 1.50 (1, m, H-5n), 1.54–1.62 (2, m, H-5x,6x), 1.69 (1, br d, J = 10.5 Hz, H-7s), 1.89 (1, m, H-6n), 2.20 (1, br d, J = 15.5 Hz, H-3n), 2.42 (br s, 1, H-4), 2.63 (1, ddd, J = 15.5, 3.5, 2.0 Hz, H-3x), 2.78 (1, br s, H-1), 7.68 and 7.77 (4, 2 dm, J = 9 Hz, Ar). Anal. C, H.

***exo*-2-(Pentafluoroethyl)-*endo*-2-norbornyl Triflate (17).** Reaction of **16** (10 g, 43 mmol) with NaH (4.5 g, 55%, 103 mmol) was followed by addition of triflic anhydride[20b] (10.5 mL, 17.8 g, 63 mmol) in ether. Workup and isolation as for *exo*-**11** gave **17** (14.6 g, crude product), which was purified by HPLC: ^{19}F NMR −76.4 (3, s, CF_3SO_2), −79.4 (3, s), −114.2/−118.0, −118.6/−122.4 (2, AB, $J_{F,F}$ = 287 Hz); ^{1}H NMR ($CDCl_3$) δ 1.20–2.20 (6, m), 2.35 (2, br s, H-3n,x), 2.50 (1, br s, H-4), 2.95 (1, br s, H-1). A solution of crude **17** (4.44, ca. 12 mmol) and NaO_2CH (4.17 g, 61 mmol) in 48 mL of HCO_2H was stirred 2 h at 25 °C and diluted with 100 mL of H_2O, and 50 mL of pentane was added. With cooling, the HCO_2H was neutralized with NaOH, and the solution was extracted four times with pentane. The combined organic layers were washed with $NaHCO_3$ and H_2O and dried with $MgSO_4$, and the pentane was distilled. Dry ether (20 mL) was added followed by $LiAlH_4$ (500 mg, 13 mmol) in 100 mL of ether, and the solution was refluxed 4 h. After aqueous workup, separation by LPLC gave **19**, **16**, and a fraction containing **13**, **18**, and **26** from which **18** was separated by PGC.

1-(Pentafluoroethyl)-*exo*-2-norbornanol (19): ^{19}F NMR ($CDCl_3$) δ −82.4 (3, s); −113.4/−113.5 (2, AB); ^{1}H NMR ($CDCl_3$) δ 1.16 (1, m, H-5n), 1.24 (1, m, H-6n), 1.51 (1, dq, J = 10, 2 Hz, H-7a), 1.53 (1, dd, J = 13, 5, 2.5 Hz, H-3x), 1.60 (1, m, H-5x), 1.69 (1, br s, OH), 1.79 (1, td, J = 13, 3 Hz, H-6x), 1.83 (1, ddt, J = 13, 7, 2 Hz, H-3n), 1.92 (1, dq, J = 10, 2 Hz, H-7s) 2.34 (1, br t, J = 4 Hz, H-4), 4.00 (1, br d, J = 7 Hz, H-2n); IR (film) 3625, 3600–3100 cm^{-1} (OH). **1-(Pentafluoroethyl)nortricyclene (18):** ^{19}F NMR ($CDCl_3$) δ −84.3 (3, s), −114.0 (2, s); ^{1}H NMR ($CDCl_3$) δ 1.33 (2, dd, J = 11, 1.5 Hz, H-3, 5x), 1.41 (2, d, J = 11 Hz, H-3, 5n), 1.46 (2, s, H-7), 1.64 (2, s, H-2, 6), 2.14 (1, m, H-4); ^{13}C NMR ($CDCl_3$) + DEPT δ 15.8 (C-2, 6), 23.4 (C-1), 31.2 (C-4), 32.9 (C-3, 5), 33.1 (C-7), 116.1 (tq, $J_{C,F}$ = 248.0, 34.5 Hz, CF_2), 119.5 (qt, J = 286.0, 39.6 Hz, CF_3). Anal. C, H.

1-(Pentafluoroethyl)-*exo*-2-norbornyl Brosylate (*exo*-12). Reaction of **19** (500 mg, 2.2 mmol) with NaH (500 mg, 55%, 11.5 mmol) was followed by addition of brosyl chloride (320 mg, 1.3 mmol) in ether. Workup and isolation as for *exo*-**11** gave *exo*-**12** (350 mg, 36%) as white crystals: mp 98–99 °C; ^{19}F NMR ($CDCl_3$) δ −81.8 (3, s), −113.7/−113.9 (2, AB); ^{1}H NMR ($CDCl_3$) δ 1.19–1.32 (2, m, H-5n,6n), 1.60 (1, br d, J = 10 Hz, H-7a), 1.64 (1, m, H-5x), 1.84–1.98 (4, m, H-3, 6x,7s), 2.41 (1, br s, H-4), 4.77 (1, t, J = 4.5 Hz, H-2), 7.68 and 7.73 (4, 2 dm, J = 9 Hz, Ar). Anal. C, H.

1-(Pentafluoroethyl)-2-norbornanone (20). Reaction of **19** (ca. 3.8 g in ether) with 17 mL of $Na_2Cr_2O_7$ in H_2SO_4 for 12 h was followed by dilution with H_2O, extraction with ether, and partial concentration by distillation to give crude **20**: ^{19}F NMR ($CDCl_3$) δ −82.0 (3, s), −117.87/−117.92 (2, AB); ^{1}H NMR ($CDCl_3$) δ 1.58 (1, dddd, J = 13, 9, 4.5, 2.5 Hz, H-6n), 1.77 (1, dddd, J = 13, 9, 4.5, 2.0 Hz, H-5n), 1.89 (1, ddd, J = 11, 4, 2.5 Hz, H-7a), 1.92–2.02 (2, m, H-5x,7s), 2.07 (1, dd, J = 18, 4 Hz, H-3n), 2.09 (1, td, J = 12.5, 4.5 Hz, H-6x), 2.28 (1, ddd, J = 18, 5, 4 Hz, H-3x), 2.73 (1, br s, H-4); IR (film) 1750 cm^{-1} (C=O).

1-(Pentafluoroethyl)-*endo*-2-norbornanol (21). A solution of **20** (1.7 g) in ether was reduced by $LiAlH_4$ (280 mg, 7.4 mmol), and after extraction with ether and washing with H_2O the ether extracts were dried with $MgSO_4$ to give a product found by GC analysis to contain a 30.6/69.4 ratio of **19**/**21**, from which **21** was isolated by preparative GC: ^{19}F NMR (C_6D_6) δ −81.2 (3, s), −116.4 (2, s); ^{1}H NMR (C_6D_6) δ 0.78 (1, dt, J = 13, 3 Hz, H-3n), 1.03 (1, d, J = 4.5 Hz, OH), 1.19 (1, ddd, J = 12, 9, 4.5 Hz, H-5n), 1.24–1.34 (3, m, H-5x,7s,a), 1.51 (1, tdd, J = 12, 4.5, 2 Hz, H-6x), 1.59 (1, dddd, J = 13, 10, 4.5, 3 Hz, H-3x), 1.70 (1, br t, J = 4.5 Hz, H-4), 2.23 (1, dddm, J = 12, 9, 4.5 Hz, H-6n), 4.08 (1, ddt, J = 10, 4.5, 2.5 Hz, H-2); IR (film) 3630, 3600–3100 cm^{-1} (OH). Anal. C, H.

1-(Pentafluoroethyl)-*endo*-2-norbornyl Triflate (25). Reaction of a solution of **21** (500 mg) in ether with NaH (400 mg, 55%, 9.2 mmol) and Tf_2O (560 mg, 2 mmol) in ether as for *exo*-**11** with purification by HPLC gave *endo*-**25** as a colorless liquid: ^{19}F NMR ($CDCl_3$) δ −76.4 (3, s, OTf), −82.0 (3, s), −117.5 (2, s); ^{1}H NMR ($CDCl_3$) δ 1.53–1.63 (2, m, H-3n,5n), 1.69 (1, dq, J = 11, 3 Hz, H-7s), 1.77 (1, dd, J = 11, 3 Hz, H-7a), 1.82–1.94 (2, m, H-5x,6x), 2.18 (1, m, H-6n), 2.34 (1, dddd, J = 14, 10, 4.5, 2.5 Hz, H-3x), 2.43 (1, br s, H-4), 5.46 (1, dt, J = 10, 2 Hz, H-2x). Anal. C, H.

1-(Pentafluoroethyl)-*endo*-2-norbornyl Brosylate (*endo*-12). Reaction of a solution of **21** (800 mg) in ether with NaH (600 mg, 55%, 13.8 mmol) and brosyl chloride (980 mg, 3.8 mmol) as for *exo*-**11** and purification by HPLC gave *endo*-**12** as colorless crystals: mp 57–59 °C; ^{19}F NMR ($CDCl_3$) δ −82.1 (3, s), −117.3 (2, s); ^{1}H NMR ($CDCl_3$) δ 1.48 (1, dt, J = 14, 3 Hz, H-3n), 1.53 (1, m, H-5n), 1.59 (1, dq, J = 10, 2 Hz, H-7s), 1.65 (1, d, J = 10 Hz, H-7a), 1.70–1.83 (2, m, H-5x,6x), 2.10–2.20 (2, m, H-3x,6n), 2.33 (1, br s, H-4), 5.07 (1, ddd, J = 10, 3, 2, H-2), 7.68 and 7.75 (4, 2 dm, AB). Anal. C, H.

4-(Pentafluoroethyl)-*exo*-2-norbornyl Chloride (22). A solution of **16** (1 g, 4.3 mmol) in 5 mL of ice–cold $ClSO_3H$ was stirred 15 min and *carefully* added to 80 g of ice. The products from 9 g (39 mmol) **16** thus prepared were combined and extracted with pentane. The extract was washed with NaOH and H_2O and dried over $MgSO_4$. The solvent was evaporated, and the residue was distilled through a short-path column at oil pump vacuum to give a mixture of **22** together with the endo 2-chloride in a 79/21 ratio by GC analysis. Separation by GC gave **22** as a colorless liquid (97.2% purity): ^{19}F NMR ($CDCl_3$) δ −82.2 (3, s), −119.5/−119.6 (2, AB); ^{1}H NMR ($CDCl_3$) δ 1.39–1.42 (2, m), 1.61 (1, dq, J = 10, 2 Hz, H-7a), 1.75–1.88 (2, m), 2.17–2.22 (3, m), 2.52 (1, br d, J = 3 Hz, H-1), 3.99 (1, br d, J = 7 Hz, H-2n). Anal. C, H.

4-(Pentafluoroethyl)-*endo*-2-norbornyl Chloride (23): ^{19}F NMR ($CDCl_3$) δ −82.2 (3 s), −120.8/−121.1 (2, AB); ^{1}H NMR ($CDCl_3$) δ 1.47–1.61 (2, m, H-5n,6n), 1.63–1.72 (2, m, H-7a,3n), 1.77 (1, ddd, J = 10, 3, 1.5 Hz, H-7s), 1.88 (1, tt, J = 12.5, 4 Hz, H-6x), 2.19 (1, m, H-5x), 2.48 (1, ddd, J = 14.5, 11, 3.5 Hz, H-3x), 2.51 (1, t, J = 4.5 Hz, H-1), 4.30 (1, dtd, J = 11, 4.5, 2 Hz, H-2). Anal. C, H.

1-(Pentafluoroethyl)-2-norbornene (26). Reaction of **22** (200 mg, 0.8 mmol) with *t*-BuOK (200 mg, 1.8 mmol) as for the preparation of **13** and purification by GC gave **26** (30 mg, 18%): ^{19}F NMR ($CDCl_3$) δ −82.5 (3, s), −118.6 (2, s); ^{1}H NMR ($CDCl_3$) δ 1.15 (1, ddt, J = 11.5, 9, 3 Hz, H-5n), 1.26 (1, ddt, J = 11.5, 9, 3 Hz, H-6n), 1.40 (1, d, J = 8 Hz, H-7a), 1.62 (1, br d, J = 8 Hz, H-7s), 1.84 (1, ddt, J = 11, 9, 3 Hz, H-5x), 1.99 (1, ddd, J = 11.5, 9.5, 3.5 Hz, H-6x), 2.97 (1, br s, H-4), 5.99 (1, br d, J = 5.5 Hz, H-3), 6.14 (1, dd, J = 5, 2.5 Hz, H-2).

4-(Pentafluoroethyl)-*exo*-2-norbornanol (24). A mixture of **22** and **23** (3.3 g, 13.3 mmol) was refluxed for 36 h in 65 mL of acetone/H_2O containing $AgNO_3$ (4.5 g, 265 mmol). The solution was combined with concentrated NaCl solution and extracted several times with pentane. The organic phase was extracted twice with NaCl and H_2O and dried over $MgSO_4$, and the pentane was distilled. To remove nitrate product the residue in 20 mL of ether was refluxed for 12 h with $LiAlH_4$ (0.7 g, 18.4 mmol) in 100 mL. Following workup as for **21** the mixture of products was purified by LPLC and PGC (1.8-m DC 200 column) to

(20) (a) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481–2490. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126.

yield **24** (1.54 g, 50%) as colorless crystals: mp 46-47 °C; ^{19}F NMR ($CDCl_3$) δ -82.2 (3, s), -119.5 (2, s); ^1H NMR ($CDCl_3$) δ 1.22 (1, m, H-6n), 1.32 (1, m, H-5n), 1.49 (t, ddt, J = 10, 2.5, 1 Hz, H-7a), 1.53 (1, s, OH), 1.63 (1, br d, J = 13 Hz, H-3x), 1.67-1.79 (2, m, H-6x,5x), 1.89 (1, ddm, J = 13, 7 Hz, H-3n), 1.97 (1, dq, J = 10, 2 Hz, H-7s), 2.26 (1, br d, J = 4 Hz, H-4), 3.94 (1, br d, J = 7 Hz, H-2); IR (CCl_4) δ 3622, 3550-3300 cm^{-2} (OH). Anal. C, H.

1-(Pentafluoroethyl)-2-deuterio-2-norbornanols (2-*d*-19 and 2-*d*-21). Reduction of **20** (2.5 g of ether solution) with $LiAlD_4$ (250 mg, 6.6 mmol) as in the preparation of **21** and separation by GC gave 2-*d*-**19** and 2-*d*-**21**, whose ^1H NMR spectra resembled those of **19** and **21** less the signals at δ 4.52 and 3.99, respectively. These were converted to the respective triflates 2-*d*-*exo*-**25** and 2-*d*-*endo*-**25** as for the undeuterated analogs.

Product Studies. Solvolysis of *exo*-**11** (20 mg, 0.045 mmol) in 1 mL of acetone/H_2O (8/2) was conducted in a sealed ampule at 70 °C for 1 h. The ampule was cooled to 0 °C and then opened, and the volatile products were distilled off through a short-path column. The residue was analyzed by HPLC, and the volatile products were analyzed by analytical GC using a 61.5-m tri-2,4-xylyl phosphate column.

For hydrolysis of **17** and *exo*- and *endo*-**25**-OTf 15 mg (0.041 mmol) of the triflate was solvolyzed in 1 mL of acetone/H_2O (8/2) containing 17.5 mg (0.163 mmol) 2,6-lutidine. The product was extracted with ether, and the organic phase was washed with 0.5 mL of 2 N HCl and dilute $NaHCO_3$, dried over $MgSO_4$, and analyzed by GC.

For trifluoroacetolysis of **17** and *exo*- and *endo*-**25**-OTf 15 mg (0.041 mmol) triflate was solvolyzed in 1 mL of CF_3CO_2H containing 28 mg (0.203 mmol) K_2CO_3. The product was cooled to 0 °C, 10 mL of 2 N NaOH was added, and the mixture was stirred for 15 min. The product was extracted with 2 mL of ether which was washed with water, dried over $MgSO_4$, and analyzed by GC.

For preparative hydrolysis of 2-*d*-*exo*-**25**-OTf (220 mg, 0.61 mmol) in 6.1 mL of acetone/H_2O (8/2) containing 2,6-lutidine (260 mg, 2.42 mmol) was kept for 30 min at 60 °C and then cooled and extracted with 10 mL of ether, which was washed with HCl and $NaHCO_3$ solution and H_2O and dried over $MgSO_4$. The ether was distilled, and the product was separated by preparative GC (1.8-m DC 200 column, 120 °C).

For preparative trifluoroacetolysis 2-*d*-*exo*-**25**-OTf (150 mg, 0.41 mmol) in 4.1 mL of CF_3CO_2H containing K_2CO_3 (285 mg, 2.06 mmol) was kept for 45 min at room temperature. Then 40 mL of ice-cold 2 N NaOH was added, and the solution was stirred 30 min and then extracted with 10 mL of ether. The organic phase was washed to neutrality with H_2O and dried over $MgSO_4$, and the ether was distilled. The residue was analyzed by GC. Hydrolysis and trifluoroacetolysis of 2-*d*-*endo*-**25**-OTf were carried out similarly at 80 °C and room temperature, respectively.

1-(Pentafluoroethyl)-1-phenylethyl Tosylate (9). Pentafluoropropiophenone (PCR, Inc.; 2 g, 8.91 mmol) in 2 mL of ether was added to an ice-cooled solution of MeLi (9.8 mmol) in 22 mL of ether, and the solution was stirred 1 h. To the ice-cooled solution was added recrystallized TsCl (1.79 g, 9.4 mmol) in 15 mL of ether, and the solution was stirred overnight at room temperature. Water was added, the solution was extracted three times with ether, and the combined ether layers were washed with $NaHCO_3$ and NaCl, dried over Drierite, and evaporated. Successive purification by radial chromatography, recrystallization from pentane, and further radial chromatography (2.5/97.5 EtOAc/petroleum ether) gave pure **9** (34 mg, 0.086 mmol, 1%) along with larger fractions still containing alcohol: mp 59-60 °C; ^1H NMR ($CDCl_3$) δ 2.30 (3, br s, Me), 2.48 (3, s, CH_3Ar), 7.61 (4, AB, Ar), 7.43 (5, s, Ph); MS m/z (rel intensity) 394 (5, M^+), 275 (56, $M^+ - C_2F_5$), 223 (69, M^+ - OTs), 222 (100, M^+ - TsOH); HRMS m/z 394.0659 (M^+ requires 394.0662).

Kinetic Measurements. Rates in alcoholic solvents were usually measured by injecting 10 μL of 0.01-0.014 M solutions of the brosylate in CH_3CN into 1.2 mL of solvent in a thermostatted quartz cell (1.0-mm pathlength) and observing the decrease in absorbance (0.25-1.0 unit) at 242 nm. For rates in acids, 10 μL of 0.12-0.14 M solutions of brosylate in 1.2 mL of solvent was used, and the decrease in absorbance (0.1 unit) at 262 nm was measured. For reactions of *endo*-**11** at 74.8 °C the reaction solution of 17 μL of 0.014 M brosylate in 2.6 mL of solvent was contained in a pressure tube with a Teflon-brand stopcock in the constant temperature bath. At intervals the tube was removed from the bath and cooled in an ice bath, and the absorption of the solution was measured at 25 °C.

For reaction of *endo*-**12** in TFA 0.0132 g (2.93×10^{-5} mol) of brosylate was dissolved in 15 mL of TFA to give a 2.0×10^{-3} M solution, and 1.2-mL aliquots were placed in ampules which were then sealed. The samples were heated in the constant temperature bath and removed at intervals and cooled, and the absorbance was measured at 267 nm at 25 °C. Two tubes were used for the infinity value, and an absorbance change of 0.3 unit was observed. Rates for *exo*-**12** in TFE at 90.1 °C were measured similarly using 14 mL of 8×10^{-5} M brosylate.

Good first-order rate constants were obtained in each case with either measured infinity values or the Guggenheim method. At least duplicate runs with a maximum deviation of ±9% were obtained in each case.

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Electrostatic Modulation of Hydroxyl Group Ionization in Acidic Media. Evidence for the Competitive Operation of Intramolecular S_N2 Reactions

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Abstract: The acid-catalyzed cyclodehydration of the cis and trans isomers of 2-substituted 1-(3-hydroxypropyl)cyclohexanols results in the formation of spirocyclic tetrahydrofurans. The stereochemical course of these reactions is highly varied, ranging from a dominant preference for retention when R = OCH_3 to modestly favored inversion when R = CH_3. Experiments with ^{18}O-labeled diols show that in the methoxyl series most of the isotope is retained irrespective of relative stereochemistry. On the other hand, the pair of phenyl-substituted isomers responds by losing approximately 50% of the label. The isotopic level in the product erodes further when R = CH_3. The stereochemical and isotopic labeling results are interpreted in terms of competing intramolecular S_N2 and classical S_N1 pathways. The extent to which cooperative nucleophilic attack with loss of the primary hydroxyl is facilitated reaches a maximum in the methoxyl-substituted diols, as a consequence of electrostatic inhibition of tertiary carbocation formation. As this effect is progressively lessened, the percentage of S_N1 response rises. At no time, however, do the stereoisomeric carbocations interconvert conformationally prior to cyclization.

Acid-catalyzed cyclodehydration reactions of diols have seen widespread use in cyclic ether formation,[1-5] yet little is known about structural effects on the stereochemistry of this reaction. Mihailovic and co-workers demonstrated that the cyclization of

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