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About the Timing of Wagner-Meerwein and Nametkin Rearrangements, 6,2-Hydride Shift, Proton Elimination and Cation Trapping in 2-Norbornyl Carbocations

Antonio García Martínez,[a]* Enrique Teso Vilar,[b]* Amelia García Fraile,[b] Antonio Herrera Fernández,[a] Santiago de la Moya Cerero[a] and Florencio Moreno Jiménez[a]

[a]Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria, E-28040 Madrid, Spain. [b]Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey s/n, E-28040 Madrid, Spain.

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Abstract: The reaction of different substituted 2-norbornanones **1** with triflic anhydride in the presence of nitriles **6** is carried out in order to study the factors that influence on the different reaction possibilities of 2-norbornyl carbocations. The syntheses of interesting annulated pyrimidine derivatives **10** and conformationally rigid 1,3 disubstituted products are described.

The reaction of substituted 2-norbornanones **1** with triflic anhydride (Tf_2O) takes place with formation of 2-(trifluoromethanesulfonyloxy)-2-norbornyl cations **2** as intermediates (Scheme 1).[1] Depending on the reaction conditions and the position of the substituents on the norbornane framework, cations **2** can undergo a Wagner-Meerwein rearrangement, leading to the cations **3**, which can suffer a Nametkin rearrangement to the cations **8** through a Nametkin rearrangement, or be trapped by the gegenion to yield *gem*-bistriflates.[1,2] In the presence of a base and at low temperature, the proton elimination in the cations **3** is the main process, affording the homochiral bridgehead triflates **4** and **5**. The triflate **9d** can be obtained from **4d** by TfOH catalysed isomerisation at low temperature.[3] Bridgehead triflates **4** and **9d** are key intermediates in the synthesis of interesting homochiral bridgehead derivatives[4-6] and cyclopentanones.[7]

Reaction of dialkyl ketones with Tf_2O involves an electrophilic attack at the carbonyl group with formation of cations analogous of **2**, yielding vinyl triflates by proton elimination.[8] However, when the reaction is carried out in the presence of aliphatic or aromatic nitriles, the intermediate cations are trapped by the corresponding nitrile affording pyrimidines.[9] This reaction is the basis of very useful methods for the preparation of functionalized pyrimidine derivatives.[10]

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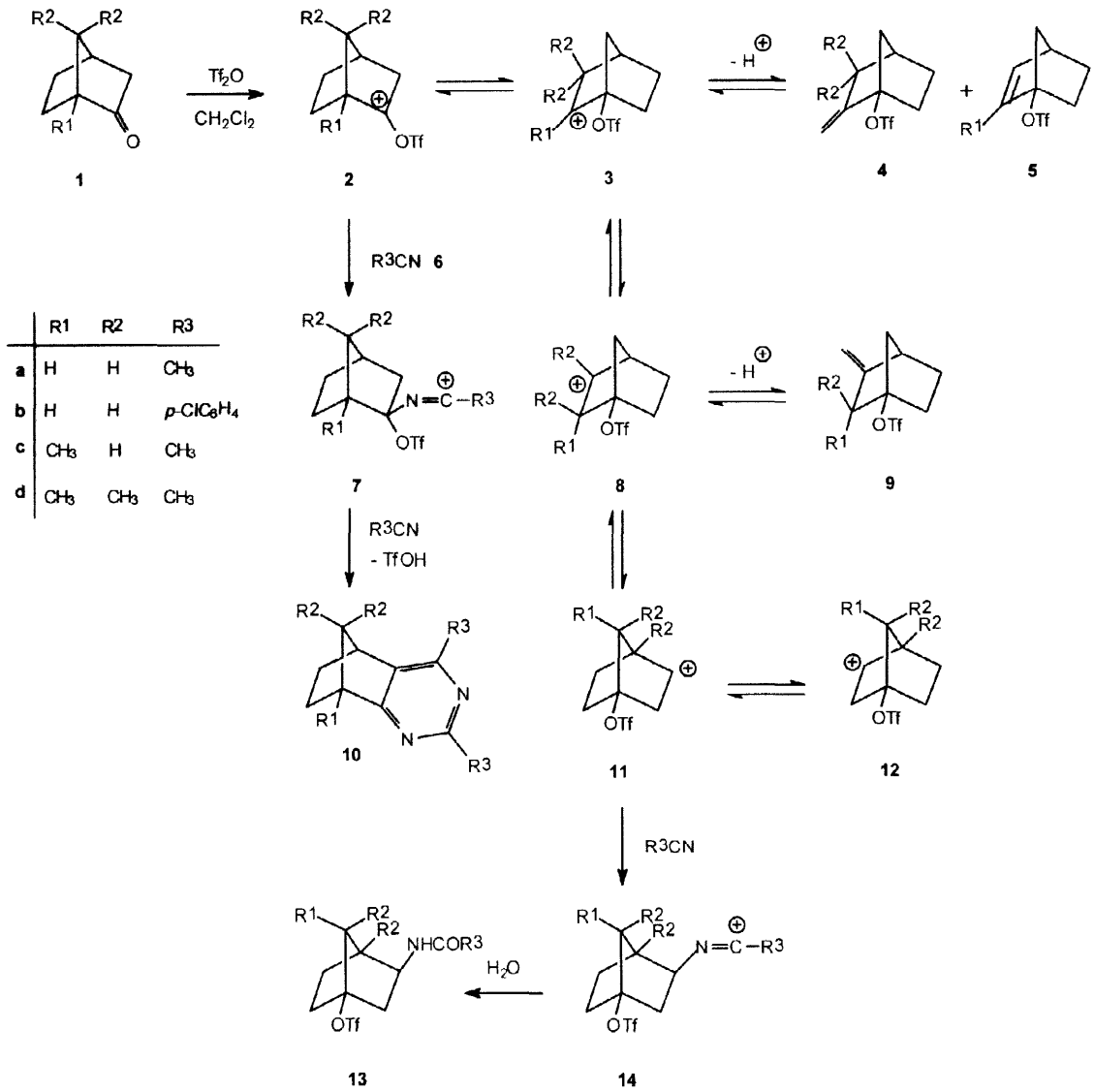
In the present work we will find out an experimental answer to a theoretical question: What is faster, the trapping reaction of carbocations of type **2** by nitriles (a Ritter type reaction)[11] or the characteristic molecular rearrangements of 2-norbornyl cations?.[12] Both reaction possibilities are also interesting due to the synthetic utility of the expected products: annulated pyrimidines[13] or functionalized bridgehead derivatives.[14] As substrates we have selected the 2-norbornanones **1a-d** whose reaction with Tf_2O affords the cations **2a-d**, which exhibit different degrees of bridging (stability)[15] as well as steric hindrance to nucleophilic attack[16] (Scheme 1). The reactions of **1** with Tf_2O in the presence of nitriles **6** were carried out under the our standard conditions used by us for the preparation of pyrimidines (CH_2Cl_2, room temperature, 24 h).[9] The results are showed in Table 1.



Scheme 1: Reaction of 2-Norbornanones **1** with Tf_2O in the presence of the nitrile **6**

The reaction of racemic 2-norbornanone ***rac*-1a** with acetonitrile **6a** or *p*-chlorobenzonitrile **6b** takes

place in the same way that the reaction of the monocyclic ketones cyclopentanone and cyclohexanone[9] yielding pyrimidine derivatives, but the yield in pyrimidines *rac*-**10a-b** is considerably lower (45-50% vs. 80-87%). Thus, after the standard reaction time (24 h) about 50 % of the starting ketone **1** is recovered after work-up. Longer reaction times do not improve the yield in isolated pyrimidine, and complicated mixtures are obtained.

Introduction of a 1-methyl substituent in the norbornane framework should decrease the energy barrier for the Wagner-Meerwein rearrangement due to electronic stabilisation of the corresponding transition state.[12] However, the reaction of racemic 1-methyl-2-norbornanone *rac*-**1c** with Tf_2O and **6a** affords the pyrimidine *rac*-**10c** as the major reaction product, and only low yields in the rearranged products **rac-4c** and **rac-5c**, formed by proton elimination from the cation **rac-3c** are obtained. The highest yield in the pyrimidine **rac-10c** is obtained for a reaction time of 55 h. Therefore, also the trapping of carbocation **2c** takes place faster than the Wagner-Meerwein rearrangement.

Table 1. Results from the reaction of ketones **1** with Tf_2O in the presence of the nitriles **6** (24 h; rt.).

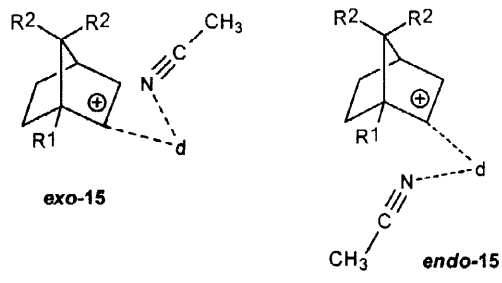
Ketone	Nitrile	Product(s)	Yield (%)[a]
rac-**1a**	**6a**	*rac*-**10a**	45[b]
rac-**1a**	**6b**	*rac*-**10b**	50[b]
rac-**1c**	**6a**	*rac*-**10c**	82[c]
		rac-**4c**	9[c]
		rac-**5c**	1[c]
(+)-**1d**	**6a**	*rac*-**13d**	55
		rac-**4d**	15
		rac-**9d**	29
(+)-**1d**	**6a**[d]	(-)-**4d**	88
		(-)-**9d**	5

[a] Isolated products.
[b] The rest until 100 % was unreacted ketone.
[c] At 55 h reaction time.
[d] 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as buffer is added.

The presence of methyl substituents at the C-7 position should not produce any considerable stabilization of the corresponding intermediate 2-norbornyl cations **2d** and **3d**.[12] Surprisingly, the reaction of (+)-camphor **1d** yields the racemic amide *rac*-**13d**. Therefore, the trapping of the corresponding cation *rac*-**11d** is preceded by a cascade of Wagner-Meerwein and Nametkin rearrangements as well as 6,2-hydride shifts (**11** ⟷ **12** isomerisation).[16] Triflate by-products **4d** and **9d** are found as racemates also, due to racemisation of the precursor carbocations **3d** and **8d** in equilibrium with the cations **11d** and **12d** (*ent*-**11d**) (see Scheme 1). In the presence of DTBMP as base, the proton elimination leading to the homochiral bridgehead triflates **(-)-4d** and **(-)-9d** is faster than the trapping and racemisation of **3d** and **8d** (Scheme 1). It seems not possible that the proton elimination leading to the triflates **4d** and **9d** may always be faster than the racemization of the carbocations **3d** and **8d**. In this case, the observed racemization in the absence of DTBMP should be due to racemization of triflates **4d** and **9d** in the presence of TfOH produced during the reaction. However, we have found that the treatment of (-)-**4d** with TfOH at room temperature, or even at 0°C, does not yield a mixture of **rac-4d** and

rac-9d, but only **rac-9d**.[3] Racemization of **8d** is avoided by lowering the reaction temperature to -15°C.[3]

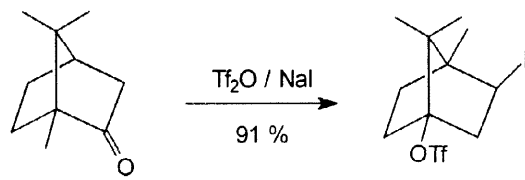
In the reaction conditions used, trapping of the 2-norbornyl cations takes place after racemising 6,2-hydride shift. The hindered trapping of the tertiary cations **2d**, **3d** and **8d** as well as the delay in the trapping of the secondary cation **11d**, can be attributed to a steric hindrance of these cations against the attack of the nitriles by the *gem*-dimethyl group. As a measure of the steric hindrance for the nitrile attack, we propose the equilibrium distance d between the carbocationic C_2 atom and the nitrogen of the nitrile **6a**, calculated by the molecular modelling method MMX[17] (see Figure 1) for the case of methyl substituted (no σ-bridged) 2-norbornyl cations **15**.



	R1	R2	d (Å)
exo-**a**	H	H	2.70
endo-**a**			2.78
exo-**c**	CH_3	H	2.73
endo-**c**			2.78
exo-**d**	CH_3	CH_3	2.80
endo-**d**			2.78

Figure 1

Increasing of steric hindrance caused by the introduction of methyl groups at the C_1 and C_7 positions of **15** is detected by an enlargement of the distance d. According to these calculations, the expected thermodynamically favoured product should be *endo*-**13d**, because the d value for *endo*-**15d** is smaller than the corresponding for the *exo* isomer. Thus, *endo* (bornyl) derivatives are formed by addition of acids to camphene under vigorous reaction conditions.[18] However, the formation of bornyl derivatives is so kinetically disfavoured, that the trapping of cations **11d** by nucleophiles usually affords *exo* (isobornyl) products of type **13d**.[16,18] We have also obtained racemic *exo*-**16d** in good yield when the reaction of **(+)-1d** was carried out with Tf_2O in presence of sodium iodide (Scheme 2).



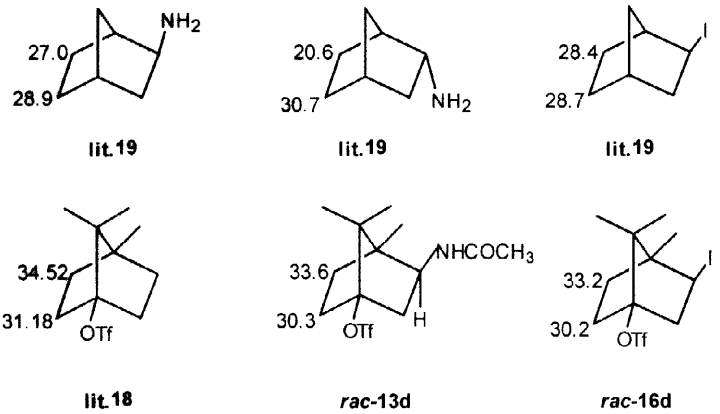
(+)-1d ***rac*-16d**

Scheme 2

The *exo* configuration of **13d** and **16d** was determined by comparison of their ^{13}C-NMR spectra with

the spectral data of analogous compounds previously described in the literature[19,20] and taking into account the strong shielding γ effect of *endo*-2 substituents (about 7 ppm).[20]

Table 2. Determination of the configuration of **13d** and **16d** from ^{13}C-NMR spectra.



In summary, the relative rate of trapping vs. molecular rearrangements is the result of a delicate equilibrium of stereoelectronic effects. In the case of steric unhindered ketones the faster reaction is the trapping by the nitriles **6** yielding annulated pyrimidines **10**, which are very difficult to synthesize by other methods.[13] On the other hand, molecular rearrangements are faster in the case of the steric hindered ketone (+)-**1c** affording interesting 1,3-difunctionalized norbornane derivatives.[14]

Experimental Section

General: ^{1}H- and ^{13}C-NMR spectra: Varian-XL 300 spectrometer with tetramethylsilane as internal standard.- IR spectra: Perkin-Elmer 781 spectrometer. - Capillary GC/MS: Shimadzu QP-17A (column type: TRB-1, 30 m) coupled to a Shimadzu QP-5000 mass-spectrometer (EI, 60 eV).). - HRMS: Varian Mat 711 (EI, 100 eV). - Anal: Perkin Elmer 2400. - Melting Points: Gallenkamp apparatus; values are uncorrected. - Elution chromatography: Merck silica gel 77340.1000 (70-230 mesh ASTM). - Molecular rotations: Perkin-Elmer 241 spectropolarimeter.- Reaction solvents were distilled from an appropriate drying agent before use.

General procedure for the reaction of 2-norbonanones ***1a-d*** *with* Tf_2O *in the presence of nitrile* ***6a-b****:* To a solution of 2-norbornanone (10.0 mmol) and nitrile (25.0 mmol) in CH_2Cl_2 (15 mL) was added a solution of Tf_2O (11.0 mmol) in CH_2Cl_2 (10 mL).After 24 h. (55 h for **1c**) at rt. (the reaction was monitored by GC/MS), the reaction mixture was treated with saturated solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (four

10-mL portions). The organic layer was washed with brine (two 10-mL portions) and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was analyzed by GC and NMR, and chromatographed (silica gel, hexane / diethyl ether 4:1 for ***rac*-10a** and ***rac*-10b**, silica gel, hexane for ***rac*-10c**, **4d** and **9d**, and silica gel, diethyl ether for *rac*-**13d**).

For **4c** and **5c** see lit.[21] For **(-)-4d**: $[\alpha]_D^{20}$ -22.9 (c= 1.6, MeOH) and **(-)-9d**: $[\alpha]_D^{20}$ -35.4 (c= 3.9, MeOH) see lit.[1,3]

(±)-2,4-Dimethyl-5,8-methane-5,6,7,8-tetrahydrobenzo[d]pyrimidine ***(rac-10a)***: ^{1}H-NMR ($CDCl_3$): δ = 3.46 (br. s, 1H), 3.33 (br. s, 1H), 2.63 (s, 3H), 2.42 (s, 3H), 2.06-1.93 (m, 2H), 1.79 (dq, J = 9.3 Hz, J = 1.8 Hz, 1H), 1.57 (dq, J = 9.3 Hz, J= 1.5 Hz, 1H), 1.22-1.18 (m, 2H) ppm. - ^{13}C-NMR ($CDCl_3$): δ = 176.5 (C8a), 164.2 and 155.6 (C2 and C4), 132.8 (C4a), 47.0 (C9), 44.7 and 39.0 (C5 and C8), 25.7 and 25.5 (C6 and C7), 24.7.and 20.5 (2 Me) ppm. - IR (KBr): ν = 1600, 1525, 1410 cm^{-1}. - MS (EI): *m/z* (%) = (174 $M^{+\cdot}$, 46), 173 (38), 159 (6), 146 (58), 105 (100), 91 (10), 77 (15), 65 (19), 42 (20).). - HRMS calcd. for $C_{11}H_{14}N_2$: 174.1157; found 174.1158.

(±)-2,4-Di(4-chlorophenyl)-5,8-methane-5,6,7,8-tetrahydrobenzo[d]pyrimidine ***(rac-10b)***: ^{1}H-NMR ($CDCl_3$): δ =8.46 (d, J = 8.7 Hz, 2H), 7.94 (d, J= 8.7 Hz, 2H), 7.51 (d, J = 8.7, 2H), 7.44 (d, J = 8.7 Hz, 2H), 3.77 (s, 1H), 3.53 (s, 1H), 2.26-2.12 (m, 2H), 1.92 (dq, J = 9.3 Hz, J = 1.8 Hz, 1H), 1.71 (dq, J = 9.3 Hz, J = 1.5 Hz, 1H), 1.52 (dd, J = 7.7 Hz, J = 2.3 Hz, 2H) ppm. - ^{13}C-NMR ($CDCl_3$): δ = 179.6 (C8a), 161.1 and 154.0 (C2 and C4), 136.8, 136.4, 136.2 and 136.0 (C1′, C1″, C4′ and C4″), 132.9 (C4a), 130.0, 129.5, 129.0 and 128.7 (C2′, C2″, C3′, C3″, C5′, C5″, C6′ and C6″,), 47.6 (C9), 45.3 and 41.2 (C5 and C8), 26.3 and 25.3 (C6 and C7) ppm.- IR (KBr): ν = 1600, 1580, 1550, 1490 cm^{-1}. - M.p. = 168.3-168.8°C (crystallisation from ethanol).- MS (EI): *m/z* (%) = 366 ($M^{+\cdot}$, 42), 351 (10), 338 (100), 201 (25), 166 (59), 147 (32), 134 (18), 100 (22), 91 (16), 63 (25). - Anal. calcd. for $C_{21}H_{16}Cl_2N_2$: C, 68.68, H, 4.39, N, 7.63, Cl, 19.30; found: C, 68.59, H, 4.41, N, 7.55, Cl, 19.45.

(±)-5,8-Methane-5,6,7,8-tetrahydro-2,4,8-trimethylbenzo[d]pyrimidine ***(rac-10c)***: ^{1}H-NMR ($CDCl_3$): δ = 3.30 (s, 1H), 2.58 (s, 3H), 2.33 (s, 3H), 2.05 (m, 1H), 1.65 (m, 1H), 1.56-1.49 (m, 2H), 1.47 (s, 3H), 1.20-1.11 (m, 2H) ppm. - ^{13}C-NMR ($CDCl_3$): δ = 177.8 (C8a), 164.5 and 155.5 (C2 and C4), 134.3 (C4a), 53.6 (C9), 50.3 (C8), 38.9 (C5), 32.3 and 28.3 (C6 and C7), 26.1 and 20.6 (Me-C2 and Me-C4), 15.1 (Me-C8) ppm. - IR (KBr): ν = 1600, 1570, 1410 cm^{-1}.- MS (EI): *m/z* (%) = 188 ($M^{+\cdot}$, 42), 173 (13), 160 (95), 119 (100), 91 (14), 77 (26), 65 (20). - HRMS calcd. for $C_{12}H_{16}N_2$: 188.1313; found: 188.1313.

(±)-3-exo-Acetamide-4,7,7-trimethyl-1-norbornyl triflate ***(rac-13d)***: ^{1}H-NMR ($CDCl_3$): δ = 5.80 (br. s, 1H), 4.10 (td, J = 9.1 Hz, J = 5.4 Hz, 1H) 2.74 (dd, J = 11.1 Hz, J = 9.1 Hz, 1H), 2.17-2.07 (m, 2H), 2.02 (m, 1H), 1.99 (s, 3H), 1.78 (m, 1H), 1.52 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H) ppm. - ^{13}C-NMR ($CDCl_3$): δ = 169.5 (CONH), 117. 9 (c, J = 334.9 Hz, CF_3), 99.9 (C1), 54.3 (C3), 49.3 (C4), 44.8 (C7), 41.0 (C2), 33.6 (C6), 30. 3 (C5), 23.2 (MeCO), 17.5 (Me), 17.2 (Me), 12.1 (Me) ppm. - IR (KBr): ν

= 3290, 3080, 1640, 1550, 1410, 1390, 1250 cm^{-1}. - M.p. = 120.8-121.4°C (crystallization from hexane) - MS (EI): *m/z* (%) = 343 ($M^{+\cdot}$, 2), 259 (4), 243 (2), 217 (8), 194 (12), 193 (11), 178 (22), 134 (87), 119 (50), 108 (43), 93 (21), 55 (27), 43 (100), 41 (36). - HRMS calcd. for $C_{13}H_{20}O_4SF_3N$: 343.1065; found: 343.1065. - Anal. calcd. for $C_{13}H_{20}O_4SF_3N$: C, 45.48, H, 5.83, N, 4.08; C, 45.59, H, 5.46, N, 4.03.

(±)-3-exo-Iodo-4,7,7-trimethyl-1-norbornyl triflate (rac-16d): To a solution of 2-norbornanone (10.0 mmol) and sodium iodide (25 mmol) in CH_2Cl_2 (15 mL), was added a solution of Tf_2O (11.0 mmol) in CH_2Cl_2 (10 mL). After 24 h at rt. (the reaction was monitored by GC/MS) the reaction mixture was treated with saturated solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (four 10-mL portions). The organic layer was washed with 10 % sodium bisulphite solution (two 10-mL portions) and brine (two 10-mL portions) and dried over magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure and the residue was analysed by GC and NMR, and cromatographed (silica gel, hexane). ^{1}H-NMR ($CDCl_3$): δ = 4.29 (dd, J = 9.4 Hz, J = 5.6 Hz, 1H), 3.01 (dd, J = 13,1 Hz, J = 9.4 Hz, 1H), 2.75 (dm, J = 13.1 Hz, 1H), 2.25-2.10 (m, 2H), 2.04 (td, J = 13.1 Hz, J = 4.7 Hz, 1H), 1.50 (ddd, J = 9.5 Hz, J = 8.4 Hz, J = 4.7 Hz, 1H), 1.32 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H) ppm. - ^{13}C-NMR ($CDCl_3$): δ = 117.9 (q, J = 324.2 Hz, CF_3), 99.2 (C1), 50.4 (C4), 45.5 (C2), 44.1 (C7), 33.2 (C5), 30.2 (C6), 29.1 (C3), 19.7, 17.7 and 17.4 (3 Me) ppm. - IR (CCl_4): ν = 2980, 1420, 1265, 1220, 1150 cm^{-1}. - MS (EI): *m/z* (%) = 285 ($M^{+\cdot}$-I, 26), 229 (31), 135 (87), 107 (40), 93 (69), 91 (35), 79 (35), 69 (83), 55 (38), 43 (100), 41 (76). - HRMS calcd. for $C_{11}H_{20}O_4F_3N$ ($M^{+\cdot}$-I): 285.0772; found: 285.0773.

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17) PC Model 4.0. Serena Sofware, Bloomington, IN 47402-3076, USA. To the MMX energy minimised structure of cations **15** was added the previously stored acetonitrile as a substructure. The substructure was moved near (3-2 Å) the carbocation-C2 atom and the resulting structure was MMX energy minimised. The same final structures ***exo*-15** or ***endo*-15** were obtained no matter which initial C2-N distance and orientation of the acetonitrile molecule were chosen. For the dielectric constant, a default value of 1.5 was used. Since both calculated equilibrium distances d (see Figure 1) and trapping rate constant k are functions of the steric demand of the substituents R^1 and R^2, a relationship between k and d is expected.

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