Ion–Molecule Complexes in 1,2 Alkyl Shifts

Andrea Gappa, Ekkehard Herpers, Roland Herrmann, Volker Hülsewede, Wilhelm Kappert, Matthias Klar, and Wolfgang Kirmse*

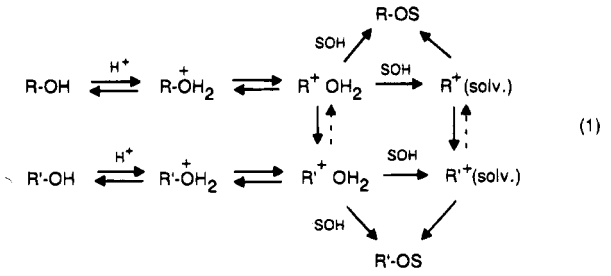
Contribution from the Fakultät für Chemie, Ruhr-Universität Bochum, D-44780 Bochum, Germany

Received July 18, 1995®

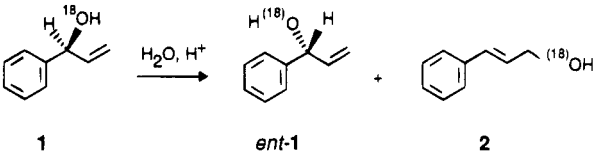
Abstract: The internal return of neutral leaving groups was studied in rearrangements of polycyclic systems (2-norpinyl → 2-norbornyl, *endo*- → *exo*-tricyclo[5.2.1.0^{2,6}]dec-8-yl, bicyclo[3.2.0]hept-2-yl → 7-norbornyl, and 4-protoadamantyl → 2-adamantyl). Acid catalysis was applied to ^{18}O-labeled alcohols in aqueous organic solvents, to alcohols in methanol, and to ethers R–O–R′ in alcohols R″–OH. The leaving group was found to attack the migration origin in competition with solvent molecules. Return:exchange ratios were obtained from product distributions, either directly or by kinetic simulation (in cases of partial exchange prior to rearrangement). If departure and return of the leaving group occur on the same side of the carbon framework, return:exchange ratios ranging from 1 to 11.5 were observed. Less internal return was found for bridged than for open carbocations. Migration of the departing molecule to the opposite face (*exo* ⇌ *endo*) or to a β carbon is a minor process (return:exchange ~ 0.1), in accordance with previous reports on inverting displacements and allylic 1,3 shifts. These data are rationalized in terms of short-lived ion–molecule (ion–dipole) complexes whose collapse competes with ligand exchange.

Introduction

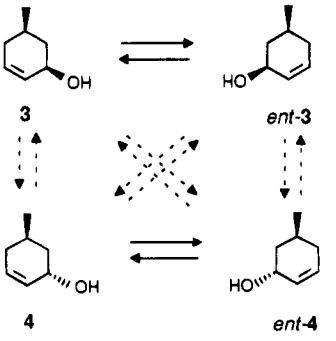
The concept of ion pairs in nucleophilic substitution, introduced by Winstein,[1] is now generally accepted.[2] Contact (intimate) as well as solvent-separated ion pairs has been invoked to explain the products, stereochemistry, and kinetics of solvolysis reactions. Much less attention has been directed to ion–molecule complexes which may intervene in the heterolysis of substrates with neutral leaving groups, particularly in acid-catalyzed reactions of alcohols and ethers, eq 1. If the complex [R$^+$OH$_2$] lives long enough for reorganization of the carbocation to occur (R$^+$ → R′$^+$), the product of recombination, R′–OH, will be formed in addition to the solvolysis products, R–OS and R′–OS (SOH = solvent).



In a pioneering study, Goering determined the rate of oxygen exchange associated with the acid-catalyzed racemization and rearrangement of (*S*)-1-phenylprop-2-en-1-ol (**1**).[3] His data show that about 4% of the 3-phenylprop-2-en-1-ol (**2**) and 22 ± 8% of the racemic **1** are produced without oxygen exchange.



Experiments with ^{18}O-labeled 5-methylcyclohex-2-en-1-ols revealed that in the *cis* isomer **3** most of the racemization is intramolecular, i.e. with return of ^{18}OH$_2$ to the allylic position. In the *trans* isomer **4**, interconversion of the enantiomers is associated with predominant exchange and *cis* ⇌ *trans* isomerization (**3** ⇌ **4**) results in complete exchange.[4] These findings indicate that the ion–molecule complex derived from **3** is sterically protected against exchange with the solvent.



Partial return of the neutral leaving group has also been observed with 2-methoxy-1-isopropylideneindan (**5a**) whose isomerization (→ **6a**) is 11 times slower than acid-catalyzed hydrolysis (→ **5b** + **6b**).[5] Under analogous conditions, the more extended rearrangement of **7** afforded exclusively the

® Abstract published in *Advance ACS Abstracts,* December 1, 1995.

(1) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc.* **1956**, *78*, 328.

(2) For reviews, see: (a) Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89. (b) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Chemistry;* Szwarc, M., Ed.; Wiley: New York, 1974; Vol. 2, p 247. (c) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1.

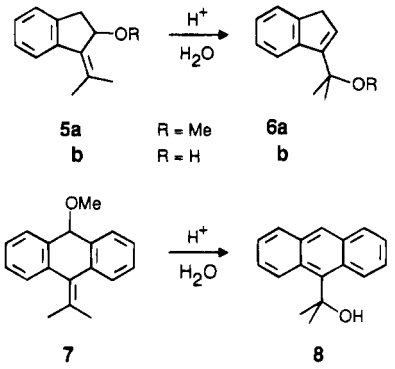
(3) Goering, H. L.; Dilgren, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 5744.

(4) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779.

(5) Thibblin, A. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1629.

0002-7863/95/1517-12096$09.00/0 © 1995 American Chemical Society

alcohol **8**.[6]



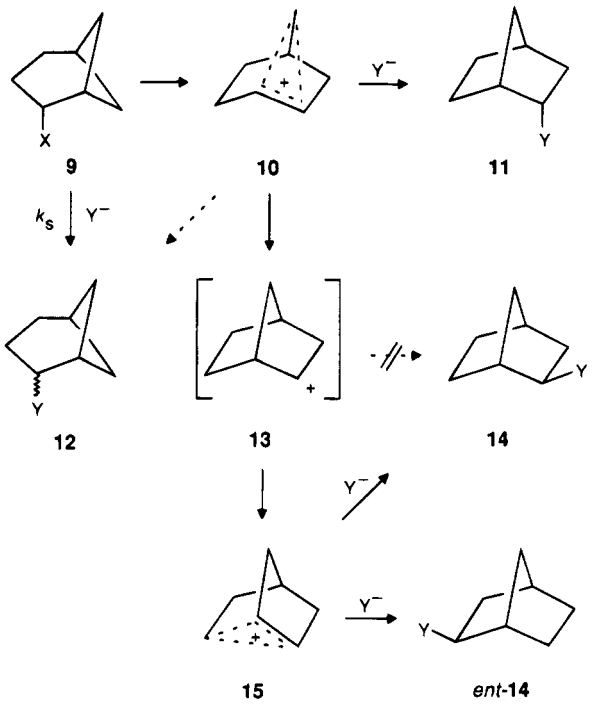
Return of the departing water to the opposite face of a carbocation has also been observed (cf. **1**→ *ent*-**1**). For both 1-phenylethanol[7] and 1-phenylpropanol[8] the rate of oxygen exchange is slower than the rate of racemization. For 1-phenylbutanol[8] and 1-phenyl-1-methoxyethane,[9] on the other hand, k_{rac} was found to equal k_{ex}. Ion–dipole pairs are likely to intervene in various elimination reactions[10,11] and explain the unusual reactivity of certain metastable ions in mass spectrometry.[12]

The ion–molecule recombinations cited above may be classified as 1,1 (to the same carbon) or 1,3 (to an allylic position). To our knowledge, the return of neutral leaving groups to neighboring carbon atoms (1,2) has not been reported in the literature. Our interest in 1,2 alkyl shifts led us to explore the role of ion–molecule complexes in Wagner–Meerwein rearrangements. Most conclusive results can be anticipated if the rearrangements are irreversible and the products ionize less readily than the substrates. In order to meet these conditions, we made use of strained ring systems; major sections of this paper refer to norpinyl → norbornyl and protoadamantyl → adamantyl rearrangements.

Results

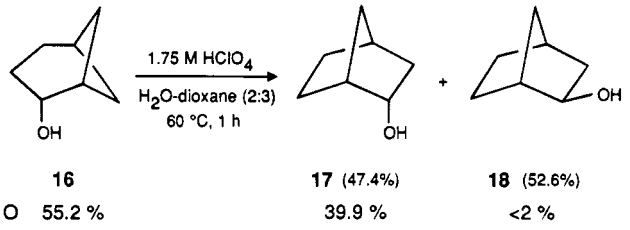
2-Norpinyl → 2-Norbornyl Rearrangements. 2-Norpinyl (bicyclo[3.1.1]hept-2-yl) substrates **9** (X = ODNB, N_2^+) are known to solvolyze with formation of *endo*- and *exo*-2-norbornyl products (**11**, **14**).[13] The fraction of *endo* products **11** increases with the nucleophilicity of the reactant Y^-, i.e. trapping of an *endo*-selective intermediate **10** competes with rearrangement to the *exo*-selective, achiral 2-norbornyl cation **15**. Nucleophilic capture of **10** gives mainly **11**, owing to unsymmetrical distribution of charge and to product stability. As a rule, only traces of **12** are found in solvolyses of **9**, exceptions being due to inverting displacement (k_s) (Scheme 1). High-level *ab initio* calculations confirm the bridged structure **10** of the norpinyl

Scheme 1



cation which is separated from **15** by a barrier of only 1.2 kcal/mol.[14] The "classical" 2-norbornyl cation **13** represents the transition state, rather than an intermediate, on the reaction path from **10** to **15**.

In accordance with Scheme 1, the acid-catalyzed rearrangement of bicyclo[3.1.1] heptan-2-ol (**16**) in aqueous dioxane afforded bicyclo[2.2.1]heptan-*endo*- and *exo*-2-ol (**17**:**18** = 47:53). Exchange of bicyclo[3.1.1]heptan-2-one with $^{18}OH_2$, followed by reduction with $NaBH_4$, provided [^{18}O]**16**. On acid-catalyzed rearrangement of [^{18}O]**16** in aqueous dioxane, 72% of the label was recovered in **17** while virtually no ^{18}O was found in **18**. The latter result may be due, at least in part, to oxygen exchange in **18** under our reaction conditions (see below). More importantly, the major route to **17** involves return of the $^{18}OH_2$ which departed from [^{18}O]**16**.



Treatment of **16** with anhydrous methanol–H_2SO_4 gave product mixtures containing **17** and **18** as well as the analogous methyl ethers (**19** and **20**, respectively) (Scheme 2). Under these conditions, **17** proved to be virtually inert whereas **18** was slowly but completely (≥98%) converted into the methyl ether **20**. Therefore, the formation of alcohols cannot be due to the adventitious precence of water in the reaction mixture. The rate constants shown in Scheme 2 were derived from the distribution of products (Figure 1 and Table 3 (Experimental Section), using an independent estimate of $k_{18,20}$.

The ratio of return to exchange for the *endo* products (**17**, **19**) is 70:30, very close to the result obtained with [^{18}O]**16** in

(6) Thibblin, A. *J. Chem. Soc., Chem. Commun.* **1990**, 697.
(7) (a) Grunwald, E.; Heller, A.; Klein, S. F. *J. Chem. Soc.* **1957**, 2604. (b) Merritt, M. V.; Bell, S. J.; Cheon, H.-J.; Darlington, J. A.; Dugger, T. L.; Elliott, N. B.; Fairbrother, G. L.; Melendez, C. S.; Smith, E. V.; Schwartz, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 3560.
(8) Merritt, M. V.; Anderson, D. B.; Basu, K. A.; Chang, I.-W.; Cheon, H.-J.; Mukundan, N. E.; Flannery, C. A.; Kim, A. Y.; Vaishampayan, A.; Yens, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 5551.
(9) Thibblin, A. *J. Phys. Org. Chem.* **1993**, *6*, 287.
(10) Herlihy, K. P. *Aust. J. Chem.* **1982**, *35*, 2221.
(11) Thibblin, A.; Sidhu, H. *J. Phys. Org. Chem.* **1993**, *6*, 374. See also: Thibblin, A. *Chem. Soc. Rev.* **1993**, *22*, 427.
(12) For reviews, see: (a) Bowen, R. D.; Williams, D. H.; Schwarz, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 451. (b) Bowen, R. D. *Acc. Chem. Res.* **1991**, *24*, 364. (c) McAdoo, D. J.; Morton, T. H. *Acc. Chem. Res.* **1993**, *26*, 297.
(13) (a) Kirmse, W.; Siegfried, R. *J. Am. Chem. Soc.* **1968**, *90*, 6504. (b) Kirmse, W.; Siegfried, R.; Wroblowsky, H.-J. *Chem. Ber.* **1983**, *116*, 1880. (c) Kirmse, W. *Acc. Chem. Res.* **1986**, *19*, 36.
(14) Sieber, S.; Schleyer, P. v. R.; Vancik, H.; Mesic, M.; Sunko, D. E. *Angew. Chem.* **1993**, *105*, 1673; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1604.

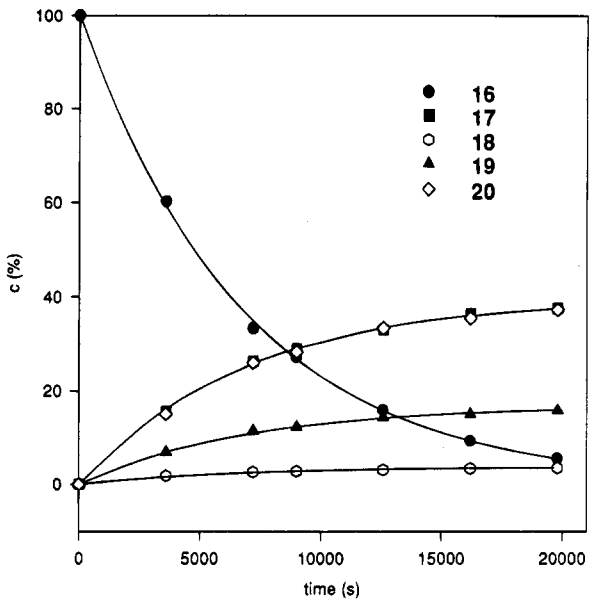


Figure 1. Product distributions from the methanolysis of bicyclo[3.1.1]-heptan-2-ol (**16**) (1.75 N H_2SO_4, 60 °C). The solid curves drawn through the data points were calculated with the rate constants given in Scheme 2.

Scheme 2

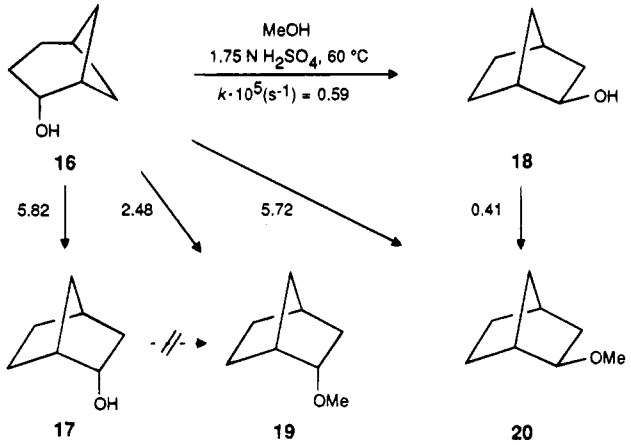


Table 1. Acidolysis of 2-RO-Bicyclo[3.1.1]heptanes (1.75 N H_2SO_4, 60 °C)

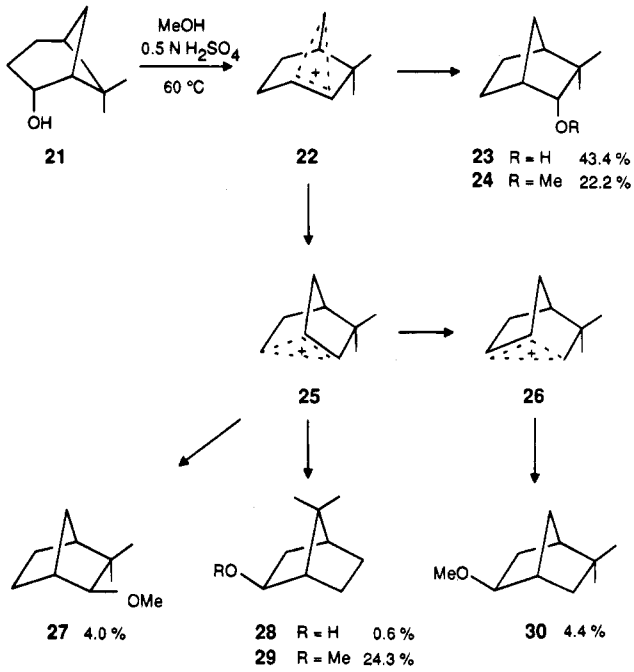
			endo products		exo products	
substrate	solvent	rate 10^5k (s^{-1})	%	ret:exch[a]	%	ret:exch[a]
16	MeOH	14.6	57	70:30	43	9:91
16-OEt	MeOH	1.95	62	76:24	38	7:93
16-OMe	EtOH	0.16	63	81:19	37	9:91

[a] Return of RO from substrate vs exchange with R'O from solvent.

aqueous dioxane. For the *exo* products (**18**, **20**), a much smaller ratio of return to exchange (9:91) is now reliably estimated. It should be emphasized that there is no exchange (**16** → **16**-OMe) prior to rearrangement.

Complementary experiments were performed with **16**-OEt in methanol and **16**-OMe in ethanol (Table 1). Considerable variation in rates is associated with only modest changes in product distributions. Comparison of **16**-OEt with **16**, both in methanol, points to enhanced return of the more nucleophilic leaving group (EtOH vs H_2O) in the formation of *endo* products. Ethanol as the solvent appears to favor internal return more strongly than methanol. However, this "solvent effect" may simply be due to the lower molarity of neat ethanol (17.1 M) relative to methanol (24.7 M) which decreases the rate of the exchange process. Within experimental error, the small ratio of return to exchange for the *exo* products is not affected.

Scheme 3

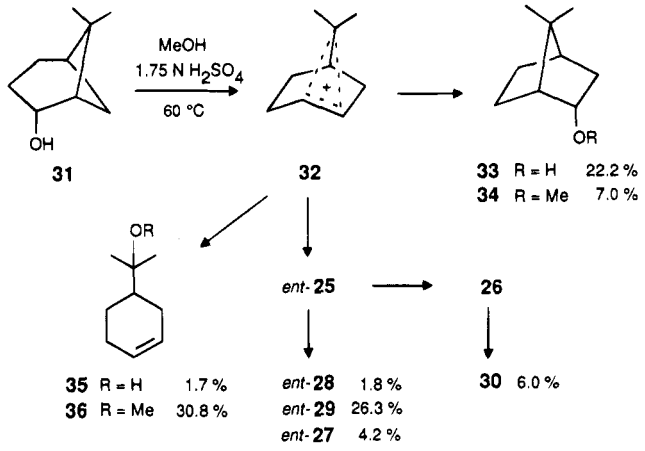


Dimethyl substitution at C-6 of **16** introduces a stereochemical label. The acid-catalyzed rearrangements of α-nopinol (1α,2β,5α-6,6-dimethylbicyclo[3.1.1]heptan-2-ol, **21**) and β-nopinol (1α,2α,5α-6,6-dimethylbicyclo[3.1.1]heptan-2-ol, **31**) in dioxane−water have been studied previously.[15] It was noticed that **21** reacts faster than **31** by factors of 10 (90 °C) to 15 (70 °C). The oxidation of **21** was also reported to proceed more rapidly than that of **31**.[16] The difference in reactivity is reasonably attributed, at least in part, to the enhanced strain of **21** (1.3 kcal/mol according to MMX calculations). In methanol at 60 °C, we required different concentrations of acid to convert **21** (0.5 N H_2SO_4, $k = 9.8 \times 10^{-4}$ s^{-1}) and **31** (1.75 N H_2SO_4, $k = 2.3 \times 10^{-4}$ s^{-1}) at convenient rates. Under these conditions, **21** was found to react stereospecifically, with exclusive migration of the CH_2 bridge (C-7) *trans* to the leaving group (Scheme 3). The primary intermediate **22** is trapped to give the *endo* products **23** and **24** in somewhat higher yield (65.6%) and slightly lower retention:exchange ratio (66:34) than was observed for the parent species **10**. Rearrangement of **22** generates the bridged ion **25** which is captured by nucleophiles, yielding predominantly 7,7-dimethyl-*exo*-2-norbornyl products (**28**, **29**), but also undergoes 6,2-H shifts (**25** → **26**) leading eventually to **30**.[17,18]

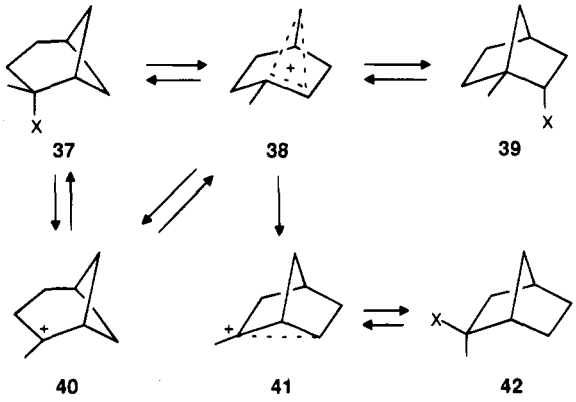
The acid-catalyzed methanolysis of **31** proceeds with exclusive migration of the $C(CH_3)_2$ bridge (C-6) *trans* to the departing OH (Scheme 4). The behavior of the norpinyl cation **32** differs from that of the isomer **22** in two points. The yield of *endo* products is lower, and the ratio of return:exchange is enhanced (**33**:**34** = 76:24). Both kinetic data[19] and computational studies[20] indicate that σ-delocalized carbocations are destabilized

(15) Indyk, H.; Whittaker, D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 646.
(16) Müller, P.; Perlberger, J.-C. *J. Am. Chem. Soc.* **1975**, *97*, 6862; **1976**, *98*, 8407.
(17) Colter, A.; Friedrich, E. C.; Holness, N. J.; Winstein, S. *J. Am. Chem. Soc.* **1965**, *87*, 378.
(18) Kirmse, W.; Brandt, S. *Chem. Ber.* **1984**, *117*, 2510.
(19) Schleyer, P. v. R.; Donaldson, M. M.; Watts, W. E. *J. Am. Chem. Soc.* **1965**, *87*, 375.
(20) Saunders, M.; Chandrasekhar, J.; Schleyer, P. v. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I, pp 34−41.

Scheme 4



Scheme 5



by methyl substitution at the bridging (pentacoordinate) carbon. As compared with **22**, the shorter lifetime of the more energetic **32** will account for the less efficient nucleophilic capture (→ **33** + **34**) and for the enhanced fraction of internal return. Furthermore, **31** undergoes Grob fragmentation,[21] leading eventually to **35** and **36**. Stereochemical evidence suggests that the fragmentation proceeds by way of **32**.[22] Formation of the alcohol **35** cannot occur without migration of the departing water to the *exo* face of **32**. It is not surprising, therefore, that the ratios of retention:exchange for *exo*-norbornyl products (**28**:**29** = 6:94) and fragmentation products (**35**:**36** = 5:95) agree closely.

Even stronger effects on carbocation structures and energies are exerted by a methyl substituent at C-2 of the 2-norpinyl system. The positive charge of the bridged ion **38** is expected to be more evenly distributed than in previous examples. In fact, 2-methyl-2-norpinyl substrates (**37**, X = OPNB, N_2^+) were found to give comparable amounts of 2-methyl-2-norpinyl (**37**, X = OR) and 1-methyl-*endo*-2-norbornyl products (**39**, X = OR).[23] Moreover, the energy difference between open and bridged norpinyl cations will be attenuated since **40** is a tertiary ion (Scheme 5). Stereochemical studies indicate partial equilibration of **38** (chiral) with **40** (achiral).[24] The rearrangement of

(21) Reviews: (a) Grob, C. A.; Schiess, P. W. *Angew. Chem.* **1967**, *79*, 1; *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1. (b) Grob, C. A. *Angew. Chem.* **1969**, *81*, 543; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Becker, K. B., Grob, C. A. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Part 2, Chapter 8.

(22) Kirmse, W.; Zander, K. *Angew. Chem.* **1988**, *100*, 1596; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1538.

(23) Banert, K.; Kirmse, W.; Wroblowsky, H.-J. *Chem. Ber.* **1983**, *116*, 2474.

(24) (a) Banert, K.; Kirmse, W.; Wroblowsky, H.-J. *Chem. Ber.* **1983**, *116*, 3591. (b) Herrmann, R. Ph.D. Thesis, Ruhr-Universität Bochum, 1993.

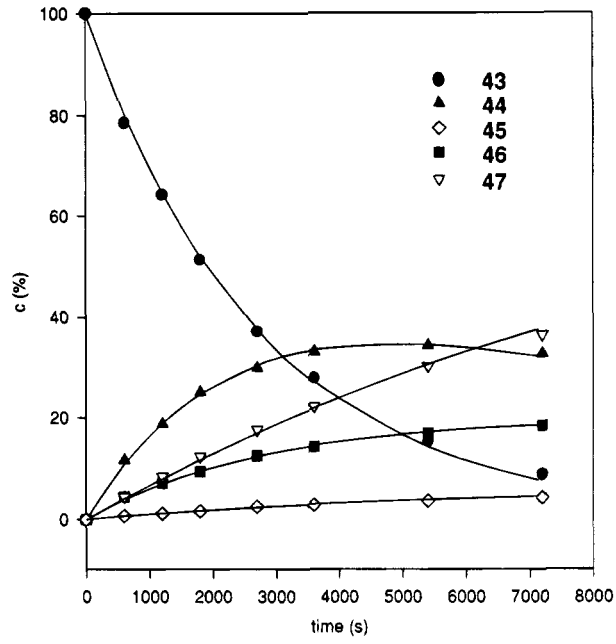
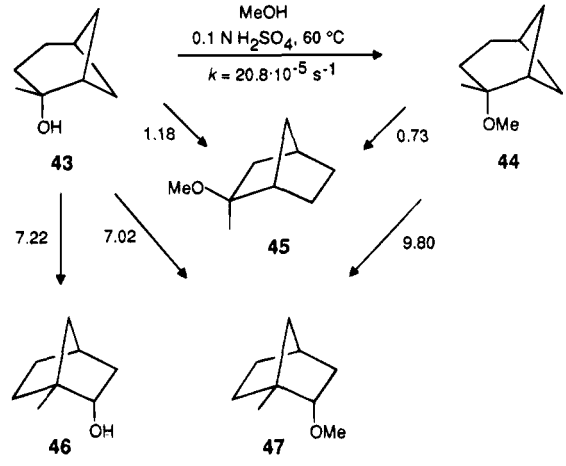


Figure 2. Product distributions from the methanolysis of 2-methylbicyclo[3.1.1]heptan-2-ol (**43**) (0.1 N H_2SO_4, 25 °C). The solid curves drawn through the data points were calculated with the rate constants given in Scheme 6.

Scheme 6

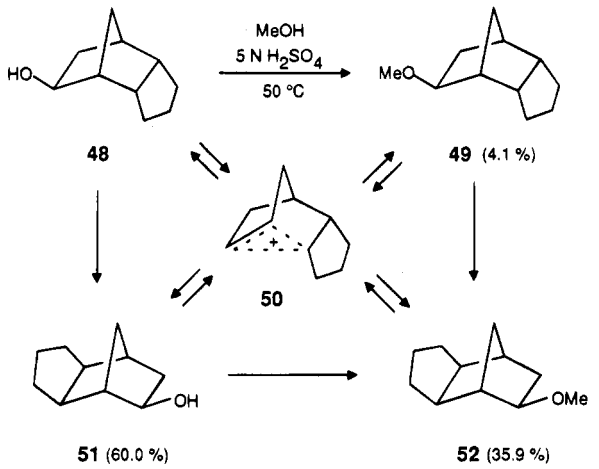


38 ⇌ **40**, proceeding through the 1-methyl-2-norbornyl cation as the transition state, gives rise to the 2-methyl-2-norbornyl cation (**41**). σ-Delocalization in **41** is known to be weak; nucleophiles are accepted almost exclusively at the tertiary carbon (→ **42**).[25]

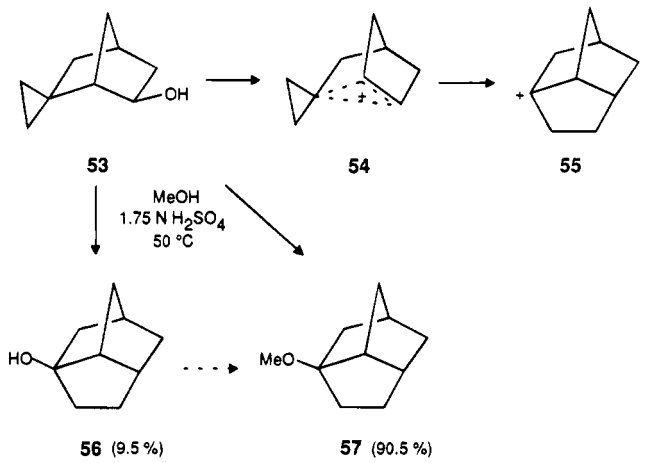
In the acid-catalyzed methanolysis of 2-methylbicyclo[3.1.1]-heptan-2-ol (**43**), exchange of OH for OMe (**43** → **44**), without rearrangement, was found to compete favorably with formation of the norbornyl products **45**–**47** (Scheme 6). This behavior, distinguishing **43** from the secondary alcohols **16**, **21**, and **31**, is consistent with the general features of tertiary 2-norpinyl systems that were outlined in the preceding paragraph. Since the ether **44** undergoes acid-catalyzed rearrangement to give **45** and **47**, the concentration of **44** passes through a maximum at 65% conversion of **43** (Figure 2). Starting from **44**, rate constants for the **44** → **45** and **44** → **47** transformations were estimated. The remaining rate constants of Scheme 6 were varied computationally to obtain the best fit of calculated and

(25) (a) Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Acc. Chem. Res.* **1983**, *16*, 440. (b) Olah, G. A.; Prakash, G. K. S.; Williams, R. E.; Fields, L. D.; Wade, K. *Hypercarbon Chemistry*; Wiley: New York, 1987.

Scheme 7



Scheme 8



experimental product distributions. The kinetic analysis reveals that direct (**43** → **45** + **47**) and indirect routes (**43** → **44** → **45** + **47**) make similar contributions to the formation of norbornyl ethers. The fraction of *exo*-2-norbornyl products from **43** and **44** (7% of **45**) is inferior to that from the parent alcohol **16** (43% of **18** + **20**). Relative to nucleophilic capture, the rearrangement of **38** proceeds ca. 10 times more slowly than that of the parent 2-norpinyl cation **10**.

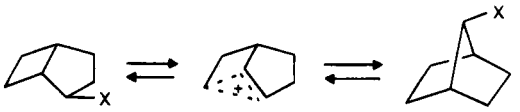
Although all data support the enhanced stability of **38** relative to **10**, the formation of **46** points to the intervention of an ion–molecule complex even of **38**. In the **38**-OH_2 pair, return of H_2O to both C-1 and C-2 will compete with exchange of H_2O for MeOH. Based on the direct formation of **46** and **47** from **43**, the return:exchange ratio of **38**-OH_2 is estimated as 51:49. If **38**-OH_2 is compared with the parent system **10**-OH_2, the moderate decrease of the return:exchange ratio (by a factor of ca. 3) points to slightly weaker association in **38**-OH_2.

2-Norbornyl → 2-Norbornyl Rearrangements. As an example of a nondegenerate 1,2 shift we chose the conversion of *endo*-tricyclo[5.2.1.$0^{2,6}$]decan-8-ol (**48**) into the *exo* isomer **51** (Scheme 7) which is associated with a decrease in strain energy of ca. 4.5 kcal/mol.[26] The methanolysis of **48**–OTs was reported to proceed 3.7 times faster than that of **51**-OTs;[27] both tosylates gave predominantly *exo* ether **52** together with 3–7% of *endo* ether **49**, presumably by capture of the bridged cation **50**.[27,28]

The methanolysis of **48**, leading to **49**, **51**, and **52**, required strongly acidic conditions and long reaction times. The products **49** and **51** also reacted with formation of **52**, albeit more slowly than **48**. Deviations from first-order kinetics precluded an exact analysis, but extrapolation of the product ratios to zero conversion gave reproducible results (Scheme 7). The data indicate a small amount of exchange (**48** → **49**) prior to rearrangement and a 63:37 ratio of return (**48** → **51**) to exchange (**48** → **52**) at the terminus of the 1,2 shift. Thus the behavior of the present system is intermediate between that of secondary and tertiary 2-norpinanols.

Spiro(bicyclo[2.2.1]heptane-2,1′-cyclopropy-6-yl) derivatives (e.g., **53**) are known to rearrange with formation of tricyclo-[4.2.1.$0^{3,7}$]non-3-yl products (e.g., **56**; Scheme 8).[29] The 6,2-carbon shift leading to **55** is thought to proceed from the bridged ion **54** since equivalence of C-1 and C-2 is achieved within $\leq 10^{-13}$ s.[30] The acid-catalyzed methanolysis of **53** afforded the alcohol **56** and the methyl ether **57** in a 9.5:90.5 ratio (extrapolated to $t = 0$ to correct for the slow conversion of **56** into **57**). In this instance, the migration terminus is γ to the origin. Hence return of the departing water molecule is a minor process, as was observed in allylic rearrangements (**1** → **2**; **5** → **6**) and fragmentation reactions (**31** → **35**).

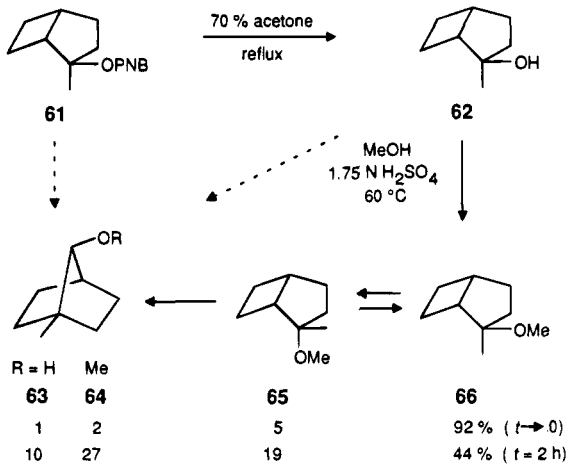
2-Bicyclo[3.2.0]heptyl → 7-Norbornyl Rearrangements. Acetolysis of either *exo*-2-bicyclo[3.2.0]heptyl brosylate (**58**-OBs) or 7-norbornyl brosylate (**60**-OBs) was found to give similar product distributions (**60**-OAc:**58**-OAc ≈ 95:5).[31] The bridged ion **59** was proposed as a common intermediate.



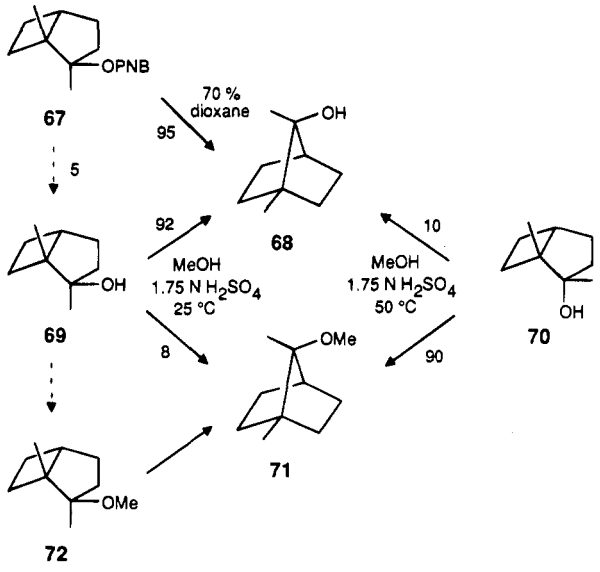
We failed to achieve clean acid-catalyzed conversions of bicyclo[3.2.0]heptan-*exo*-2-ol (**58**-OH) into 7-norbornanol (**60**-OH), dehydration being the major process. The more reactive *endo*-2-methylbicyclo[3.2.0]heptan-*exo*-2-ol (**62**) has been reported to rearrange smoothly with formation of 1-methyl-7-norbornanol (**63**, 98% yield).[32] However, **63** appears to be the product of thermodynamic control since hydrolyses of both *endo*-2-methylbicyclo[3.2.0]hept-*exo*-2-yl *p*-nitrobenzoate (**61**) and 1-methyl-7-norbornyl triflate (**63**, R = CF_3SO_2) afford >90% of **62** and <5% of **63**[33] (Scheme 9). Nucleophilic capture of the intermediate carbocation(s) at the tertiary position clearly prevails under conditions of kinetic control. Accordingly, we found that the acid-catalyzed methanolysis of **62** proceeds predominantly with OH/OMe exchange to give *exo*-2-methoxy-*endo*-2-methylbicyclo[3.2.0]heptane (**66**). More slowly, **66** equilibrates with the *endo*-2-methoxy-*exo*-2-methyl isomer **65**, and the mixture is eventually converted into 7-methoxy-1-methylnorbornane (**64**). A small amount (2–3%) of 1-methyl-7-norbornanol (**63**) was also obtained but does not necessarily arise from **62**. We observed an *increase* of **63** (to ca. 10%)

(26) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.
(27) Takeuchi, K.; Oshika, T.; Koga, Y. *J. Chem. Soc. Jpn.* **1965**, *38*, 1318.
(28) Cristol, S. J.; Seifert, W. K.; Johnson, D. W.; Jurale, J. B. *J. Am. Chem. Soc.* **1962**, *84*, 3918.
(29) (a) Adam, W.; Carballeira, N.; Peters, E. M.; Peters, K.; v. Schnering, H. G. *J. Am. Chem. Soc.* **1983**, *105*, 5132. (b) Altmann-Schaffner, E.; Grob, C. A. *Helv. Chim. Acta* **1987**, *70*, 43.
(30) Kirmse, W.; Landscheidt, H.; Schleich, A. *J. Phys. Org. Chem.* **1992**, *5*, 19.
(31) (a) Winstein, S.; Gadient, F.; Stafford, E. T.; Klinedinst, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5895. (b) Svensson, T. *Chem. Scripta* **1974**, *5*, 20.
(32) Kirmse, W., Streu, J. *Synthesis* **1983**, 994.
(33) Kirmse, W.; Streu, J. *J. Org. Chem.* **1985**, *50*, 4187.

Scheme 9



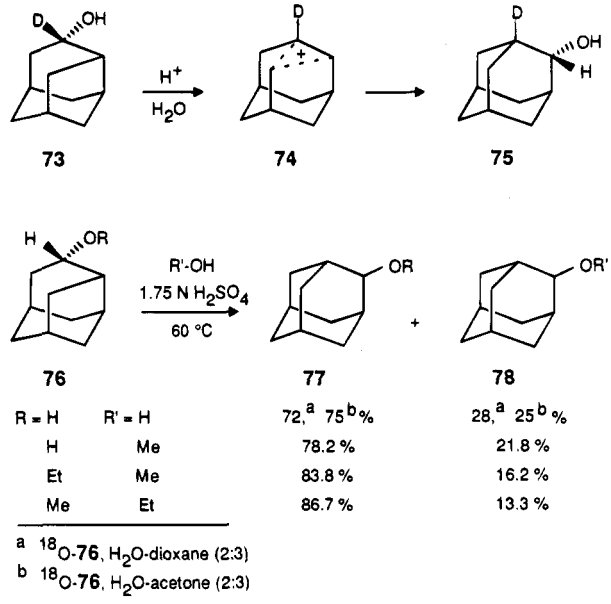
Scheme 10



after **62** had been consumed, suggesting that cleavage of **64** occurs under these strongly acidic conditions. We conclude that the recombination of ion–molecule complexes to give **63** occurs to a very minor extent, if at all.

The reaction profile is changed dramatically by introducing a second methyl group at C-1. The *p*-nitrobenzoate **67** was found to solvolyze with predominant formation of 1,7-dimethyl-7-norbornanol (**68**), attesting to the enhanced driving force for rearrangement which the generation of a tertiary 7-norbornyl cation provides (Scheme 10). In the acid-catalyzed methanolysis of 1,*endo*-2-dimethylbicyclo[3.2.0]heptan-*exo*-2-ol (**69**), return of the departing water to the neighboring carbon afforded **68** as the major product. The ratio of return to exchange, 92:8, surpasses all previous examples. Although **72** was not detected, we cannot exclude a small amount of exchange prior to rearrangement since **72** reacts faster ($k \approx 6.1 \times 10^{-4}$ s^{-1}) than **69** ($k \approx 3.2 \times 10^{-4}$ s^{-1}). The unusual order of reactivities, OMe > OH, can be attributed to enhanced relief of F-strain in the heterolysis of **72**-H$^+$, as compared with **69**-H$^+$. The acid-catalyzed methanolysis of 1,*exo*-2-methylbicyclo[3.2.0]heptan-*endo*-2-ol (**70**) proceeded less readily than that of the epimer **69** to give predominantly **71**. In this case, the departing water must relocate from the *endo* to the *exo* face of the molecule in order to produce **68**. Hence the return:exchange ratio is low (10:90), as was observed in norpinyl → *exo*-2-norbornyl rearrangements.

Scheme 11



4-Protoadamantyl → 2-Adamantyl Rearrangements. Much experimental and computational effort has been directed to the 4-protoadamantyl → 2-adamantyl rearrangement, an important step in the synthesis of adamantoid hydrocarbons.[34–37] The prominent role of the bridged ion **74** has recently been confirmed (Scheme 11). The acid-catalyzed rearrangement of optically active *exo*-4-protoadamantanol-*4-d* (**73**) was found to give 2-adamantanol-*1-d* (**75**) with 97% ee.[38] Although the *endo* isomer of **73** reacted similarly, rather vigorous conditions were required which led to partial racemization of **75**. Therefore, only *exo*-4-protoadamantanol (**76**-OH) was included in the present work. The ^{18}O-labeled compound afforded 72–75% of ^{18}O-2-adamantanol on acid-catalyzed rearrangement in aqueous organic media. In neat methanol, **76**-OH reacted to give 78% of 2-adamantanol (**77**-OH) and 22% of 2-methoxyadamantane (**78**-OMe). The return:exchange ratio increased further in the methanolysis of **77**-OEt and ethanolysis of **77**-OMe (Scheme 11). No exchange of OR for OR′ in **76** and no interconversion of 2-adamantanol with its ethers was observed.

In the 4-methyl-4-protoadamantyl cation, charge stabilization attenuates the rate of the protoadamantyl → adamantyl rearrangement. Thus hydrolysis of *endo*-4-methyl-*exo*-4-protoadamantyl *p*-nitrobenzoate (**79**-OPNB) gave the parent alcohol **79** and 1-methyl-2-adamantanol (**81**) in a 24:76 ratio[35b,39] while methanolysis of **79**-OPNB afforded the analogous methyl ethers **83** and **84** in a 78:22 ratio (Scheme 12). Accordingly, the fastest reaction in the acid-catalyzed methanolysis of *endo*-4-methyl-*exo*-4-protoadamantanol (**79**) was exchange of OH for OMe (**79** → **82** + **83**), with predominant retention of configuration (Figure 3). The reaction conditions applied to **79** converted **83** into **84** and a small amount of the more stable epimer **82**, with the rate

(34) For a review, see: Sorensen, T. S.; Whitworth, S. M. In *Cage Hydrocarbons*; Olah, G. A., Ed.; Wiley: New York, 1990; pp 86–91.

(35) (a) Lenoir, D.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 2138. (b) Lenoir, D.; Raber, D. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 2149.

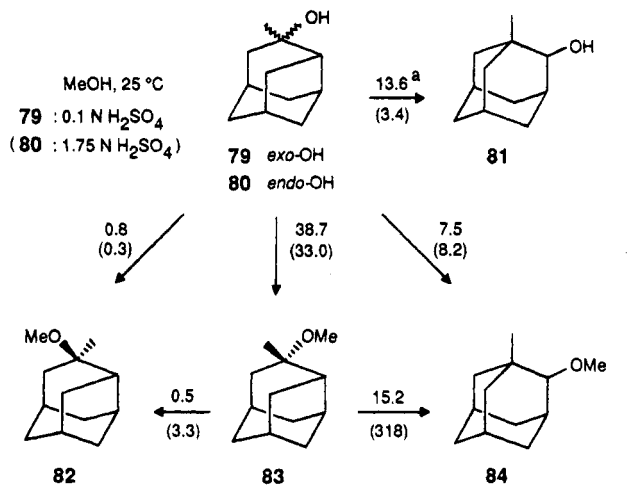
(36) (a) Nordlander, J. E.; Haky, J. E.; Landino, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7487. (b) Nordlander, J. E.; Haky, J. E. *J. Am. Chem. Soc.* **1981**, *103*, 1518.

(37) (a) Dutler, R.; Rauk, A.; Sorensen, T. S.; Whitworth, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 9024. (b) Dutler, R.; Rauk, A.; Whitworth, S. M.; Sorensen, T. S. *J. Am. Chem. Soc.* **1991**, *113*, 411.

(38) Herpers, E.; Kirmse, W. *J. Chem. Soc., Chem. Commun.* **1993**, 160.

(39) Kovacevic, D.; Goricnik, B.; Majerski, Z. *J. Org. Chem.* **1978**, *43*, 4008.

Scheme 12[a]



[a] Regular numbers are rate constants ($10^5 k$ s^{-1}). Numbers in brackets refer to **80**, 1.75 N H_2SO_4.

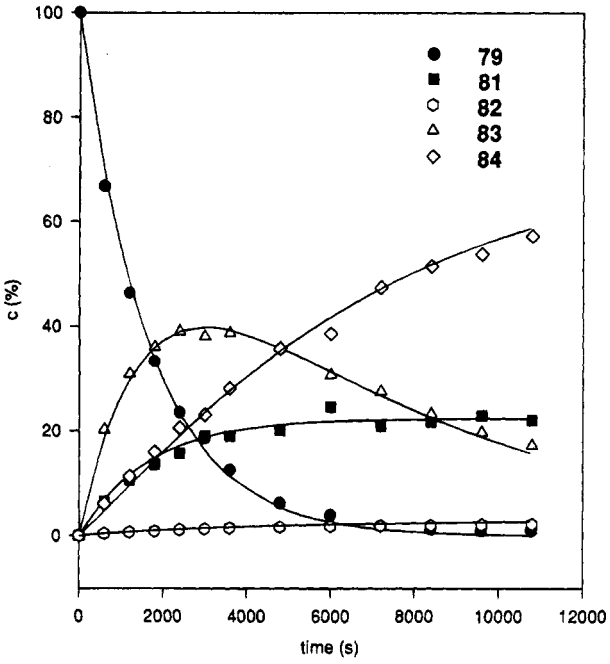


Figure 3. Product distributions from the methanolysis of *endo*-4-methyltricyclo[4.3.1.0^{3,8}]decan-exo-4-ol (**79**) (0.1 N H_2SO_4, 25 °C). The solid curves drawn through the data points were calculated with the rate constants given in Scheme 12.

constants specified in Scheme 12. The remaining rate constants were estimated by kinetic simulation of the product distributions, as described above for **43**. The rates at which **79** gives rise to 1-methyl-2-adamantanol (**81**) and 2-methoxy-1-methyladamantane (**84**) indicate a return to exchange ratio of 64:36 at the migration origin.

The methanolysis of *exo*-4-methyl-*endo*-4-protoadamantanol (**80**) required strongly acidic solutions in order to proceed at convenient rates. Exchange of OH for OMe in **80** produced **83** as the predominant product, as was observed with **79**. In accordance with previous solvolytic results,[35b,36b] the stereochemistry of the exchange process is controlled by the intervening carbocation rather than by the precursor. In MeOH−1.75 N H_2SO_4, the rearrangement of **83** was too fast for direct measurement. Therefore, the kinetic simulation of Scheme 12 is less reliable for **80** (numbers in brackets) than for **79** (Figure 4). As compared with **79**, a lower ratio of return to exchange, 29:71, was found for the conversion of **80** into **81** and **84**. In

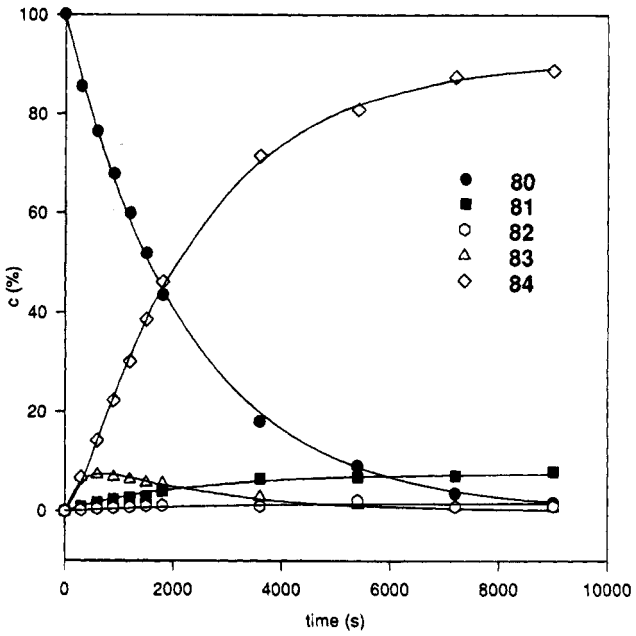


Figure 4. Product distributions from the methanolysis of *exo*-4-methyltricyclo[4.3.1.0^{3,8}]decan-endo-4-ol (**80**) (1.75 N H_2SO_4, 25 °C). The solid curves drawn through the data points were calculated with the rate constants given in Scheme 12.

Table 2. Return:Exchange Ratios in 1,2 Alkyl Shifts

substrate		leaving group	solvent	return:exchange same side	return:exchange opposite face
sec-2-norpinyl	**16**	$H_2{}^{18}O$	H_2O[a]	2.6	<0.10
	16	H_2O	MeOH	2.3	0.10
	16-OEt	EtOH	MeOH	3.2	0.08
	16-OMe	MeOH	EtOH	4.3	0.10
	21	H_2O	MeOH	1.9	0.02
	31	H_2O	MeOH	3.2	0.06
tert-2-norpinyl	**43**	H_2O	MeOH	1.0	n.a.[b]
2-norbornyl	**48**	H_2O	MeOH	1.7	n.a.
2-bicyclo[3.2.0]heptyl	**69**	H_2O	MeOH	11.5	n.a.
	70	H_2O	MeOH	n.a.	0.11
sec-4-protoadamantyl	**76**	$H_2{}^{18}O$	H_2O[a]	2.6	n.a.
	76	H_2O	MeOH	3.5	n.a.
	76-OEt	EtOH	MeOH	5.3	n.a.
	76-OMe	MeOH	EtOH	6.7	n.a.
tert-4-protoadamantyl	**79**	H_2O	MeOH	1.8	n.a.
	80	H_2O	MeOH	n.a.	0.41

[a] H_2O−dioxane (2:3). [b] Not applicable.

order to generate **81**, the water molecule departing from **80**-H^+ has to travel by a longer distance than that departing from **79**-H^+.

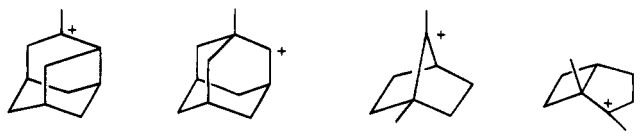
Discussion

The 1,2 shifts we have studied (Table 2) are mediated by rapidly equilibrating or σ-delocalized carbocations in which the distribution of positive charge is attained on the time scale of molecular vibrations, within $\sim 10^{-13}$ s. Nucleophilic capture by the solvent proceeds more slowly. As a rule, similar product ratios are obtained on solvolytic generation of these ions from appropriate isomeric substrates (e.g., **79**-ODNB and **81**-OTs).[35b] These product distributions reflect the relative rates of solvent attack at the migration terminus (k_t) and origin (k_o). With $k_o/k_t \geq 10$, acidolyses of alcohols proceed without significant exchange of OH for OR at the migration terminus; thus the ratio of return to exchange at the migration origin is readily estimated (cf. **16**, **21**, **31**, **48**, **69**, and **76**). If $k_o \sim k_t$, the desired data can be derived, although less directly, by kinetic simulations

(cf. **43**, **79**, and **80**). In the case of $k_o/k_t \leq 0.1$, no meaningful results are obtained, due to prevailing exchange at the migration terminus (cf. **62**).

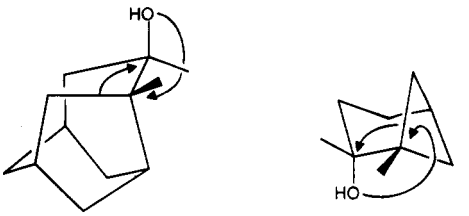
For a discussion of internal return, two types of rearrangement will be distinguished. (i) In 1,2 shifts proceeding with inversion at both the migration terminus and origin, the leaving group returns to the neighboring carbon atom on the same side of the molecular framework from which it departed. The distance covered by the migrating molecule is virtually the same for all rearrangements of this type. However, the return to exchange ratios vary from 11.5 for **69** to 1.0 for **43**. It seems reasonable to relate the return:exchange ratios to cation stabilities since increasing stability should decrease the rate of nucleophilic capture. Although this correlation is applicable to the series of norpinyl cations derived from **16**, **21**, **31**, and **43**, it does not pass the test of structural diversity. According to solvolysis rates, the 7-methyl-7-norbornyl cation is more stable than the 1-methyl-2-adamantyl cation,[40,35b] yet the return:exchange ratio for the former (→ **68** + **71**, 92:8) exceeds that for the latter (→ **81** + **84**, 64:36).

The same absence of a correlation between the thermodynamic stability of α-substituted benzyl cations and their reaction rates with nucleophiles has been noted previously.[41] The electronic and structural reorganization that occurs upon capture of delocalized ions is thought to raise the intrinsic barrier of nucleophilic attack relative to more localized species. The products **81** and **84** arise from a delocalized ion whose structure should be intermediate between the more strained but tertiary 4-methyl-4-protoadamantyl cation (**85**) and the less strained but secondary 1-methyl-2-adamantyl cation (**86**).[35b] On the other hand, **68** and **71** originate from the localized, tertiary 7-methyl-7-norbornyl cation (**87**) to which the more strained 1,2-dimethylbicyclo[3.2.0]hept-2-yl structure (**88**) makes only a minor contribution. Other examples, such as **48** and **76**, also support the view that the return:exchange ratios depend more on the extent of charge delocalization than on the thermodynamic stabilitiy of the intervening carbocations.



85 **86** **87** **88**

(ii) Retention at either the migration origin or the terminus of a 1,2 shift requires the leaving group to approach the neighboring carbon from the face opposite to that from which it departed. For comparison with type i rearrangements, we focus on substrates that give rise to diastereomeric products (2-norpinyl → *exo*- and *endo*-2-norbornyl) and on diastereomeric substrates that afford the same product(s) (**69**/**70**, **79**/**80**). In each case, the return:exchange ratio for type ii rearrangements was much lower than that for type i rearrangements. However, enhanced return was found for **80** as compared with **16** and **70** (Table 2). Inspection of molecular models shows that **80** is converted into **81** by an *eq* → *eq* shift of water on a six-membered ring, as indicated in **89**. In contrast, the formation of **18** from **16** can be viewed as an *ax* → *ax* shift (see **90**). The geometry of type ii rearrangements, in particular the distance covered by the migrating molecule, obviously affects the return: exchange ratios.



89 **90**

Our findings are conveniently interpreted in terms of ion–molecule (ion–dipole) complexes whose collapse competes with exchange of the complexed molecule. In order to gain insight into the lifetime of ion–molecule complexes, we compare the rate of "ligand exchange" with the rate of purely diffusional processes. Upon generation of di- and triarylcarbenium ions by laser flash photolysis, rate constants $k_s \leq 10^9$ s^{-1} were measured for the pseudo-first-order reactions of these ions with protic solvents.[42] A linear correlation of k_s vs pK_{R^+} was obtained from which $k_s = 10^{10.5}$ s^{-1} for the *tert*-butyl cation was derived by a small extrapolation. The carbocations we have studied are very close to *tert*-butyl in stability. Therefore we adopt $k \sim 10^{10.5}$ s^{-1} for the rate of collapse of ion–molecule complexes. With an average return:exchange ratio of ~3, we arrive at $k_{ex} \sim 10^{10}$ s^{-1} for the rate of "ligand exchange". Diffusional exchange in bulk water occurs at a rate of $\sim 2 \times 10^{11}$ s^{-1}.[43] Spectroscopic methods, in particular nuclear magnetic resonance relaxation, indicate that the mobility of water molecules in the solvation shell of large monovalent ions ("structure breakers") may be enhanced relative to that of bulk solvent. Thus our estimate for the rate of diffusion into and out of the solvation shell is $k_{diff} = 10^{11}$–10^{12} s^{-1}, which exceeds k_{ex} by only 1–2 orders of magnitude. These estimates are consistent with weakly bonded carbocation–molecule complexes that reside in flat potential wells.

Conclusions

In acid-catalyzed rearrangements of bicyclic and polycyclic alcohols or ethers, return of the departing ROH molecule to a neighboring position competes with capture of the intervening carbocations by the solvent R′OH. If the leaving group departs and returns on the same side of the carbon framework, return: exchange ratios ranging from 1 to 11.5 have been observed. Carbocations with extensive charge delocalization show less internal return than species with localized charges. Migration of the departing molecule to the opposite face (*endo* ⇌ *exo*) or to a β carbon is a minor process (return:exchange ~ 0.1). The internal return in favorable 1,2 alkyl shifts greatly exceeds that previously reported for racemization and allylic rearrangement. Our observations are interpreted in terms of ion–molecule (ion–dipole) complexes whose collapse competes with ligand exchange. Kinetic arguments suggest short lifetimes ($\leq 10^{-10}$ s) and low potential barriers (≤2 kcal/mol) for carbocation–molecule complexes.

(40) (a) Tanida, H.; Hata, Y.; Ikegami, S.; Ishitobi, H. *J. Am. Chem. Soc.* **1967**, *89*, 2928. (b) Lustgarten, R. K.; Lhomme, J.; Winstein, S. *J. Org. Chem.* **1972**, *37*, 1075. (c) Gassman, P. G.; Pascone, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 7801. (d) Fisher, R. D.; Seib, R. C.; Shiner, V. J., Jr.; Szele, I.; Tomic, M.; Sunko, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 2408.

(41) (a) Richard, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 1455. (b) Richard, J. P.; Amyes, T. L.; Bei, L.; Stubblefield, V. *J. Am. Chem. Soc.* **1990**, *112*, 9513. (c) Amyes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1867. (d) Amyes, T. L.; Richard, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 200.

(42) (a) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966. (b) Bartl, J.; Steenken, S.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 7710.

(43) Hertz, H. G. In *Water;* Franks, F., Ed.; Plenum Press: New York, 1973; Vol. 3, Chapter 7.

Experimental Section

General Methods. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 80 (Bruker WP 80) and 400 MHz (Bruker AM-400). ^{2}H (61.42 MHz) and ^{13}C (100.61 MHz) NMR spectra were recorded on the Bruker AM-400 spectrometer. Chemical shifts in $CDCl_3$ are reported in δ relative to tetramethylsilane unless otherwise indicated. Gas chromatography (GC) was performed by the use of a Siemens Sichromat equipped with glass capillary columns (length, stationary phase, and temperature for the individual mixtures are given below). Varian Aerograph instruments equipped with packed glass columns were used for preparative gas chromatography (PGC). High-pressure liquid chromatography with LDC (Milton Roy) chromatographs and refractometric detection. Mass spectra were obtained on a Varian MAT CH5 instrument (70 eV). Kinetic simulations were performed with a program kindly provided by Dr. R. Fink and Prof. Dr. W. R. Roth. The program uses a Marquardt routine in varying the rate contants to obtain the best fit of calculated and experimental product distributions.

[^{18}O]Bicyclo[3.1.1]heptan-2-ol (16). Bicyclo[3.1.1]heptan-2-one[44] (1.00 g, 9.08 mmol), anhydrous tetrahydrofuran (5 mL), $^{18}OH_2$ (2 mL, ca. 55% ^{18}O), and concentrated HCl (1 μL) were heated at reflux for 48 h. After being cooled to room temperature, the mixture was extracted with pentane. The organic phase was dried ($MgSO_4$) and concentrated by distillation (18 cm Vigreux column) to give 1.0 g of crude (≥96%, GC) [^{18}O]bicyclo[3.3.1]heptan-2-one. IR ($CDCl_3$): 1726 (C=O) and 1695 (C=^{18}O) cm^{-1}.

To sodium borohydride (280 mg, 7.4 mmol) in water (1.5 mL) was added at 0 °C [^{18}O]bicyclo[3.3.1]heptan-2-one (900 mg, 8.12 mmol) in methanol (0.6 mL). After the mixture was stirred for 12 h, acetic acid was added dropwise to destroy the excess $NaBH_4$. The mixture was extracted with ether (4 × 10 mL); the combined extracts were washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated in vacuo to give 820 mg (89.5%) of [^{18}O]**16**. ^{1}H NMR ($CDCl_3$): δ 1.03 (dd, J = 9.5 and 8.0 Hz, 1 H), 1.52−1.68 (m, 3 H), 1.78−1.87 (m, 2 H), 2.05 (s, OH), 2.08−2.17 (m, 2 H), 2.25−2.33 (m, 2 H), 4.06 (m, 1 H), in agreement with the spectrum reported for **16**.[44b] ^{13}C NMR ($CDCl_3$): δ 25.36 (CH_2), 26.44 (CH_2), 26.60 (CH_2), 33.73 (CH), 34.13 (CH_2), 41.53 (CH), 71.785 (CH-^{18}O), 71.812 (CH-^{16}O). The peaks of C-2 were too broad for an estimate of the ^{18}O content. Therefore, [^{18}O]**16** was converted to the 3,5-dinitrobenzoate[13b] (92%, mp 74 °C) which showed sharp peaks at δ 78.301 (55.2%) and 78.343 (44.8%).

[^{18}O]Bicyclo[3.1.1]heptan-2-ol ([^{18}O]**16**, 110 mg, 0.97 mmol) was dissolved in 11 mL of a 1.75 M solution of $HClO_4$ in dioxane−water (3:2). After having been heated at 60 °C for 1 h, the mixture was extracted with ether (20 mL). The extract was washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated in vacuo. The residue, containing bicyclo[2.2.1]heptan-*endo*-2-ol (**17**, 46.8%) and bicyclo[2.2.1]heptan-*exo*-2-ol (**18**, 53.2%), was treated with 3,5-dinitrobenzoyl chloride (225 mg, 0.976 mmol) in pyridine (1 mL). After being stirred at room temperature for 12 h, the mixture was dissolved in ether. The organic phase was washed with 10% aqueous HCl, aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated in vacuo. HPLC (Si 100-5, hexane−ether (9:1)) afforded **17**-ODNB,[45] mp 121−122 °C (^{13}C NMR ($CDCl_3$): δ 78.886 (C-2-^{18}O, 39.9%), 78.928 (C-2-^{16}O, 60.1%)) and **18**-ODNB,[46] mp 104−105 °C (^{13}C NMR ($CDCl_3$): δ 80.753 (C-2-^{16}O)).

Acidolyses of Bicyclo[3.1.1]heptan-2-ol (16), 2-Ethoxybicyclo[3.1.1]heptane (93), and 2-Methoxybicyclo[3.1.1]heptane (94). The substrates **16**,[44b] **93**,[13b] and **94**[45] (20−50 mg) were dissolved in 2−5 mL of methanolic (ethanolic) 1.75 N H_2SO_4. The mixtures were heated in a circulating water bath at 60 ± 0.1 °C. Aliquots (50−200 μL) were removed with a syringe through a septum and quenched by mixing with ether (0.5 mL) and $NaHCO_3$ (15−60 mg). The ether solutions were dried ($MgSO_4$) and analyzed by GC (58.5 M Edenol 1800, 70 °C for ethers, 140 °C for alcohols). Bicyclo[2.2.1]heptan-*endo*-2-ol (**17**) (Aldrich), bicyclo[2.2.1]heptan-*exo*-2-ol (**18**) (Aldrich), *endo*-2-methoxybicyclo[2.2.1]heptane (**19**)[46], *exo*-2-methoxybicyclo[2.2.1]-heptane (**20**),[46] *endo*-2-ethoxybicyclo[2.2.1]heptane (**91**),[13b] and *exo*-2-ethoxybicyclo[2.2.1]heptane (**92**)[13b] were identified by comparison with authentic samples.

Table 3. Acidolysis of Bicyclo[3.3.1]heptan-2-ol (**16**) in Methanol (1.75 N H_2SO_4, 60 °C)

time (h)	19	20	18	17	16	17:19
0	-	-	-	-	100	-
1	7.0	15.1	1.9	15.7	60.3	2.24
2	11.5	26.1	2.7	26.4	33.3	2.30
2.5	12.4	28.4	2.9	29.1	27.2	2.33
3.5	14.4	33.4	3.2	33.0	16.0	2.29
4.5	15.1	35.5	3.5	36.5	9.4	2.42
5.5	15.9	37.3	3.6	37.6	5.6	2.36

Table 4. Acidolysis of Bicyclo[2.2.1]heptan-*exo*-2-ol (**18**) in Methanol (1.75 N H_2SO_4, 60 °C)

time (h)	0	1	2	2.5	3.5	4.5	5.5	24
18	100	98.7	97.0	96.5	94.9	93.5	92.3	69.8
20	-	1.3	3.0	3.5	5.1	6.5	7.7	30.2

The product distributions obtained from **16** (Table 3) indicate that the ratio of *endo* products (**17**:**19**) was virtually constant whereas the ratio of *exo* products (**18**:**20**) decreased slightly. Under the conditions applied to **16**, the conversion of **18** into **20** was found to proceed with $k = (0.41 \pm 0.01) \times 10^{-5}$ s^{-1} (Table 4). This number was used in simulating the product distributions of Table 3 with rate constants (estimated error ±3%) for the competing reactions of **16** (Scheme 2). The ratios $k_{16,17}$:$k_{16,19}$ = 2.34 and $k_{16,18}$:$k_{16,20}$ = 0.103 agree closely with the average product ratios **17**:**19** = 2.32 and **18**:**20** = 0.103, respectively, from Table 3. We conclude that the slow conversion of **18** into **20** does not affect the results significantly. Therefore, no analogous corrections were applied to the acidolyses of **93** in methanol (Table 5S, supporting information) and of **94** in ethanol (Table 6S). The ratios of retention to exchange recorded in Table 1 were obtained from the average product distributions of Tables 5S and 6S.

Methanolyses of 6,6-Dimethybicyclo[3.1.1]heptan-2β-ol (21) and 6,6-Dimethylbicyclo[3.1.1]heptan-2α-ol (31). Reduction of 6,6-dimethylbicyclo[3.1.1]heptan-2-one (nopinone) with $LiAlH_4$ afforded 82% of **21**.[47,48] Heating of **21** (0.20 g, 1.4 mmol) with aluminum isopropoxide (285 mg, 1.4 mmol), isopropyl alcohol (1.7 mL), and acetone (0.02 mL) at 120 °C for 96 h yielded 102 mg (51%) of **31**.[47] In contrast to the reported procedures, purification of the alcohols was achieved by HPLC (Lichrosphere 100-5, pentane−ether (2:3)). The ^{13}C NMR spectra of **21** and **31** were in agreement with published data.[49] Methanolyses were performed as described for **16**. GC: 58.5 M Edenol, 120 °C, and 26.5 M PPG, 90 °C. Product distributions are recorded in Tables 7S and 8S. 3,3-Dimethylbicyclo[2.2.1]heptan-*endo*-2-ol (**23**),[17] 7,7-dimethylbicyclo[2.2.1]heptan-*exo*- and *endo*-2-ol (**28**, **33**),[17] 2-(cyclohex-3-en-1-yl)propan-2-ol (**35**),[47] and the methyl ethers **24**, **29**, **30**, **34**, and **36** were available from earlier work.[18]

(44) (a) Musso, H.; Naumann, K.; Grychtol, K. *Chem. Ber.* **1967**, *100*, 3614. (b) Grychtol, K.; Musso, H.; Oth, J. F. M. *Chem. Ber.* **1972**, *105*, 1798. (c) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron Lett.* **1975**, 3661. (d) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404.

(45) Siegfried, R. *Chem. Ber.* **1974**, *107*, 1472.

(46) Jensen, F. R.; Miller, J. J.; Cristol, S. J.; Beckley, R. S. *J. Org. Chem.* **1972**, *37*, 4341.

(47) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 3054.

(48) Coxon, J. M.; Garland, R. P.; Hartshorn, M. P. *Aust. J. Chem.* **1972**, *25*, 947.

(49) Coxon, J. M.; Hydes, G. J.; Steel, P. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1351.

Methanolysis of 2-Methylbicyclo[3.1.1]heptan-2-ol (43). By following the procedure described for **16**, samples of **43**[50] in 0.1 N methanolic H_2SO_4 were reacted at 25 °C. GC: 58.5 M Edenol, 80 → 100 °C. The products (Scheme 6, Table 9S) were identified by comparison with authentic samples of 2-methoxy-2-methylbicyclo[3.1.1]heptane (**44**),[23] *exo*-2-methoxy-*endo*-2-methylbicyclo[2.2.1]heptane (**45**),[23] 1-methylbicyclo[2.2.1]heptan-*endo*-2-ol (**46**),[51] and *endo*-2-methoxy-1-methylbicyclo[2.2.1]heptane (**47**).[23] The formation of **45** and **47** from **44** in 0.1 N methanolic H_2SO_4 was also monitored (Table 10S). The rate constants thus obtained were used in simulating the product distributions of Table 9S according to Scheme 6. The conversion of *endo*-2-methylbicyclo[2.2.1]heptan-*exo*-2-ol[52] into **45** (Table 10S) was found to be slow enough to exclude formation of the tertiary alcohol in significant amounts from **43**.

Methanolysis of *endo*-Tricyclo[5.2.1.0^{2,6}]decan-*exo*-8-ol (48). Hydroboration of *endo*-tricyclo[5.2.1.0^{2,6}]dec-8-ene afforded **48**,[53] mp 81 °C. ^{13}C NMR ($CDCl_3$): δ 26.20 (CH_2), 27.03 (CH_2), 28.36 (CH_2), 36.37 (CH_2), 39.21 (CH_2), 40.66 (CH), 43.62 (CH), 43.91 (CH), 49.69 (CH), 69.98 (CH). The methanolysis of **48** at 50 °C proceeded slowly ($k \approx 2.8 \times 10^{-6}$ s^{-1}) even with 5 N H_2SO_4 (Table 11S). At temperatures above 50 °C, a colorless solid (polymer?) precipitated and product distributions were not reproducible. GC analysis (43.5 M Edenol, 150 °C) indicated the formation of *exo*-tricyclo[5.2.1.0^{2,6}]decan-*exo*-8-ol (**51**),[53] *exo*-8-methoxy-*endo*-tricyclo[5.2.1.0^{2,6}]decane (**49**),[28] and *exo*-8-methoxy-*exo*-tricyclo[5.2.1.0^{2,6}]decane (**52**).[28] The reaction conditions applied to **48** slowly converted **51** into **52** (1770 min, 3%; 3000 min, 5%; 8685 min, 15.5%). Simulation of the product distributions was inconclusive, due to deviations from first-order kinetics, but the fractions of **51** and **52** extrapolated linearly to 60.0 and 35.9%, respectively, for $t \rightarrow 0$.

Methanolysis of Spiro(bicyclo[2.2.1]heptane-2,1′-cyclopropan)-*exo*-6-ol (53). The reaction of **53**[29b,30] in methanolic 1.75 N H_2SO_4 at 50 °C, producing tricyclo[4.2.1.0^{3,7}]nonan-3-ol (**56**)[29b, 30] and the analogous methyl ether **57**, was monitored by GC (22 M Marlophen, 80 °C) (Table 12S). The reaction conditions led to slow conversion of **56** into **57** (1.5% after 50 h) while **57** was found to be inert.

In a preparative run, **53** (1.5 g, 10.9 mmol) was dissolved in methanolic 1.75 N H_2SO_4 (140 mL). The mixture was heated at 30 °C for 24 h and then distributed between water and ether. The combined ether solutions were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated by distillation (15 cm Vigreux column). HPLC (Lichrosphere 100-5, hexane–ether (40:1)) of the residue afforded 1.1 g (67%) of 3-methoxytricyclo[4.2.1.0^{3,7}]nonane (**57**). ^{1}H NMR ($CDCl_3$): δ 0.79 (dm, J = 12 Hz, 1 H), 1.25 (dd, J = 12.0 and 2.2 Hz, 1 H), 1.29–1.38 (m, 2 H), 1.59 (dm, J = 9.6 Hz, 1 H), 1.70–1.80 (m, 2 H), 1.82–1.97 (m, 3 H), 2.10–2.15 (m, 2 H), 2.21 (dm, J = 5.1 Hz, 1 H), 3.19 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 28.45 (CH_2), 32.97 (CH_2), 35.87 (CH), 36.40 (CH), 37.75 (CH_2), 40.73 (CH_2), 45.73 (CH_2), 50.03 (CH), 50.93 (CH_3), 89.32 (C).

Methanolysis of *endo*-2-Methylbicyclo[3.2.0]heptan-*exo*-2-ol (62). The reaction was carried out in a fashion similar to that described for **16**. GC: 107 m Carbowax + KOH, 120 °C. At 40 °C, the exchange of OH for OMe (**62** → **66**) predominated (Table 13S). At 60 °C, conversion of *exo*-2-methoxy-*endo*-2-methylbicyclo[3.2.0]heptane (**62**) into the epimer **65** and into 7-methoxy-1-methylbicyclo[2.2.1]heptane (**64**) took place and 1-methylbicyclo[2.2.1]heptan-7-ol (**63**) increased slowly, presumably due to cleavage of **64**. Samples of all products were available from previous work.[32,33]

Solvolysis of 1,*endo*-2-Dimethylbicyclo[3.2.0]hept-*exo*-2-yl *p*-Nitrobenzoate (67). 1,*endo*-2-Dimethylbicyclo[3.2.0]heptan-*exo*-2-ol (**69**)[32] (50 mg, 0.35 mmol) was dissolved in anhydrous THF (1 mL). The solution was purged with N_2, *n*-butyllithium (1.6 M in hexane, 0.31 mL) was added, and the mixture was stirred for 30 min. After addition of *p*-nitrobenzoyl chloride (74 mg, 0.4 mmol) in THF (0.5 mL), the reaction mixture was refluxed for 1 h and then allowed to cool to room temperature. Ether was added, the solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. HPLC (silica gel, hexane–ether (3:2)) of the residue afforded 70 mg (69%) of **67**, mp 104 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3 H), 1.55 (s, 3 H), 1.6–2.4 (m, 8 H), 2.85 (m, 1 H), 8.15 (m, 4 H). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.27; H, 6.81; N, 4.89.

The *p*-nitrobenzoate **67** (20 mg, 0.069 mmol), dioxane–water (7:3, 2 mL), and 2,6-dimethylpyridine (15 mg, 0.14 mmol) were heated at 80 °C for 3 d. After conventional workup, GC (29 M OV1, 90 °C) showed 5.5% of **69** and 94.5% of 1,7-dimethylbicyclo[2.2.1]heptan-7-ol (**68**).[32]

Methanolyses of 1,*endo*-2-Dimethylbicyclo[3.2.0]heptan-*exo*-2-ol (69) and 1,*exo*-2-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (70). In methanolic 1.75 N H_2SO_4 at 25 °C, **69**[32] afforded 1,7-dimethylbicyclo[2.2.1]heptan-7-ol (**68**)[32] and 7-methoxy-1,7-dimethylbicyclo[2.2.1]heptane (**71**) in a 92:8 ratio with $k \approx 3.2 \times 10^{-4}$ s^{-1} (Table 15S). Under these conditions, *exo*-2-methoxy-1,*endo*-2-dimethylbicyclo[3.2.0]heptane (**72**) rearranged to give **71** at a rate ($k \approx 6.1 \times 10^{-4}$ s^{-1}) faster than that of **69** (Table 16S). Methylation of the appropriate alcohols with NaH–MeI (THF, reflux) provided samples of **71** (^{1}H NMR ($CDCl_3$): δ 0.85 (s, 3 H), 1.10 (s, 3 H), 1.10–2.05 (m, 9 H), 3.21 (s, 3 H)) and **72** (^{1}H NMR ($CDCl_3$): δ 0.98 (s, 3 H), 1.10 (s, 3 H), 1.1–2.4 (m, 9 H), 3.08 (s, 3 H)).

Addition of methyllithium to 1-methylbicyclo[3.2.0]heptan-2-one[32] afforded 89% of 1,*exo*-2-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (**70**). ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 3 H), 1.12 (s, 3 H), 1.22 (s, 1 H), 1.2–2.5 (m, 9 H). When **70** was treated with 1.75 N H_2SO_4 at 50 °C for 1 h, 3.5% of **68**, 31.5% of **71**, and 65% of unreacted **70** were obtained.

Acidolysis of [^{18}O]Tricyclo[4.3.1.0^{3,8}]decan-*exo*-4-ol (76-^{18}OH). Tricyclo[4.3.1.0^{3,8}]decan-4-one[54] (900 mg, 6 mmol), anhydrous THF (3 mL), $^{18}OH_2$ (2 mL, ca. 55% ^{18}O), and concentrated HCl (1 μL) were heated at 80 °C for 12 h. After cooling to room temperature, the mixture was extracted with pentane. The extracts were dried ($MgSO_4$) and concentrated to give 850 mg (94%) of crude [^{18}O]tricyclo[4.3.1.0^{3,8}]decan-4-one. IR ($CDCl_3$): 1721 (C=O) and 1686 (C=^{18}O) cm^{-1}. ^{13}C NMR ($CDCl_3$): δ 216.901 (C=^{18}O) and 216.953 (C=O).

Reduction of the ketone with $LiAlH_4$, according to the published procedure,[35a] afforded 34% of **76**-^{18}OH and 58% of the *endo* isomer which were separated by chromatography (silica gel, hexane–ether (3:2)). The ^{13}C NMR spectrum of **76**-^{18}OH was not sufficiently resolved for a precise ^{18}O analysis. Therefore, we prepared the 3,5-dinitrobenzoate[35a] (85%, mp 142 °C), whose ^{13}C NMR spectrum showed excellent resolution of the peaks at δ 76.749 (C-4-^{18}O, 54.5%) and 76.793 (C-4-^{16}O, 45.4%).

The rearrangement of **76**-^{18}OH (50 mg, 0.33 mmol) was carried out in a 1.75 M solution of $HClO_4$ in dioxane–water (3:2, 60 °C, 2.5 h). The [^{18}O]tricyclo[3.3.1.1^{3,7}]decan-2-ol (**77**-^{18}OH) thus produced was converted to the *p*-toluenesulfinate for an improved analysis. The residue obtained by conventional workup of the acidolysis mixture (see [^{18}O]**16**) was dissolved in pyridine (1 mL), and *p*-toluenesulfinyl chloride (63 mg, 0.36 mmol) was added. The reaction mixture was stirred at 25 °C for 16 h and then partitioned between ether and 10% HCl. The organic phase was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by HPLC (Lichrosphere 60-5, hexane–ether (9:1)) to give 76 mg (79%) of **77**-^{18}OSO-$C_6H_4CH_3$, mp 96 °C. ^{13}C NMR ($CDCl_3$): δ 21.41 (CH_3), 26.73 (CH), 27.03 (CH), 31.17 (CH_2), 31.22 (CH_2), 33.44 (CH), 33.61 (CH), 36.37 (CH_2), 36.48 (CH_2), 37.19 (CH_2), 81.885 (C-2-^{18}O, 39.2%), 81.925 (C-2-^{16}O, 60.8%), 124.91 (CH), 129.46 (CH), 142.18 (C), 142.91 (C). The unlabeled 2-adamantyl *p*-toluenesulfinate has been reported, mp 95–96 °C.[55] An analogous rearrangement of **76**-^{18}OH with 1.75 M $HClO_4$ in acetone–water (3:2, 60 °C, 30 min) gave **77**-OH containing 40.8% ^{18}O.

Acidolyses of Tricyclo[4.3.1.0^{3,8}]decan-*exo*-4-ol (76-OH), *exo*-4-Methoxytricyclo[4.3.1.0^{3,8}]decane (76-OMe), and *exo*-4-Ethoxytricyclo[4.3.1.0^{3,8}]decane (76-OEt). Methylation of **76**-OH (304 mg, 2 mmol) with sodium hydride (144 mg, 6 mmol) and methyl iodide (852 mg, 6 mmol) in THF (8 mL) at 45 °C for 2 h afforded 160 mg (48%) of **76**-OMe. ^{1}H NMR ($CDCl_3$): δ 1.24–1.36 (m, 3 H), 1.43 (dd, J =

(50) Kirmse, W.; Siegfried, R. *Chem. Ber.* **1972**, *105*, 2754.
(51) Beckmann, S.; Mezger, R. *Chem. Ber.* **1956**, *89*, 2783.
(52) Brown, H. C.; Kawakami, J. H.; Ikegami, S. *J. Am. Chem. Soc.* **1967**, *89*, 1525.
(53) Cristol, S. J.; Seifert, W. K.; Soloway, S. B. *J. Am. Chem. Soc.* **1960**, *82*, 2351.
(54) Majerski, Z.; Hamersak, Z. *Org. Synth.* **1980**, *59*, 147.
(55) Lee, C.; Field, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1989**, *45*, 35.

10.9 and 3.0 Hz, 1 H), 1.60 (m, 1 H), 1.66−1.97 (m, 6 H), 2.09 (m, 1 H), 2.15 (q, J = 6.5 Hz, 1 H), 2.52 (m, 1 H), 3.29 (s, 3 H), 3.57 (dd, J = 6.5 and 3.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.44 (CH), 32.14 (CH_2), 32.26 (CH), 34.67 (CH_2), 35.22 (CH_2), 35.42 (CH), 37.60 (CH), 39.52 (CH_2), 42.39 (CH_2), 55.90 (CH_3), 79.67 (CH). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.37; H, 10.83. Analogous ethylation of **76**-OH with NaH−EtI (85 °C, 2 h) gave 210 mg (58%) of **76**-OEt. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 3 H), 1.25−1.36 (m, 3 H), 1.43 (dd, J = 11.0 and 2.8 Hz, 1 H), 1.60 (m, 1 H), 1.65−1.77 (m, 2 H), 1.82−1.93 (m, 3 H), 1.99 (m, 1 H), 2.09 (m, 1 H), 2.17 (q, J = 6.5 Hz, 1 H), 2.51 (m, 1 H), 3.44 (m, 2 H), 3.67 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 15.75 (CH_3), 27.48 (CH), 32.18 (CH_2), 32.38 (CH), 35.28 (CH_2), 35.33 (CH_2), 35.44 (CH), 37.95 (CH), 39.60 (CH_2), 42.40 (CH_2), 63.16 (CH_2), 77.42 (CH). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.83; H, 11.17.

Acidolyses of **76**-OH in methanol (Table 17S), **76**-OEt in methanol (Table 18S), and **76**-OMe in ethanol (Table 19S), as described above (see **16**), gave virtually constant ratios of **77**-OH:**77**-OMe[56] and **77**-OMe:**77**-OEt,[57] respectively (GC: 40 M OV 17, 130 °C).

Methanolyses of *endo*-4-Methyltricyclo[4.3.1.0^{3,8}]decan-*exo*-4-ol (79) and *exo*-4-Methyltricyclo[4.3.1.0^{3,8}]decan-*endo*-4-ol (80).[35b,39] Methanolyses were performed at 25 °C, using 0.1 N H_2SO_4 for **79** (Table 20S) and 1.75 N H_2SO_4 for **80** (Table 21S). GC: 58.5 M Edenol, 140 °C. Methylation (NaH−CH_3I, THF, 45 °C, 2 h) of the appropriate alcohols afforded *endo*-4-methoxy-*exo*-4-methyltricyclo-[4.3.1.0^{3,8}]decane (**82**). ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 3 H), 1.1−2.3 (m, 14 H), 3.17 (s, 3 H), *exo*-4-methoxy-*endo*-4-methyltricyclo-[4.3.1.0^{3,8}]decane (**83**). ^{1}H NMR ($CDCl_3$): δ 1.19 (s, 3 H), 1.1−2.4 (m, 14 H), 3.17 (s, 3 H), and 2-methoxy-1-methyltricyclo[3.3.1.1^{3,7}]-decane (**84**). ^{1}H NMR ($CDCl_3$): δ 0.81 (s, 3 H), 0.95−2.2 (m, 13 H), 2.88 (br.s, 1 H), 3.30 (s, 3 H). The methanolysis of **83** in methanolic 0.1 N H_2SO_4 (Table 22S) provided rate constants which were used to simulate the product distributions recorded in Tables 20S and 21S (see Scheme 12).

Acknowledgment. Financial support from the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Tables 5−22, reporting product distributions of acidolyses and reference reactions (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA952377O

(56) (a) Duddeck, H.; Hollowood, F.; Karim, A.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 360. (b) Kropp, P. J.; Adkins, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 2709.

(57) Kropp, P. J.; Gibson, J. R.; Snyder, J. J.; Poindexter, G. S. *Tetrahedron Lett.* **1978**, 207.