The 9-Homocubyl Cation

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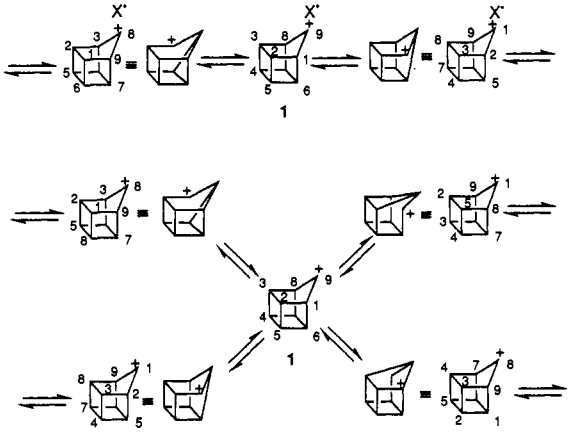
Abstract: The solvolysis of 9-homocubyl triflate-9-*d* (**8**-9-*d*), the deamination of 9-homocubylammonium chloride-9-*d* (**15**-9-*d*), and most likely also the fluorodeiodination of 9-homocubyl iodide-9-*d* (**13**-9-*d*) take place in a highly stereoselective manner. Both deamination and solvolysis products have the deuterium label scrambled only over one face of the homocubyl cage (*syn* to the substituent) and are formed with retention at C(9). In more nucleophilic media, the solvolysis of **8**-9-*d* loses the stereoselectivitiy due to partial S_N2 substitution, and under nonionizing, very nucleophilic conditions, a pure S_N2 displacement of the triflate takes place. NMR experiments show that the S_N1 reaction of **8**-9-*d* proceeds *via* repeated internal return of the triflate leaving group. A similar mechanism involving internal return in the deamination and fluorodeiodination reactions is unconvincing because of the low nucleophilicity (N_2) or the instability (IF_2^-) of the corresponding leaving groups. The observed preservation of the steric information is best explained by a nonclassical ground-state structure, **1b**, for the homocubyl cation which additionally undergoes rapid stereoselective automerizations. No evidence was found for a degenerate cation involving all nine homocubyl positions as had been proposed earlier.[1a]

Introduction

The cation obtained by formally adding $(CH)^+$ to a regular polyhedron is expected to be fluxional,[1a] since every possible 1,2 Wagner–Meerwein shift leads to an identical cation. This was previously demonstrated for the homocubyl cation (**1**)[1-4] and the homotetrahedryl[5] and homododecahedryl cations.[6] All of the previous experimental work on the 9-homocubyl cation was reported simultaneously in 1967 by the groups of Schleyer[1a] and Pettit.[4] Two possible solvolysis mechanisms were considered. Mechanism A involves a stereoselective automerization process in which only the carbon–carbon bonds *trans* to the leaving group undergo a Wagner–Meerwein shift; the five positions become eventually undistinguishable (eq 1a). Mechanism B involves a C_{2v} symmetrical cation in which all four adjacent bonds can migrate and all nine positions become equivalent for an indefinite number of carbon bond shifts (eq 1b). In Schleyer's experiment,[1a] the solvolysis of 9-homocubyl tosylate-9-*d* in refluxing formic acid gave 9-homocubyl formate containing 10% deuterium at C(9). Mechanism A predicts that the deuterium label remaining at C(9) must always be equal to or larger than 20% because a stereoselective reaction distributes the label over five positions. On the other hand, mechanism B predicts a complete degeneracy involving all nine positions if the number of rearrangements is large. As the experimental measurement was 10% deuterium at C(9), the authors concluded that mechanism B had occurred. In a similar experiment, namely by acetolysis of 3,4,5,6-d_4 and 2,3,6,7-d_4 9-homocubyl tosylates, Pettit and co-workers found, in contrast to Schleyer, that the reaction was "clearly stereoselective if not entirely stereospecific".[4,7] A S_N2-type displacement of the leaving group was not considered at the time, but as will be seen, it is in fact the predominant mechanism in nucleophilic media.



Interest in the homocubyl cation **1** was recently renewed in connection with studies on the unique homocubene–homocubylidene (**2**–**3**) system.[8,9] If a homocubene or homocubylidene precursor is generated in the presence of methanol-*O*-*d*, the two isotopomeric ethers **4**-1-*d* and **4**-9-*d* are obtained.[9] A first explanation to account for this observation is that homocubylidene (**3**) and homocubene (**2**) react with methanol-*O*-*d* in a concerted fashion or *via* an ylide intermediate to give each of the corresponding methyl ethers. In this case, ether **4**-9-*d* results from the reaction of **3** with methanol-*O*-*d* and ether **4**-1-*d* from the reaction of **2** with methanol-*O*-*d*. In a second explanation,

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(7) Apparently, Brousard and Pettit found later that the acetolysis takes place under retention of configuration, but these results have never been published.[5] Broussard, J. A.; Pettit, R. Unpublished results, 1970. Broussard, J. A. Dissertation, University of Texas at Austin, 1970.

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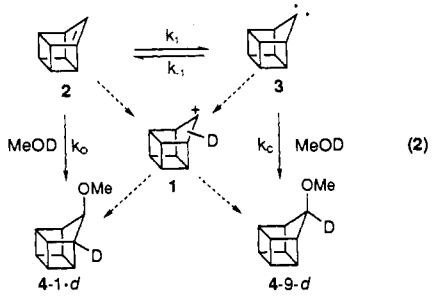
homocubylidene (**3**) is protonated (deuteronated) by methanol-*O-d*, giving the homocubyl cation-9-*d* (**1**-9-*d*) which either reacts directly with methanol to give ether **4**-9-*d* or rearranges to **1**-1-*d* and then reacts with methanol to produce **4**-1-*d*. In this case, both isotopomeric methyl ethers **4**-1-*d* and **4**-9-*d* could arise from homocubylidene. Therefore, the question is whether or not homocubylidene is protonated during the reaction with methanol.



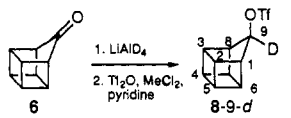
(2)

Kirmse has shown that carbenes leading to particularly stabilized carbocations are protonated by alcohols (e.g., tropylidene is protonated to tropyllium).[10a-c] On the other hand, electrophilic carbenes form ylide intermediates with alcohols which are subsequently protonated to the corresponding ethers. But how about alkylcarbenes like homocubylidene which if protonated do not result in particularly stabilized carbocations and are not very electrophilic either? In the present work, this problem is addressed not by further studying the homocubylidene-homocubene system but rather by trying to understand the nature of the homocubyl cation **1**. As will be seen, the chemistry of **1** is in fact far richer than previously thought.

Results

Solvolysis of 9-Homocubyl Triflate-9-*d*. At the time when the original work on the homocubyl cation was done, the triflate leaving group was not known. Therefore, the solvolytic conditions were drastic and only very ionizing solvents could be used. In order to resolve the discrepancy between the results reported by Pettit[4] and Schleyer,[1] solvolysis experiments were undertaken employing 9-homocubyl triflate **8**-9-*d* instead of the tosylate.

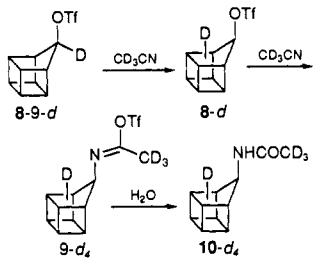
Homocubanone (**6**) is the parent for all 9-homocubanes. It was readily synthesized from 1-bromohomocubanone ethylene acetal[11] in a similar way as previously reported.[1a,12,13] 9-Homocubyl triflate-9-*d* (**8**-9-*d*) was synthesized from homocubanone by reduction and esterification (eq 3). In the ^{1}H NMR spectrum



(3)

of **8**-9-*d*, the protons of the homocubyl skeleton appear at 3.65, 3.46, 3.39, and 3.30 ppm as four sets of multiplets each integrating for two protons. The coupling patterns of the multiplets at 3.65 and 3.39 ppm are identical and therefore belong to H(2,3) and H(6,7). It was essential to assign H(2,3) and H(6,7) multiplets specifically because this would allow us to differentiate between the two faces of the homocubyl skeleton (*syn* or *anti* to the substituent). Comparing the H(2,3) and H(6,7) chemical shifts in homocubane[12,13] (3.25 ppm, 4H), homocubanol **7** (3.27 ppm, 2H and 3.57 ppm, 2H), and homocubanone ethylene glycol ketal (**5**)[12] (3.56 ppm, 4H), it became evident that the proximity of the oxygen (approximately 3 Å, PCMODEL 4.2) is shifting the H(2,3) multiplet downfield by 0.3 ppm. This assignment was confirmed by the addition of shift reagent to homocubanol **7**,[14] which preferentially moves the signals of the hydrogens on the *syn* face downfield. The assignment was generalized to all 9-heteroatom-substituted homocubanes.

Triflate **8**-9-*d* was solvolyzed in methanol, acetonitrile, formic acid, 25% aqueous acetic acid, and hexafluoro-2-propanol–acetonitrile (Table I). In acetonitrile, **8**-9-*d* solvolyzes, undergoing a Ritter reaction (eq 4) to give amide **10**-d_4. In the complete



(4)

absence of water, a different product, **9**-d_4, is formed which upon addition of water is immediately converted to **10**-d_4. For reasons not understood, the solvolysis in neat hexafluoro-2-propanol even at 0 °C led to a complex mixture of cage-opened compounds. This could be prevented by adding 10% by wt acetonitrile to the hexafluoro-2-propanol. The other solvolysis experiments led to the corresponding solvent-derived products. The deuterium distributions in the products were determined by ^{2}H NMR[15] with the following results: In all products obtained from the solvolysis of **8**-9-*d*, the label was scrambled to different extents but only over five positions of the nine homocubyl sites (Table I). Deuterium was incorporated at positions 2 and 3 (*syn* to the substituent) but not in positions 6 and 7 (*anti* to the substituent), which is in agreement with Pettit's results.[4] The only economic explanation for the observed stereoselective label distribution is that, within experimental error, only the C–C bonds *trans* to the leaving group undergo Wagner–Meerwein shifts.

The experiments revealed that the extent of label scrambling in the solvolysis products was highly dependent on the nucleophilicity of the solvent. The extent of scrambling in amide **10**-d_4 from the solvolysis of **8**-9-*d* in acetonitrile and in formate **11**-*d* from the solvolysis in formic acid was very similar, despite the fact that formic acid is a much more ionizing solvent (acetonitrile $\epsilon = 37$,[16a] formic acid $\epsilon = 58$[16b]). Interestingly, the scrambling in these two solvents is temperature *in*dependent[17] (Table I, entries 4–7). Methyl ether **4**-*d* obtained from the solvolysis in methanol ($\epsilon = 32$)[16b] (Table I, entries 1 and 2) showed a significantly reduced and strongly temperature-dependent extent of scrambling. The label in the isolated hexafluoroisopropyl ether **12**-*d* (Table I, entry 9) was more scrambled than that in **10**-d_4 or **11**-*d*.

Internal Return of the Triflate. Pettit reported that the label in unsolvolyzed tosylate, isolated from the reaction mixture, had already been scrambled.[4] When the solvolysis reaction of **8**-9-*d* in acetonitrile-d_3 was followed by ^{1}H NMR, the following

(10) (a) Kirmse, W.; Kilian, J. *J. Am. Chem. Soc.* **1990**, *112*, 6399. (b) Krisme, W.; Van Chiem, P.; Henning, P. G. *J. Am. Chem. Soc.* **1983**, *105*, 1695. (c) Krisme, W.; Loosen, K.; Sluma, H.-D. *J. Am. Chem. Soc.* **1981**, *103*, 5935.

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(12) Hamlin, J. E.; Toyne, K. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2731.

(13) Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Org. Chem.* **1968**, *33*, 1454.

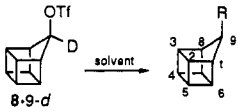
(14) The relative shfits are as follows: 5.50 (C(9)–H), 3.08 (C(1,8)–H), 2.38 (C(2,3)–H), 1.15 (C(7,6)–H), 1.00 (C(4,5)–H) ppm, Eu[(ButCO)$_2$CH)]$_3$.

(15) The relative integration of the deuterium signals (Table I) was reproducible to ±2% in repeated experiments.

(16) (a) *CRC Handbook of Chemistry and Physics*, 68th ed.; CRC Press Inc.: Boca Raton, FL, 1987. (b) Reichardt, Ch. *Solvents and Solvent Effects in Organic Chemistry*; 2nd ed; Verlag Chemie: New York, 1988; p 408.

(17) This observation seems to violate classical transition-state theory. The extent of scrambling in the solvolysis products is determined by the rate of automerization versus the rate of solvolysis. The ratio of these two rates should change with temperature and so should the label distribution. For a discussion, see: Carpenter, B. K. *Acc. Chem. Res.* **1992**, *25*, 520.

Table I. Deuterium Distribution in Solvolysis Products of 9-Homocubyl Triflate-9-*d* (**8**-9-*d*)

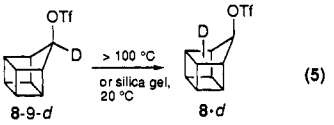


entry	solvent	product, R	compd no.	T (°C)	$t_{1/2}$ (min)	% D at position, ±2%[a] 9	1,8	2,3	4,5,6,7
1	MeOH	OMe	**4**-*d*	25	130	45	44	11	*b*
2	MeOH	OMe	**4**-*d*	65		39	45	16	*b*
3	MeOH, 12% MeONa	OMe	**4**-*d*	25		92	8	0	0
4	HCOOH	OCHO	**11**-*d*	25		28	45	27	0
5	HCOOH	OCHO	**11**-*d*	90	≪5	28	45	27	0
6	CD_3CN	$NHCOCD_3$	**10**-d_4	25	140	25	46	29	0
7	CD_3CN	$NHCOCD_3$	**10**-d_4	65	<5	25	46	29	0
8	CH_3COOH, 25% H_2O	OH	**7**-*d*	25		30	43	27	0
9	$(CF_3)CDOD$, 10% CD_3CN	$OCD(CF_3)_2$	**12**-d_2	25	≪5	24	43	33	0

[a] On the basis of reproducibility of the experiment. [b] It cannot be excluded that there is ≤5% D at C(6,7). No deuterium was found at C(4,5).

observation was made. The C(9) ^1H NMR signal at 5.32 ppm[18] of triflate **8**-9-*d* was, due to the labeling, hardly detectable in the beginning of the experiment, but it grew and passed through a maximum as the solvolysis proceeded. This demonstrates that, as in the case of the tosylate, the deuterium label is scrambled before the triflate group is replaced by the solvent molecule. Thus, the scrambling process in the solvolysis of the triflate and the tosylate happens *via* internal return of the leaving group (eq 4).

Exposure of triflate **8**-9-*d* to silica gel or, to a lesser extent, Celite or magnesium sulfate *catalyzes* a nonsolvolytic scrambling process to give **8**-*d*. Additionally, triflate **8**-9-*d* exhibits thermally induced fluxional behavior a few degrees below its decomposition temperature. The amount of deuterium at C(9) at 105 °C in toluene-d_8 dropped to 40% within 25 min, triflate **8**-*d* was isolated, and the deuterium distribution was measured by ^2H NMR (eq 5). Both the catalytic and thermal nonsolvolytic scrambling

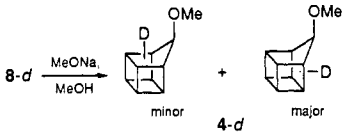


(5)

processes are stereoselective. Since the label in the unsolvolyzed triflate is scrambled *syn* to the substituent, the internal return must occur with retention of the configuration at C(9). Therefore, the overall solvolysis also proceeds with *retention* at C(9) because the label in the solvolysis product still remains on the *syn* face.

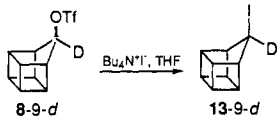
S_N2 Mechanism. The scrambling in the solvolysis clearly depends on the nucleophilicity of the solvent. In order to probe the influence of the substantially increased nucleophilicity of the medium, triflate **8**-9-*d* was solvolyzed in 12% methanolic NaOMe (Table I, entry 3). Indeed, very little scrambling was observed. The smaller the extent of scrambling, the more difficult it is to determine the stereochemistry of the process. If the deuterium is spread only over positions 1, 8, and 9, there is no way to distinguish a stereoselective process from a nonselective process because the paths can be differentiated only after the second carbon bond shift. In order to determine the extent of stereoselectivity, the solvolysis was repeated using triflate in which the label was prescrambled on one face (20% at positions 2 and 3) by stirring **8**-9-*d* with silica gel in chloroform for 1 h. From the ^2H NMR, it was evident that the label of the product was preferentially spread over the face *anti* to the methoxy group, suggesting that the configuration at C(9) had been mostly *inverted* (eq 6). Therefore, 9-homocubyl triflate undergoes S_N2 substitution in the presence of strong nucleophiles like sodium methoxide.

(18) The signal was identified by comparison with the unlabeled compound **8**.



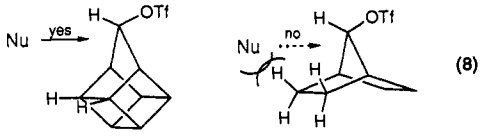
(6)

The solvent nucleophilicity has a 2-fold influence on the reaction. First, it limits the number of rearrangements in the S_N1 reaction by replacing the triflate counterion. Under more nucleophilic (and less ionizing) conditions, the steric information is partially lost during the solvolysis. Consequently, under nonionizing conditions and in the presence of strong nucleophiles, a pure S_N2 displacement takes place. Triflate **8**-9-*d* can readily be converted to iodide **13**-9-*d* without any scrambling of the label (eq 7).



(7)

The fact that 9-homocubyl triflate undergoes S_N2 substitution is in sharp contrast to the behavior of 7-norbornyl triflate, which can be seen as a 9-homocubyl triflate substructure and undergoes S_N2 reactions only under drastic conditions.[19] The differing reactivities can be explained by comparing the geometry of the two molecules (eq 8). The norbornyl system is flatter (angle



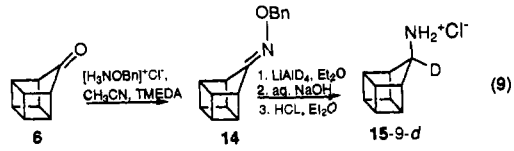
(8)

[C(2) C(1) C(6)] = 109°, PCMODEL 4.2) than the corresponding part of the homocubyl skeleton (angle [C(2) C(1) C(6) = 88°). Therefore, the norbornyl hydrogens at positions 2 and 3 are closer to the bridging carbon (distance H(2)–C(7) = 2.8 Å) and shield it more efficiently than the corresponding homocubyl hydrogens at C(2,3) (distance H(2)–C(9) = 3.3 Å).

Deamination of 9-Homocubylammonium Chloride-9-*d*. The triflate anion is a very weak nucleophile; nevertheless, during the solvolysis of triflate **8**, the leaving group can return several times. But, what happens if the leaving group is even less nucleophilic, as is the case in the deamination reaction?

9-Homocubylammonium chloride-9-*d* (**15**-9-*d*) was synthesized from homocubanone (**6**) by reaction with *O*-benzylhydroxylammonium chloride to give oxime **14** which was reduced with lithium aluminum deuteride[20] (eq 9). 9-Homocubylammonium chloride

(19) Creary, X.; McDonald, S. R. *J. Org. Chem.* **1985**, *50*, 474.
(20) Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717.



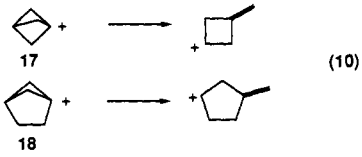
15-9-*d* was treated with 4 equiv of $NaNO_2$ in aqueous acetic acid for 24 h, which resulted in a mixture of homocubanol **7**-*d* and its acetate (Scheme I). The mixture was treated with sodium hydroxide in methanol, and **7**-*d* was isolated in 70% yield from the ammonium salt **15**. In order to obtain a direct comparison, a sample of triflate **8**-9-*d* was solvolyzed under the same conditions (Table I, entry 8).

The extent of scrambling in **7**-*d* isolated from the deamination reaction is, as expected, lowered: C(9) 49%, C(1,8) 44%, and *C(2,3) 7%* (Scheme I). Surprisingly, there was significant deuterium incorporation at positions 2 and 3, but no deuterium was found at positions 6 and 7. A control experiment showed that the deamination products do not undergo rearrangements under the reaction conditions. The deamination is therefore again highly stereoselective.

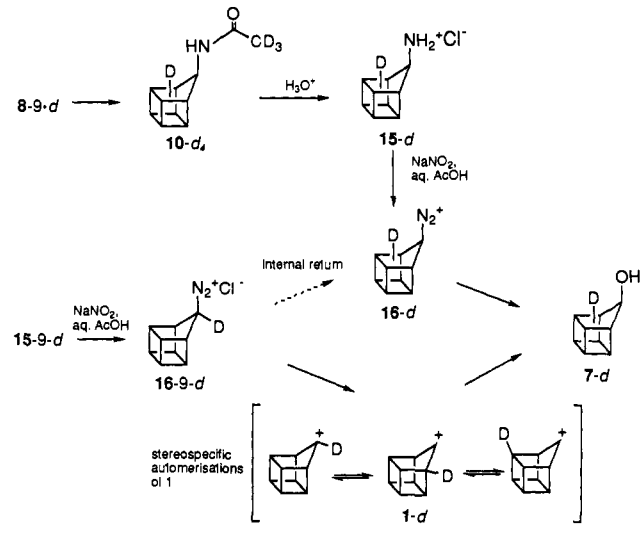
The fact that the label in the product is scrambled only over the *syn* face of the homocubyl cage establishes that the carbon–carbon shifts in **1** and the final trapping by the solvent occur in a stereoselective manner. However, it cannot be differentiated whether or not the initial formation of the cation is also stereoselective. Therefore, stereoselective scrambling alone does not establish the stereochemistry at the C(9) position. For this reason, the deamination was repeated with 9-homocubylammonium chloride **15**-*d* with the label prescrambled *syn* to the ammonium group. This compound was obtained by hydrolysis of amide **10**-d_4, which was a product from the triflate solvolysis experiments (Scheme I). The product from the deamination of **15**-*d* had the label scrambled again only *syn* to the substituent, which proves that the configuration at C(9) is *retained.*

There are two possible explanations for this behavior (Scheme I). First, the cation **1** could recapture the nitrogen, and the same mechanistic considerations would apply as for the triflate solvolysis. Second, the cation **1** could in fact undergo two or more stereoselective Wagner–Meerwein shifts without internal return. The latter explanation requires the assumption that **1** has geometry which allows it to maintain the steric information throughout the rearrangement. In this case, the symmetry of **1** would have to be lower than C_{2v} at all points along the reaction coordinate.

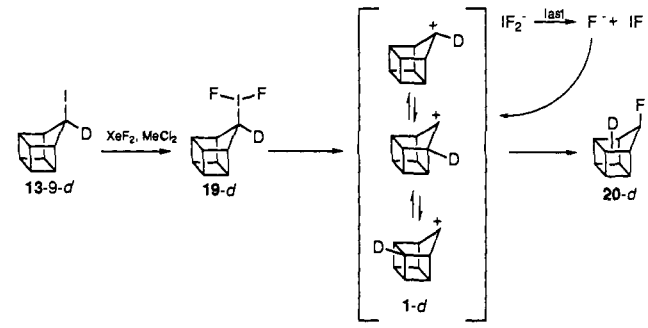
Fluorodeiodination of 9-Homocubyl Iodide-9-*d*. Della and Head[21] recently reported that bridgehead iodides reacted with xenon fluoride to produce the corresponding bridgehead fluorides. The mechanism is believed to proceed *via* the bridgehead cations: xenon fluoride fluorinates the iodide to the difluoroiodonium group which is a very strong nucleofuge. The IF_2^- group is unstable and quickly loses fluoride, which then recombines with the cation to form the fluoro compounds. The substrates which were successfully converted to the corresponding fluorides also included bicyclo[1.1.1]pent-1-yl iodide and bicyclo[1.1.2]hex-1-yl iodide. Both intermediate cations **17** and **18** are subject to facile rearrangement[22] (eq 10) and have never been trapped before by a nucleophile in their unrearranged form. This implies that the lifetime of the cations generated by fluorodeiodination is short. Therefore, this method might allow the trapping of the homocubyl cation in a very early stage after little or no rearrangement. Additionally, an internal return of the leaving group should be prevented because of its instability. Therefore, a scrambling mechanism *via* internal return, as observed in the solvolysis of **8**-9-*d*, seems unlikely.



Scheme I



Scheme II



9-Homocubyl iodide-9-*d* (**13**-9-*d*) was, as mentioned earlier, prepared from triflate **8** and tetrabutylammonium iodide in THF (eq 7). No scrambling of the label could be detected by NMR. The fluorodeiodination was carried out according to the procedure by Della and Head (Scheme II). 9-Homocubyl fluoride **20**-*d* could be isolated and purified in modest yield. Surprisingly, the ^2H NMR of fluoride **20**-*d* revealed an even higher extent of label scrambling than that in the alcohol **7** from the deamination reaction: C(9) 28%, C(1,8,6,7) 47%, and *C(2,3) 25%.* Unfortunately, it was not possible to assign the stereochemistry of the process because of overlapping NMR signals. However, the pattern of the deuterium incorporation (C(2,3) 25%) suggests again a stereoselective mechanism.

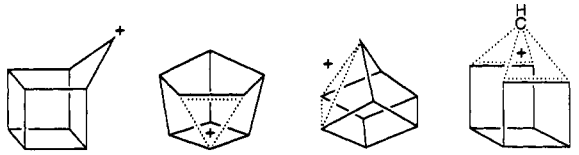
As a side result, this experiment clearly confirms that the fluorodeiodination involves a cationic intermediate and is not a radical reaction or a concerted rearrangement.

Discussion

The reaction rate measured by Schleyer[1a] for the acetolysis of 9-homocubyl tosylate is much higher than that predicted by the Foote–Schleyer correlation[23] or molecular mechanics,[24] suggesting that neighboring carbon participation plays a role in the solvolytic

(21) Della, E. W.; Head, N. J. *J. Org. Chem.* **1992**, *57*, 2850.
(22) (a) Wiberg, K. B.; Williams, V. Z., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 3373. (b) Della, E. W.; Taylor, D. K. *Aust. J. Chem.* **1990**, *43*, 945 and references herein.
(23) (a) Foote, C. S. *J. Am. Chem. Soc.* **1964**, *86*, 1853. (b) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1964**, *86*, 1854, 1856.
(24) Smith, M. R.; Harris, J. M. *J. Org. Chem.* **1978**, *43*, 3588.

process.[25] Since the S_N1 solvolysis of **8-9-*d*** is stereoselective, two of the four neighboring carbon bonds must migrate preferentially or even exclusively. The fact that the scrambling of the label in the solvolysis of triflate **8-9-*d*** occurs *syn* (positions 2 and 3) to the substituent and with retention at C(9) can only be rationalized by assuming that bonds *trans* to the leaving group migrate. Since the solvolysis and the deamination proceed with retention, the geometry of the cation in the ion pair must be substantially different from that of the triflate. In fact, one face of the molecule must be effectively shielded against nucleophilic attack because the parent homocubyl geometry does not obstruct S_N2-type displacements at the C(9) position. One explanation is that anchimeric assistance leads to a nonclassical structure of type **1b**, **1c**, or **1d**,[26] all three of which could only give products in which the stereochemistry is retained. This is supported by the extensive work by Dilling and co-workers performed on the 1,3-bishomocubyl cation.[27,28] Their results indicated an intermediate 1,2 σ-bridged carbonium ion analogous to **1b** in the solvolysis of 1,3-bishomocubyl-1-tosylate.

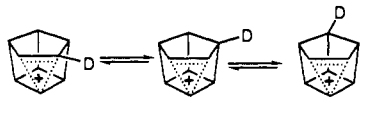


1a **1b** **1c** **1d**

In order to move the deuterium from C(9) to C(2,3), at least two formal Wagner–Meerwin shifts are necessary and during every stage of the rearrangement, the two faces of the molecule must remain distinguishable. The label in the triflate scrambles stereoselectively before solvolysis takes place, and the stereoselective scrambling can be triggered without solvolysis at all. This observation can be explained by a scrambling mechanism *via* internal return: The triflate, assisted by a *trans* C–C bond, leaves, and a (nonclassical) contact ion pair forms. The leaving group can recombine either with the carbon atom from which it dissociated or with a neighboring carbon. The latter case results in a stereoselective movement of the label. But one has to remember that the results of the triflate solvolysis and the deamination were similar, except that the extent of scrambling was reduced in the deamination product. Although internal return of the nitrogen has been postulated for aryl diazonium salts, it seems not to be applicable to **1** since aryl cations are more reactive and the measured internal return never exceeded 20%.[29] Similarly, in the case of the fluorodeiodination, it seems rather unlikely that the IF_2^- group is recaptured by the cation because of its instability and extremely low nucleophilicity.

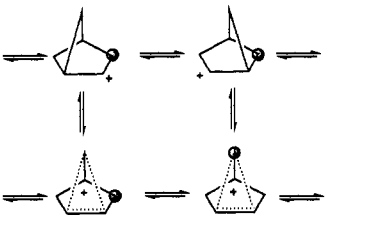
Memory effects[30,31] in deamination (for instance, the deamination of a chiral amine can give a nonracemic product) are commonly explained by ion-pairing phenomena or by an early transition state in the cation formation (vertical transition), but in the present case, such a memory effect would have to last over two Wagner–Meerwein shifts, which seems unlikely. However, it can be explained, assuming the symmetry of **1** is lower than that in **1a**, as is the case for the structures **1b–d**.

If we look at the classical structure **1a** and the conceivable nonclassical structures **1b–d**, it becomes evident that the label distribution in the solvolysis products should be different depending on the cation from which it derived. Structure **1d**, for example, is incompatible with the observed deuterium distribution, since positions 1,8 and 2,3 would become equivalent. For the structures **1b** and **1c**, the same kind of conclusion is not so obvious. Evidence against **1c** comes from MINDO/3 calculations by Jorgensen[26] which indicated energy minima for ions **1a**, **1b**, and **1d** but not for **1c**. If **1b** or **1c** describes the ground state of **1** properly, it remains unclear how the label in the deamination or the fluorodeiodination (no internal return) is moved stereoselectively to the C(2,3) position unless **1b** or **1c** could undergo automerizations *without* passing a transition state of higher symmetry like **1a** (eq 11). The comparison of **1** with **17** and **18** (fluorodeiodination) implies that such automerizations would have to be fast. Similar behavior has been reported for the bicyclo[1.1.2]-hex-2-yl cation **21**.[32] However, the reactions involving **21** as an intermediate lack the stereoselectivity observed here (eq 12).



(11)

1b



(12)

21

Simulation of the Deuterium Distribution. Simulations of the label distribution were performed first assuming that the cation is classical (**1a**) and second assuming that the nonclassical structure **1b** is correct. Schemes IIIa and IIIb describe the two situations. The cation, once generated, can either be trapped by the solvent or rearrange to an isotopomeric cation; the former process happens with probability p and the latter with probability $2r$. The average number of rearrangements a cation undergoes before being trapped is given by $N = 2r/p$. The equations derived from both schemes were numerically solved for $\mathbf{A} = \mathbf{A}(N)$, $\mathbf{B} = \mathbf{B}(N)$, and $\mathbf{C} = \mathbf{C}(N)$ and compared (least-squares difference) with the experimental data (Table II). The results of the two simulations are graphically shown in Figures 1 and 2. The expected deuterium incorporation is plotted versus the average number of rearrangements N.[33]

If **1** had a classical structure (**1a**, Figure 2), the amount of deuterium at C(1,8) must begin at 0% and increase with the

(25) (a) Hoffmann, R. W.; Kurz, H. R.; Becherer, J. *Chem. Ber.* **1978**, *111*, 1275. (b) Ohkata, K.; Doecke, C. W.; Klein, G.; Paquette, L. A. *Tetrahedron Lett.* **1980**, *21*, 3253.

(26) Jorgensen, W. L. *J. Am. Chem. Soc.* **1977**, *99*, 4272.

(27) (a) Dilling, W. L.; Alford, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 3615. (b) Dilling, W. L.; Reineke, C. E. *Tetrahedron Lett.* **1967**, 2547. (c) Dilling, W. L.; Alford, J. A. *Tetrahedron Lett.* **1971**, 761. (d) Dilling, W. L.; Reinke, C. E.; Plepys, R. A. *J. Org. Chem.* **1969**, *34*, 2605. (e) Dilling, W. L.; Plepys, R. A.; Kroening, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 8133. *Ibid.* **1969**, *91*, 3404.

(28) (a) Olah, G. A.; Prakash, G. K. S.; Liang, G. *J. Org. Chem.* **1976**, *41*, 2820. (b) Dilling, W. L.; Plepys, R. A.; Afford, J. A. *J. Org. Chem.* **1974**, *39*, 2856.

(29) Bergstrom, R. G.; Landells, R. G. M.; Wahl, G. H., Jr.; Zollinger, H. *J. Am. Chem. Soc.* **1976**, *98*, 3301.

(30) For a discussion, see: Lowry, T. H.; Richardson, K. T. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row Publishers: New York, 1987; pp 446–448.

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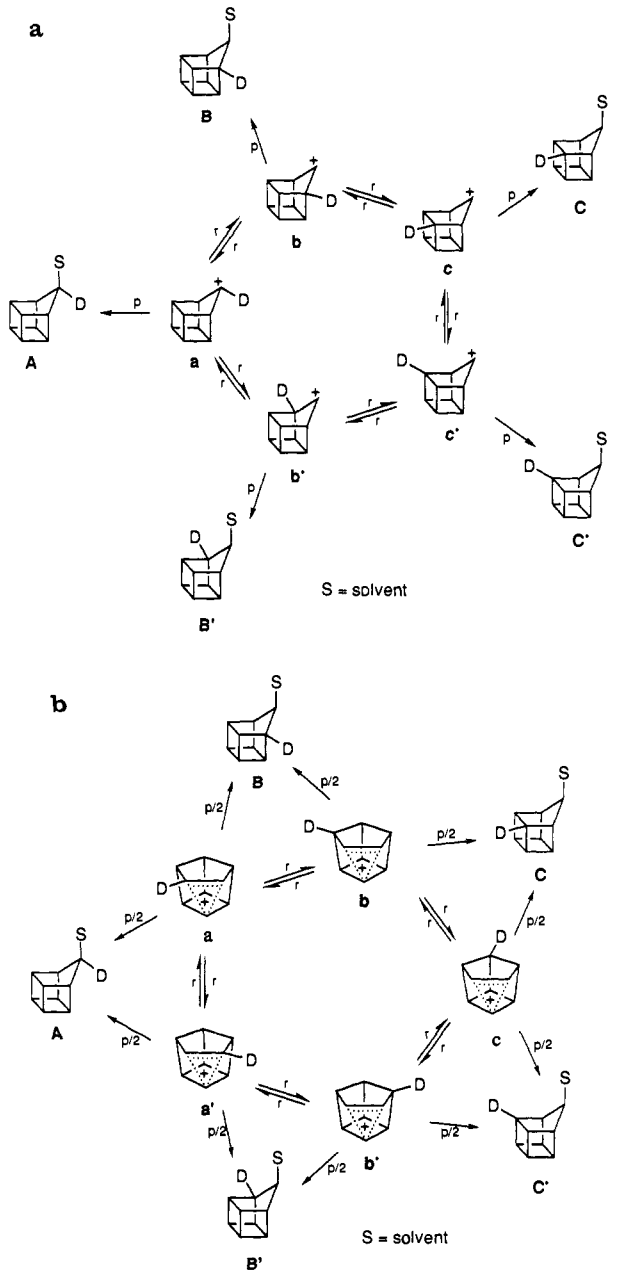
(32) (a) Kirmse, W.; Zander, K. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1538. (b) Kirmse, W.; Kampmann, K.-H.; Zellmer, V. *Chem. Ber.* **1987**, *120*, 1301 and references herein.

(33) A detailed description of the calculations is given as supplementary material.

Scheme III



number of rearrangements, asymptotically approaching the statistical value of 40%. However, if **1** is a nonclassical species (**1b**, Figure 2), the relative deuterium content at positions 1 and 8 should immediately jump to 50% and then drop to 40% as the number of rearrangements increases. In all the experiments which proceeded with an S_N1 mechanism, the amount of deuterium at C(1,8) was always equal to or larger than 40% and was higher after a smaller number of rearrangements, as predicted for the nonclassical case.

Quantitative analysis of the numbers shows that the simulation for cation **1b** matches the experimental results within the error of measurement except for the methanolysis at low temperature (Table II, entry 1)[34] and the deamination (Table II, entry 10). The deviation of the deamination results is not surprising considering the different mechanisms of deamination and solvolysis reactions.[30] Interestingly, the discrepancy between experiment and calculation disappeared when the deamination reaction was repeated under very high liquid pressure, 6000–10 000 atm(Table II, entry 11).[35]

(34) The reasons for the difference between the methanolysis at 20 °C and the other solvolysis experiments are not clear. It might be due to the high nucleophilicity of methanol so that solvent-assisted ionization is competing with the anchimeric effect.

Conclusions

The experimental results presented here strongly suggest that the 9-homocubyl cation in its ground state is best described by the nonclassical structure **1b**. No evidence was found for a degenerate cation involving all nine homocubyl positions as proposed by Schleyer.[1a]

Although the label in **8** is clearly scrambled *via* ionization and internal return, it appears that the highly stereoselective rearrangement of **1b** also occurs in the absence of a recombining leaving group, suggesting that **1b** can automerize without passing through a transition state of higher symmetry and retain the steric information throughout the reaction. Thus, structure **1b** seems to be a "molecular gear" where a five-membered ring is rotating against a four-membered one.

Regarding the question of whether the homocubylidene (**3**) is protonated in the reaction with methanol, one has to remember that the automerizations of **1** are fast, so that even in nucleophilic media significant amounts of label are carried over two Wagner–Meerwein shifts. The fact that *no* label was found in the reactions of homocubylidene with methanol-*O-d* at positions other than 9 and 1[9] suggests the absence of **1** as an intermediate. Therefore, carbene **3** seems to react either in a concerted fashion, as does the homocubene (**2**), or *via* the ylide pathway, indicating that the cationic OH-insertion mechanism does not generally apply for alkylcarbenes.

In general, labeled **1** is certainly a very sensitive probe for cationic intermediates, and it might find use as such in mechanistic research as shown here for the fluorodeiodination reaction.

Experimental Section

NMR spectra were run in chloroform-*d* at ambient probe temperature unless otherwise noted, ^1H NMR at 400 MHz and referenced to internal tetramethylsilane or chloroform and ^{13}C NMR spectra at 100.6 MHz and referenced to the central line of the solvent. Proton chemical shifts are reported to a precision of ±0.02 ppm. Carbon chemical shifts are given to a precision of ±0.1 ppm. Coupling constants (added parenthetically) are reported to a precision of ±0.2 Hz. ^2H NMR spectra were run at 61.4 MHz in chloroform and referenced to internal chloroform-*d*. FT-IR spectra were obtained at a digital resolution of 2 cm^{-1}. Low-resolution mass spectra (70 eV, EI mode) were obtained on material eluting OV-17 coated (0.25-mm film) capillary GC column (15 m × 0.248 mm) and are reported to unit mass. Solvents were removed *in vacuo* on a rotary evaporator unless stated differently. Since some of the compounds are volatile, the bath of the rotary evaporator was kept at room temperature and only a gentle vacuum was applied (40–50 mm). Merck silica gel 60 (230–400 mesh) was used for column chromatography.

Homocubanone Ethylene Acetal (5). 1-Bromohomocubanone ethylene acetal[12,13] (0.87 g, 3.4 mmol) was dissolved in THF (30 mL) and cooled to −78 °C. *tert*-Butyllithium (7 mL, 1.7 M in pentane) was added at a rate such that the temperature did not exeed −60 °C (measured internally). The reaction was quenched after 30 min with methanol (3 mL), and the mixture was allowed to warm up to room temperature. The mixture was poured into water (100 mL) and extracted with *n*-pentane (2 × 20 mL). Removal of the solvent left **5** as a clear oil (603 mg, 100%): ^1H NMR δ 3.93 (s, 4H), 3.25 (m, 2H), 2.96 (m, 2H), fully consistent with reported values.[13]

Homocubanone (6). A mixture of water (3.0 g) and concentrated sulfuric acid (9.0 g) was cooled to 0 °C and added dropwise to homocubanone acetal **5** (600 mg, 3.4 mmol) at 0 °C. The reaction mixture

(35) It has been suggested that a cation generated by deamination retains more of the precursor geometry (vertical transition) than if generated by solvolysis.[30,31] Therefore, the homocubyl cation generated in a deamination might have more of the positive charge remaining at the C(9) position than the cation in the solvolysis. This might account for the higher than expected label contents at C(9) in the deamination product. At very high pressures, the loss of nitrogen becomes much less favorable. The reaction profile of the deamination at high pressure might therefore be more similar to the profile of the solvolysis reaction, which would explain the observed pressure dependence of the label distribution. Eaton, P. E.; Spitz, U. P. Unpublished results.

Table II. Comparison of Experimental Deuterium Distributions with Calculations Assuming a Classical Structure, **1a**, and a Nonclassical Structure, **1b**, for the Homocubyl Cation

				calculated							
	experiment ±2%,[a] % D at position			nonclassical cation, %D at position				classical cation, % D at position			
entry[b]	9	1,8	2,3	N[c]	9	1,8	2,3	N[c]	9	1,8	2,3
1	45	44	11	0.4	43	49	8	1.8	47	36	17
2	39	45	16	1.0	37	47	16	2.6	41	38	21
4	28	45	27	3.2	29	44	27	7.0	30	40	31
5	28	45	27	3.2	29	44	27	7.0	30	40	31
6	25	46	29	4.0	27	44	29	9.0	28	40	32
7	25	46	29	4.0	27	44	29	9.0	28	40	32
8	30	43	27	3.0	29	44	27	6.0	31	39	30
9	24	43	33	8.0	24	42	34	13.0	26	40	35
10[d]	49	44	7	0.2	45	50	5	1.6	50	35	15
11[e]	40	50	10	0.5	41	49	10	2.8	40	38	22
12[f]	28	47	25	2.8	30	45	26	9.0	28	40	32

[a] On the basis of reproducibility of the experiments. [b] See Table I. [c] Average number of rearrangements before trapping. [d] Deamination reaction. [e] Deamination at 145 000 psi. [f] Fluorodeiodination, assuming the reaction is stereospecific.

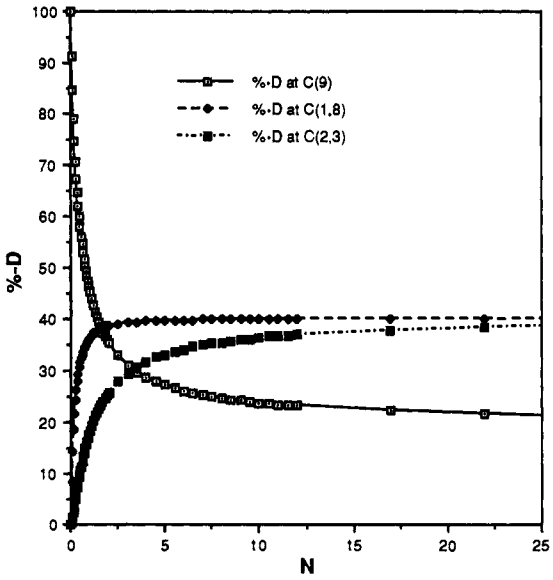


Figure 1.

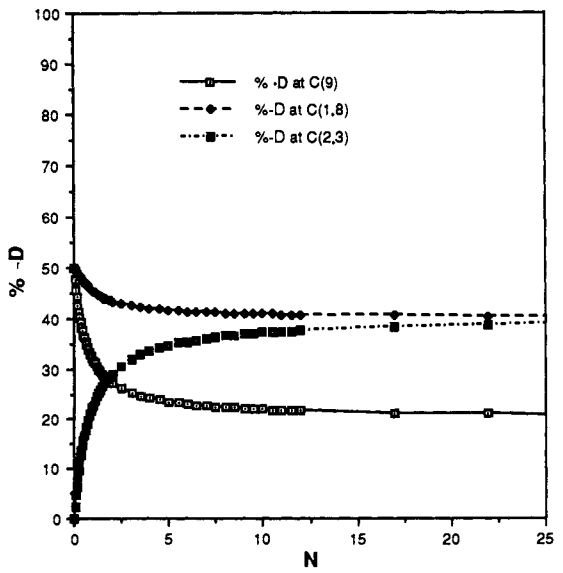


Figure 2.

was stirred in an ice bath until it turned dark purple and then kept in a refrigerator (0 °C) for 48 h. The viscous solution was transferred to a separatory funnel containing ice (2 g) and extracted with methylene chloride (3 × 10 mL). The extract was washed with water and saturated aqueous ammonium chloride and then dried over a mixture of sodium sulfate and potassium carbonate. The solvent was evaporated and the product chromatographed on silica gel (20 g) eluting with pentane–methylene chloride (1:1 by volume). First, fractions containing homocubanone (**6**) were obtained and evaporated. The ketone was isolated as white crystals (622 mg, 71%). Later fractions contained starting materials **5**, which was obtained as a colorless oil after evaporation of the solvent (173 mg, 14%). **6**: mp 70–72 °C (lit.[12] mp 72–74 °C); ^{1}H NMR δ 3.68 (m, 4H), 3.56 (m, 2H), 3.03 (m, 2H), fully consistent with reported values.[12]

9-Homocubanol-9-*d* (7-9-*d*). A solution of 240 mg (1.82 mmol) of homocubanone (**6**) in 5 mL of dry ether was added to a suspension of $LiAlD_4$ (56 mg, 1.34 mmol, >98% D). After the stolution was stirred for 30 min, the reaction was quenched carefully with ice water. Hydrochloric acid (10%) was added until all solid dissolved, and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried over sodium sulfate and evaporated to dryness leaving the title compound **7-9-*d*** as white crystals (234 mg, 97%): mp 154–155 °C (lit.[1a] mp 157 °C); IR (neat) ν 3272 (s), 2980 (s), 1287 (m), 1248 (m), 1102 (m) cm^{-1}; ^{1}H NMR δ 3.57 (m, 2H), 3.27 (m, 2H), 3.22 (m, 2H), 3.13 (m, 2H), consistent with reported values;[1a] ^{13}C NMR δ 87.0 (t, $^1J_{CD}$ = 22.8 Hz), 48.2, 42.7, 42.1, 41.6; MS m/z 135 (M^+, 7), 134 (50), 116 (85), 106 (100), 92 (99), 79 (78); HRMS calcd for C_9H_9DO (M^+) 135.0794, found 135.0770.

9-Homocubyl Triflate-9-*d* (8-9-*d*). Alcohol **7-1-*d*** (95 mg, 0.70 mmol) and pyridine (98 μL, 1.2 mmol) were dissolved in dry methylene chloride (2.5 mL). The mixture was cooled in an ice bath, and triflic anhydride (190 μL, 1.13 mmol) was added. The reaction mixture was stirred for 15 min and then kept for 12 h at 0 °C. Pentane (15 mL) was added to the reaction mixture which then was transferred to a separatory funnel containing water (10 mL). The organic layer was separated, and the aqueous phase was extracted with pentane (10 mL). The extract was washed with water (10 mL) and 1% aqueous hydrochloric acid (10 mL), and dried over sodium sulfate. The solvent was evaporated to give the title compound **8-9-*d*** as a colorless oil (171 mg, 91%). The neat product is unstable and must be kept in pentane solution for storage: IR (neat) ν 2996 (s), 1409 (s), 1248 (s), 1205 (s), 1147 (s), 920 (s) cm^{-1}; ^{1}H NMR δ 3.65 (m, 2H), 3.46 (m, 2H), 3.39 (m, 2H), 3.30 (m, 2H); ^{13}C NMR δ 118.5 (q, $^1J_{CF}$ = 318.9 Hz), 100.3 (t, $^1J_{CD}$ = 24.4 Hz), 45.8, 42.6, 42.0, 40.2. Anal. Calcd for $C_{10}H_8DF_3O_3S$: C, 44.94; H, 3.77; S, 12.00. Found: C, 44.88; H, 3.57; S, 12.00.

9-Homocubylammonium Chloride-9-*d* (15-9-*d*). (a) Homocubanone *O*-Benzyloxime (14). The general procedure of Liu[20] was followed. Homocubanone (**6**) (107 mg, 0.81 mmol) and *O*-benzylhydroxylammonium chloride (142 mg, 0.89 mmol) were dissolved in acetonitrile (5 mL). Tetramethylenediamine (150 μL, 0.1 mmol) was added, and the mixture was refluxed for 1.5 h. The solution was evaporated to dryness and the residue triturated with *n*-pentane (20 mL). The pentane solution was washed with water (2 × 5 mL) and saturated aqueous ammonium chloride (5 mL). After being dried over sodium sulfate, the solution was evaporated and the residue was dried *in vacuo* leaving **14** as a yellowish oil (195 mg, 100%): IR (neat) ν 2985 (s), 1454 (m), 1236 (m), 1020 (s) cm^{-1}; ^{1}H NMR δ 7.33 (m, 5H), 5.05 (s, 2H), 4.08 (m, 1H), 3.61 (m, 4H), 3.49 (m, 1H), 3.31 (m, 2H); ^{13}C NMR δ 175.0, 138.0, 128.3, 128.1, 127.7, 75.5, 43.2 (2 peaks), 42.9, 42.6, 42.5, 38.1.

(b) 9-Homocubylammonium Chloride-9-*d* (15-9-*d*). $LiAlD_4$ (39 mg, 0.93 mmol) was added carefully to a solution of oxime **14** (95 mg, 0.81

mmol) in dry ether (5 mL) and stirred for 12 h. Methanol (2 mL) was added to quench the reaction followed by slow addition of 10% aqueous sodium hydroxide until all solid disappeared. The aqueous phase was extracted with ether (3 × 10 mL), and the ether extracts were washed with water. The ether solution was concentrated to approximately 3 mL. Ether saturated with HCl was added dropwise until no more material precipitated. The product was filtered off and purified by precipitation from chloroform by the addition of ether. Finally, **15-9-*d*** was washed with ether (2 mL) and dried *in vacuo* to give the title compound as white crystals (120 mg, 86%): mp > 310 °C dec; IR ($CHCl_3$) ν 2978 (s), 2899 (s), 1605 (m), 908 (m) cm^{-1}; ^1H NMR δ 8.15 (s, b), 3.69 (m, 2H), 3.49 (m, 2H), 3.38 (m, 2H), 3.24 (m, 2H); ^{13}C NMR δ 64.9 (t, $^1J_{CD}$ = 20.1 Hz), 45.7, 42.1, 42.0, 41.0. Anal. Calcd for $C_9H_{11}DClN$: C, 63.33; H, 7.68; N, 8.21. Found: C, 63.19; H, 7.14; N, 8.33.

9-Homocubylammonium Chloride-*d* (15-*d*). *N*-9-Homocubylacetamide-d_4 (**10-d_4**) (obtained from the solvolysis of **8-9-*d*** in acetonitrile, 44 mg, 25 μmol) was refluxed for 24 h in 10% aqueous HCl (4 mL). The reaction mixture was cooled in an ice bath, slowly basified by 10% aqueous NaOH, and extracted with ether (3 × 5 mL). The extract was dried over sodium sulfate and concentrated to 1 mL. A freshly prepared saturated solution of HCl in ether was added dropwise until complete precipitation of the product. The product was filtered off and washed with a small amount of ether to yield **15-*d*** as a white solid (20 mg, 47%); ^1H NMR δ 3.69 (m), 3.64 (m, C*H*NH_3^+), 3.49 (m), 3.37 (m), 3.24 (m).

9-Homocubyl Iodide-9-*d* (13-9-*d*). A saturated solution of tetrabutylammonium iodide (250 mg, 0.68 mmol) in THF (2 mL) was added to homocubyl triflate **8-9-*d*** (58 mg, 0.22 mmol) and the mixture was stirred at room temperature for 12 h. Pentane (5 mL) was added, and the solid which had precipitated was filtered off. The filtrate was washed with water (2 × 3 mL), dried over sodium sulfate, and concentrated. The crude product was chromatographed on silica gel (3 g) eluting with pentane. Fractions containing the product were evaporated leaving **13-9-*d*** as a clear viscous oil (46.4 mg, 86%): IR (neat) ν 2984 (s), 1242 (m), 1018 (m), 849 (m) cm^{-1}; ^1H NMR (CD_2Cl_2) δ 3.44 (m, 2H), 3.38 (m, 2H), 3.22 (m, 2H), 3.14 (m, 2H); ^{13}C NMR δ 52.5, 44.9, 43.4, 41.8 (t, $^1J_{CD}$ = 23.6 Hz), 39.8; MS *m/z* 127 (I^+, 4), 118 (34), 116 (100), 92 (32). Anal. Calcd for C_9H_8DI: C, 44.11; H, 4.11; I. 51.78. Found: C, 44.20; H, 3.89; I, 52.02.

Solvolysis of 8-9-*d*. *N*-9-Homocubylacetamide-d_4 (10-d_4). Solvolysis at 25 °C. Homocubyl triflate **8** (12.1 mg, 45 μmol) was dissolved in acetonitrile-d_3 (1 mL). The mixture was kept at 25 °C, and the reaction was followed by proton NMR; after 24 h, no starting material remained. The dark solution was poured in water (5 mL) and extracted with ether (3 × 3 mL). The organic layer was dried over sodium sulfate and evaporated to dryness, leaving **10-d_4** as a yellowish solid (7.7 mg, 95%): IR ($CHCl_3$) ν 3023 (s), 2928 (s), 1657 (s), 1512 (s), 1207 cm^{-1}; ^1H NMR δ 4.25 (m), 3.45 (m), 3.27 (m), 3.22 (m, 4H); ^2H NMR δ 4.26, 3.44, 3.27, 1.89 (3D); ^{13}C NMR δ 170.9, 66.5–66.4 (m), 46.8–46.5 (m), 42.1–41.9 (m), 41.6–41.2 (m), 22.3 (m, CD_3); MS *m/z* 178 ($(M-1)^+$, 2), 134 (50), 118 (23), 117 (100), 78 (12); HRMS (CI) calcd for $C_{11}H_9D_4NO$ 179.1248, found 179.1292. **Solvolysis at 65 °C.** **8-9-*d*** (10.5 mg, 40 μmol) was dissolved in acetonitrile-d_3 and kept in a preheated oil bath (65 °C) for 3.5 h. The reaction was worked up as before to give **10-d_4** (4.9 mg, 70%).

9-Homocubyl Formate-*d* (11-*d*). Solvolysis at 25 °C. Triflate **8-9-*d*** (16.6 mg, 62 μmol) was stirred with formic acid (0.5 mL, 98%) at 25 °C for 3 h. The dark green reaction mixture was poured into water (5 mL) and extracted with pentane (3 × 3 mL). The pentane extract was washed with water (3 mL) and saturated aqueous sodium bicarbonate solution (3 mL) and filtered through sodium sulfate. After evaporation of the solvent, **11-*d*** was obtained as a clear oil (7.7 mg, 76%): IR (neat) ν 2984 (s), 1725 (s), 1171 (s) cm^{-1}; ^1H NMR δ 5.21 (m), 3.54 (m), 3.33 (m), 3.25; ^2H NMR δ 5.22, 3.54, 3.34; ^{13}C NMR δ 161.1, 88.0–87.9 (m), 45.7–45.4 (m), 43.1–42.8 (m), 42.1–41.8 (m), 41.0–40.7 (m); MS (CI) *m/z* 164 ($[M+1]^+$, 15), 118, (100); HRMS calcd for $C_{10}H_9DO_2$ ($[M+1]^+$) 164.0822, found 164.0815. **Solvolysis at 90 °C.** Formic acid (0.5 mL, 98%) was heated to 90 °C and added to triflate **6** (11.3 mg, 43 μmol). The mixture was kept in an oil bath at 90 °C for 5 min and worked up as before to give **11-*d*** (4.2 mg, 60%).

8-Methoxyhomocubane-*d* (4-*d*). Solvolysis at 25 °C. Triflate **8-9-*d*** (12.5 mg, 47 μmol) was dissolved in absolute methanol (0.5 mL) and kept at 25 °C for 24 h. The solution was poured in water (5 mL) and extracted with (3 × 3 mL) pentane. The extract was washed with water (3 mL), filtered through sodium sulfate, and evaporated. Methyl ether **4-*d*** was obtained as a colorless oil (6.3 mg, 90%). The sample was chromatographed on silica gel (2 g) eluting with *n*-pentane–methylene chloride (1:1 by volume): IR ($CHCl_3$) ν 2981 (s), 1602 (m), 1098 (s) cm^{-1}; ^1H NMR δ 3.93 (m), 3.52 (m), 3.29 (s, 3H), 3.26 (m), 3.22; ^2H NMR δ 3.94, 3.52, 3.28; ^{13}C NMR δ 95.8, 57.5, 45.4–45.1 (m), 43.2–43.0 (m), 42.4–42.1 (m), 41.2–40.7 (m), fully consistent with reported values for **4-9-*d***;[9d] MS *m/z* 149 (M^+, 3), 148 (22), 118 (100), 116 (93), 106 (51), 78 (42). **Solvolysis at 65 °C.** Triflate **8-9-*d*** (11.1 mg, 42 μmol) was dissolved in 0.5 mL at absolute methanol and kept in a preheated oil bath for 3.5 h. The reaction was worked up as before to give **4-*d*** (4.5 mg, 72%). **Solvolysis in 12% Sodium Methoxide in Methanol.** Triflate **8-9-*d*** (12.3 mg, 46 μmol) was stirred with sodium methoxide in methanol (1 mL, 12% methoxide by weight) for 24 h and worked up as above to give **4-*d*** (5.9 mg, 86%). **Solvolysis of Triflate with Scrambled Label in 12% Sodium Methoxide in Methanol. (a) Prescrambling of the Deuterium Label in 8-9-*d*.** Triflate **8-9-*d*** (14.7 mg, 55 μmol) was stirred with silica gel (50 mg, 70–230 mesh) in chloroform (2 mL) for 1 h. The silica was filtered off, and the solution was evaporated to yield a mixture of isotopomeric triflates **8-*d*** (5.2 mg, 35%, the product contained approximately 10% 9-homocubanol): ^2H NMR δ 5.32, 3.65, 3.45. **(b) Solvolysis in 12% Sodium Methoxide in Methanol.** The same procedure was employed as before, but the product was chromatographed on silica gel (2 g) eluting with *n*-pentane-*n*-methylene chloride (1:1 by volume). The solvent was removed by *slow distillation* at atmospheric pressure to give a small amount of pure **4-*d*** (approximately 2 mg, 14% from unscrambled triflate): ^2H NMR δ 3.93, 3.27, 3.24 (shoulder).

9-Homocubyl Hexafluoroisopropyl Ether-d_2 (12-d_2). A mixture of hexafluoro-2-propanol-d_2 (980 mg) and acetonitrile-d_3 (150 mg) was added to **8-9-*d*** (25.5 mg, 95 μmol). The resulting solution was stirred at 20 °C for 1.5 h. GC and GC/MS analysis revealed hexafluoroisopropyl ether **12-d_2** (43%) and acetamide **10-d_4** (42%) as the two major products. The reaction mixture was diluted with ether (3 mL), washed with water (2 × 1 mL), and then filtered through sodium sulfate. The solvent was evaporated, and the residue was chromatographed on silica gel (2 g) to give, after evaporating the solvent, the hexafluoroisopropyl ether as a clear oil (5.1 mg, 19%): ^1H NMR δ 4.43 (m), 3.56 (m), 3.30 (m), 3.25 (m); ^{13}C NMR δ 121.5 (q, $^1J_{CF}$ = 285.6 Hz), 97.4, 45.5–45.3 (m), 43.1–42.9 (m), 42.2–41.9 (m), 40.9–40.7 (m) (due to multiple coupling, the $CD(CF_3)_2$ signal could not be found, even after prolonged acquisition time); ^2H NMR δ 4.43, 4.00 (1D), 3.55, 3.29; MS *m/z* 286 (M^+, 0.6), 118 (100), 116 (40), 106 (68), 92 (13), 78 (11).

Thermal Scrambling of the Label in 8-9-*d*. Triflate **8-9-*d*** (15.7 mg, 60 μmol) was dissolved in toluene-d_8 and sealed in an NMR tube. The sample was heated in a carefully thermostated oil bath. The growth of the C(9) ^1H NMR signal at 5.31 ppm was measured periodically. Heating over longer periods of time or at temperatures above 105 °C led to complete decomposition of the starting material. **8-*d*** was isolated by evaporation of the solvent: ^2H NMR δ 5.33, 3.66, 3.47.

Deamination of 15. (a) Deamination of 15-9-*d*.[20a] 9-Homocubylammonium chloride **15-9-*d*** (60.8 mg, 0.36 mmol) was dissolved in aqueous acetic acid (2.5 mL of acetic acid and 0.5 mL of water) and cooled in an ice bath. Sodium nitrite (95.1 mg, 134 μmol) was added in one portion to the solution. The mixture was allowed to warm to room temperature over a period of 4 h. Stirring was continued for an additional 20 h. The mixture was diluted with water (10 mL) and extracted with methylene chloride (3 × 5 mL). The aqueous phase was basified with 10% aqueous sodium hydroxide and extracted with ether. The ether was dried over sodium sulfate and evaporated to dryness, yielding unreacted 9-homocubylamine (4.1 mg, 8.5%). The organic phase was washed with water (2 × 5 mL) and saturated aqueous sodium bicarbonate solution. The solvent was evaporated, and the residue was redissolved in methanol (3 mL). Sodium hydroxide (50 mg) was added, and the mixture was stirred for 24 h. The mixture was poured in water (10 mL) and extracted with ether (3 × 5 mL). The organic layer was separated, dried over sodium sulfate, and evaporated to dryness to give **7-*d*** (33.8 mg, 69.5%). Minor impurities were removed by chromatographing the product on silica gel (10 g) eluting with methylene chloride: ^2H NMR δ 4.34, 3.57, 3.14.

(b) Deamination of 15-*d*. The deamination was repeated as above employing 9-homocubylammonium chloride-*d* (**15-*d***) (20.0 mg, 117 μmol) and sodium nitrite (38 mg, 540 μmol) in 50% aqueous acetic acid (0.6 mL). The product was chromatographed on silica gel (3 g) to give 9-homocubanol-*d* **7-*d*** (6.3 mg, 40%): ^2H NMR δ 4.38, 3.57, 3.13.

(c) Control Experiment. 9-Homocubanol **7-9-*d*** (29.8 mg, 0.22 mmol) was dissolved in acetic anhydride (1 mL). Pyridine (50 μL) was added, and the resulting solution was stirred until the complete conversion of alcohol **7** to its acetate. The mixutre was poured into 50% aqueous acetic acid (4 mL), and 15 min later, sodium nitrite (100 mg) was added. The mixture was stirred for 12 h at 20 °C. The reaction was worked up and the obtained acetate was hydrolyzed back to alcohol **7** as described above

for the deamination reaction. The recovered alcohol **7** was redissolved in 75% aqueous acetic acid and stirred with sodium nitrite (100 mg) for another 12 h. The mixture was worked up as before to give **7** as a white solid (9.6 mg, 32% recovery): ^{1}H NMR δ 3.57 (m, 2H), 3.27 (m, 2H), 3.22 (m, 2H), 3.13 (m, 2H). The absence of the C(9)–H signal demonstrates that neither 9-homocubyl acetate nor 9-homocubanol rearranges under the reaction conditions of the deamination.

Florodeiodination of 13. 9-Fluorohomocubane-*d* (20-*d*). Iodohomocubane **13**-9-*d* (42 mg, 17 μmol) was dissolved in dry methylene chloride (0.7 mL). XeF_2 (64 mg, 37 μmol) was added in one portion. The mixture was stirred for 4 h. GC/MS analysis indicated that besides the desired fluoride, a second homocubyl compound was formed, which could not be identified with certainty (MS *m/z* 283 (0.2), 177 (23), 166 (100), 92 (38), 78 (6)). The dark red solution was poured into saturated aqueous sodium sulfate (3 mL). The product was extracted with pentane (5 mL), and the organic layer was separated and filtered through sodium sulfate. The solution was concentrated to 1 mL by slowly distilling the solvent off. The residue was chromatographed on silica gel (2 g) eluting with pentane. The fractions were analyzed by GC, and those containing the product were combined. Removal of the solvent by distillation afforded the title compound as a colorless oil (approximately 8 mg, 34%): ^{1}H NMR (CD_2Cl_2) δ 5.12 (dm, $^2J_{FH}$ = 54.8 Hz), 3.59 (m), 3.26 (m); ^{2}H NMR ($CHCl_3$) δ 5.16 ($^3J_{FD}$ = 8.5 Hz), 3.64, 3.31; ^{13}C NMR (CD_2Cl_2) δ 106.6 (dm, $^1J_{FC}$ = 186.1 Hz), 46.3–46.0 (m), 43.5–43.3 (m), 42.9–42.7 (m), 40.9–40.7 (m); MS *m/z* 137 (M^+, 9), 136 (100), 116 (52), 92 (8); HRMS calcd for $C_9H_8DF(M^+)$ 137.0751, found 137.0769.

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Supplementary Material Available: Derivitizations of differential equations and numerical solutions (3 pages). Ordering information is given on any current masthead page.