Nucleophilic Capture of 2-Bicyclo[2.1.1]hexyl Cations

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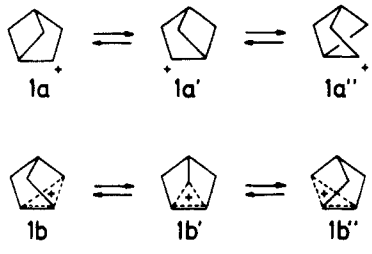
Abstract: The degenerate rearrangements of the parent 2-bicyclo[2.1.1]hexyl cation (**1**) in aqueous media have been probed with the aid of optically active, deuterium-labeled, and ^{13}C-labeled substrates. Diazonium ion precursors (**12**) proved to be more rewarding than brosylates (**9**), as the ionic reactions of the latter were obscured by internal return and inverting displacement (k_s). The redistribution of labels attached to C-3 of the precursor excludes rapid equilibration of open ions (**1a**). Equivalence of C-1 and C-2 and also C-3 and C-5 is therefore attributed to bridging (**1b**). A double-labeling experiment, employing [2-^{2}H,3-^{13}C]-**12**, identifies the slower exchange of all methylene groups as an interconversion of bridged ions. The estimated barrier to interconversion is ca. 3 kcal·mol^{-1}. In contrast to **1**, the 1,2-dimethyl-2-bicyclo[2.1.1]hexyl cation (**16**) behaves as a classical ion, equilibrating faster than the acyclic 2,3,3-trimethyl-2-butyl cation (**14**). The present study indicates that the energy profiles of carbocations in aqueous solution resemble those observed in nonbasic media. Nucleophilic solvation does not appreciably affect the relative stabilities of bridged and open ions.

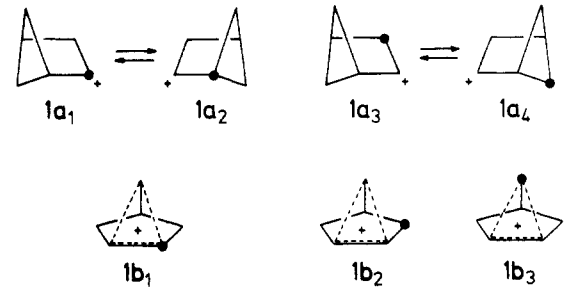
The 2-bicyclo[2.1.1]hexyl cation (**1**) has attracted attention because of its degenerate rearrangements. Under stable ion conditions, the three methylene groups of **1** were found to be



equivalent on the time scales of ^1H and ^{13}C NMR spectroscopies, even at −130 °C.[1,2] The NMR spectra require rapid equilibration between sets of open (**1a**) or bridged (**1b**) cations. Although the small isotopic splitting in the ^{13}C NMR spectrum of [^{2}H]-**1** supports a σ-delocalized structure,[3] the rapid equilibration points to a small difference in energy between **1a** and **1b** (the open ions **1a** may be viewed as transition states for the interconversion of bridged ions **1b** and vice versa). Similar conclusions were reached from a determination of the energy separation between secondary and tertiary 2-bicyclo[2.1.1]hexyl cations (7.0–9.8 kcal·mol^{-1}).[4] Sorensen pointed out that the thermodynamic and spectroscopic properties of **1** are intermediate between those found in 2-norbornyl cations, on the one hand, and cyclopentyl or aliphatic cations, on the other.[4]

These properties invite an investigation of nucleophilic solvation and capture of **1**. The localized charge of open ions is thought to be better stabilized by solvation than the delocalized charge of bridged ions.[5] Thus, the relative stabilities of **1a** and **1b** might be reversed in nucleophilic media. The initially formed intermediates might be identified by quenching prior to or competitively with rearrangement. Previous results from the solvolysis and deamination of 2-bicyclo[2.1.1]hexyl derivatives have been interpreted in favor of bridged intermediates by some authors[6] and in terms of open ions by others.[7] None of these studies refer to the parent system and its unique symmetry. The only record of a labeled 2-bicyclo[2.1.1]hexyl precursor concerns the acetolysis of the [2-^{2}H]tosylate which led to 2-bicyclo[2.1.1]hexyl acetate with the deuterium equally distributed between positions 1 and 2.[1]

The information to be obtained from 2-labeled precursors is important but insufficient. An excess of 2-labeled product may be due to predominant capture of the open ion $\mathbf{1a}_1$, i.e., to relatively



slow Wagner–Meerwein rearrangement. Solvolytic displacement (k_s) is another possibility, readily confirmed (or excluded) with the aid of optically active substrate. A 1:1 distribution of the label, as reported for the acetolysis of [2-^{2}H]bicyclo[2.1.1]hexyl tosylate,[1] does not distinguish rapidly equilibrating open ions ($\mathbf{1a} \rightleftarrows \mathbf{1a}_2$) from a bridged intermediate ($\mathbf{1b}_1$). A label at position 3 is more revealing. Rapid equilibration of open ions distributes the label equally between positions 3, 5, and 6. (For the sake of simpicity, we ignore chirality induced by the label and write only one enantiomer of $\mathbf{1a}_4$, $\mathbf{1b}_2$, etc., to represent the racemates. If isotope effects are neglected, the equilibrium mixture of open ions consists of $\mathbf{1a}_3$, $\mathbf{1a}_4$, and the enantiomer of $\mathbf{1a}_4$, in a 1:1:1 ratio. Analogous considerations apply to subsequent schemes in this paper.) The initially formed bridged ion $\mathbf{1b}_2$, on the other hand, distributes the label only between positions 3 and 5 of the product, provided that the interconversion of $\mathbf{1b}_2$ with $\mathbf{1b}_3$ is slow as compared with nucleophilic capture. Before reporting our experiments directed along these lines, we should like to recall that labels define no more than the symmetry of the intermediates. Thus, in the present paper the bridged ion formulation **1b** merely accounts for a plane of symmetry bisecting the C_1–C_2 bond.

Results and Discussion

Syntheses of Labeled and Optically Active Substrates. Deuterium proved to be an excellent label for position 2 but was less well applicable to position 3. Although bicyclo[2.1.1]hexan-2-one (**7**)[8] exchanged 3-H for deuterium in MeOD–MeONa (2.6 M, 68-h reflux), difficulties were initially encountered in analyzing

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(8) Bond, F. T.; Jones, H. L.; Scerbo, L. *Tetrahedron Lett.* **1965**, 4685. Bond, F. T.; Jones, H. L.; Scerbo, L. *Org. Photochem. Synth.* **1971**, *1*, 33.

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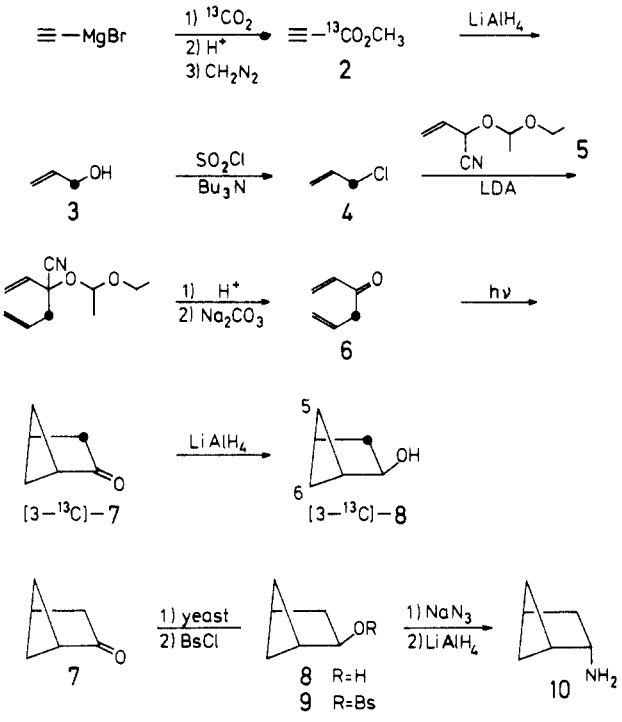
Scheme I



the deuterium distribution of $[^2H_2]$bicyclo[2.1.1]hexan-2-ol. Before these problems were solved[9] we resorted to ^{13}C as a label. The synthesis of [3-^{13}C]-**7** started from [1-^{13}C]methyl propiolate (**2**), readily accessible from ethynylmagnesium bromide and [^{13}C]carbon dioxide[10] (Scheme I). One-pot reduction of the ester group ($LiAlH_4$, −78 °C) and of the triple bond ($LiAlH_4$, 25 °C) afforded [1-^{13}C]-2-propen-1-ol (**3**). Thionyl chloride–tributylamine converted **3** to the analogous chloride **4**.[11] The enolate of O-protected acrolein cyanohydrin (**5**)[12] was allylated and hydrolyzed to give [4-^{13}C]hexa-1,5-dien-3-one (**6**). Photocycloaddition of **6** provided [3-^{13}C]-**7** with 96% of the label at C-3 and 4% at C-5,6 (i.e., allylic rearrangement in the course of the synthesis occurred to a very minor extent). Lithium aluminum hydride reduction of [3-^{13}C]-**7** led to [3-^{13}C]bicyclo[2.1.1]hexan-2-ol with an analogous distribution of ^{13}C. The ^{13}C NMR spectrum of [3-^{13}C]-**8** necessitated reassignment of the CH_2 signals C-3 δ 38.3, C-5 δ 34.7; and C-6 δ 39.2.[13] The low-field signal at δ 34.7 was assigned to C-5 on the basis of its greater LIS, as compared to C-6 (δ 39.2).

Fermenting yeast reduction of **7** yielded (−)-**8** of 82 ± 1% ee. The enantiomeric purity of (−)-**8** was estimated by GC on a capillary column coated with optically active poly(propylene glycol).[14] The absolute configuration of (−)-**8** was not established. Displacement of the optically active brosylate **9** with azide, followed by reduction with $LiAlH_4$, provided optically active bicyclo[2.1.1]hexan-2-amine (**10**), ee 76% (estimated by GC of the *N*-(trifluoroacetyl)-(*S*)-propyl amide[15]). Optically inactive **10** and [2-^{2}H]-**10** were more conveniently prepared from **7** by way of $LiAlH_4$ ($LiAlD_4$) reduction of the oxime.

Solvolyses of 2-Bicyclo[2.1.1]hexyl Brosylate. After solvolysis in trifluoroacetic acid, the deuterium of [2-^{2}H]-**9** was distributed equally between positions 1 and 2 of 2-bicyclo[2.1.1]hexyl trifluoroacetate (estimated by ^2H NMR analysis of the alcohol **8**).

Table I. Solvolyses of 2-Bicyclo[2.1.1]hexyl Brosylates (**9**)[a]

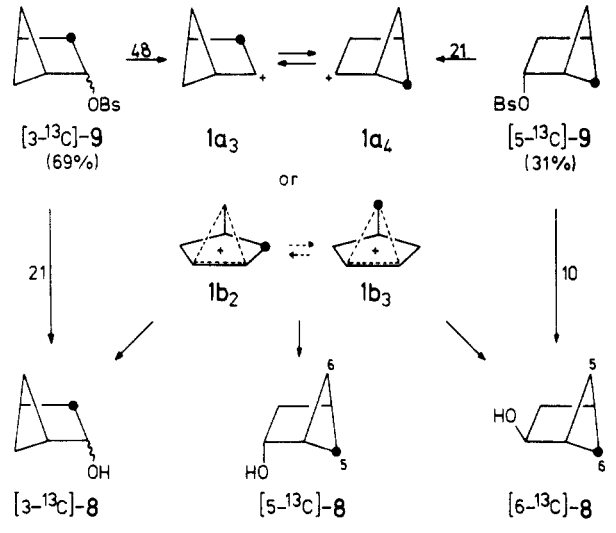
cmpd	conditions	% conv	[3-^{13}C]-**8**	[5-^{13}C]-**8**	[6-^{13}C]-**8**
[3-^{13}C]-**9**	CF_3CO_2H, CF_3CO_2Na, 25 °C	100	37	33	30
	60% aq acetone, 2,6-lutidine, 80 °C	100	49.5	29.5	21
		63	52	31	17

cmpd	conditions	% conv	[2-^{2}H]-**8**	[1-^{2}H]-**8**
[2-^{2}H]-**9**	CF_3CO_2H, CF_3CO_2Na, 25 °C	100	50.6	49.4
	60% aq acetone, 2,6-lutidine, 80 °C	100	56.3	43.7
		90	56.5	43.5
		69	58.3	41.7
		18	63.2	36.8

cmpd	conditions	% conv	net inversion, %
(−)-**9**	60% aq acetone, 2,6-lutidine, 80 °C	100	11.0
		69	16.3
		45	24.1

[a] Values listed are percentages.

Scheme II



The ^{13}C label of [3-^{13}C]-**9** approached a statistical distribution between C-3, C-5, and C-6 (Table I). The weakly nucleophilic TFA sustains the same degeneracy as was observed spectroscopically in nonbasic media.[1,2]

In contrast, the results obtained in aqueous acetone deviate significantly from a statistical distribution (Table I). In order to elucidate the origin of these deviations, a closer examination of the solvolyses of [2-^{2}H]-**9** and of (−)-**9** will be helpful. The agreement of net inversion with excess 2-^{2}H reveals that the unequal distribution of deuterium is entirely due to solvolytic displacement (k_s). Extrapolation of the data to 0% conversion indicates that 31 ± 2% of the brosylate follows the k_s path. The decrease of net inversion (excess 2-^{2}H) with increasing conversion is reasonably attributed to racemization (^{2}H-scrambling) of the brosylate, i.e., to internal return from ion pairs. It follows from comparison of the data for 0% and 100% conversion that 62 ± 3% of the products arises from racemic (equilibrated) brosylate, if the solvolysis of **9** in aqueous acetone is carried to completion.

Now we address the solvolysis of [3-^{19}C]-**9** under identical conditions (Scheme II). Reisolation and ^{13}C NMR spectroscopy of the unreacted brosylate after 62% conversion revealed that the label had been distributed between C-3 (55%) and C-5 (44%); less than 1% was found at C-6. The stereospecificity of internal return is readily explained in terms of the bridged intermediate $\mathbf{1b}_2$ but is also compatible with equilibrating open ions $\mathbf{1a}_3 \rightleftarrows \mathbf{1a}_4$ if the counterion retains its orientation throughout the lifetime of the ion pair. By application of the results obtained above, the average composition of the ^{13}C-labeled brosylate in a complete solvolysis is estimated as 69% (62/2 + 38) [3-^{13}C]-**9** and 31%

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Table II. Dediazoniation of Labeled Bicyclo[2.1.1]hexane-2-diazonium Ions[a]

cmpd	conditions	8 or 13	
		2-^{2}H	1-^{2}H
[2-^{2}H]-**10**	$NaNO_2$, aq $HClO_4$ (pH 3.5)	52.8	47.2
11	D_2O, 0.2 M DONa, *hν*	53.1	46.9
11	MeOD, 0.2 M MeONa, *hν*	62	38

cmpd	conditions	8 or13		
		3-^{13}C	5-^{13}C	6-^{13}C
[3-^{13}C]-**11**	0.2 M NaOH, *hν*	49	43	8
[3-^{13}C]-**11**	MeOH, 0.2 M MeONa, *hν*	62	33	5

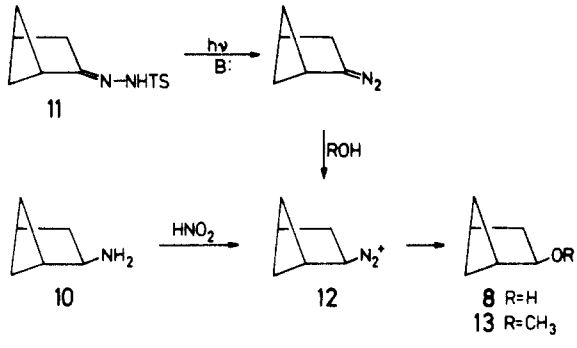
cmpd	conditions	8		
		3-^{2}H	5-^{2}H	6-^{2}H
[3-^{2}H]-**11**	0.2 M NaOH, *hν*	47	45	8[b]
		50	43	7[c]

[a] Values listed are percentages. [b] From ^{2}H NMR spectroscopy; see ref 9. [c] From ^{13}C NMR spectroscopy; see ref 9.

[5-^{13}C]-**9**. Inverting displacement is undergone by 31% of each isotopomer, leading to 21% [3-^{13}C]-**8** and 10% [6-^{13}C]-**8**, respectively. The 69% of **9** proceeding by ionic reaction paths must then produce 28.5% [3-^{13}C]-8, 29.5% [5-^{13}C]-**8**, and 11% [6-^{13}C]-**8**. The 41:43:16 distribution thus obtained indicates that complete degeneracy of **1** is not achieved in aqueous acetone. The result may be rationalized in terms of the bridged ion $\mathbf{1b}_2$ as the major intermediate, undergoing substitution and rearrangement ($\rightarrow \mathbf{1b}_3$) in a 6:1 ratio. Our data are inconsistent with competitive capture and rearrangement of open ions $\mathbf{1a}_3 \rightarrow \mathbf{1a}_4$. A significant contribution of this mechanism would lead to 3-^{13}C > 5-^{13}C = 6-^{13}C; moreover, the difference of 2-^{2}H and 1-^{2}H should exceed net retention.

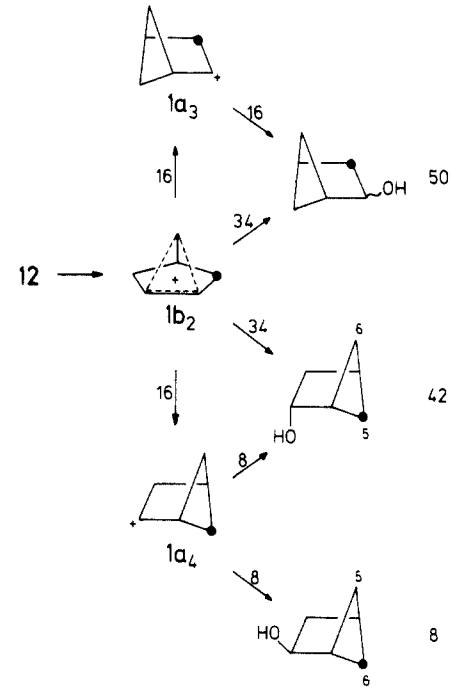
In summary, we have observed a distinct influence of nucleophilicity on the degenerate rearrangement of bicyclo[2.1.1]hexyl cations. However, with brosylate **9**, the unavoidable consequence of nucleophilic media is enhanced solvolytic displacement (k_s) and internal return. These ramifications tend to obscure the effects we set out to observe and force us into regrettably indirect argumentation. A better leaving group might solve these problems.

Dediazoniation of Bicyclo[2.1.1]hexane-2-diazonium Ions. The considerations of the preceding paragraph directed our efforts toward bicyclo[2.1.1]hexane-2-diazonium ions (**12**). The return



of nitrogen to aliphatic carbocations is an unlikely event; even arenediazonium ions undergo N_α–N_β rearrangement only under special conditions and to a minor extent.[16] Solvolytic displacement and ion pairing are quite common for dediazoniation reactions in weakly polar solvents but play a minor role, if any, in water.[14,17] We obtained entirely racemic (±1%) alcohol **8** in the nitrous acid deamination of optically active (82% ee) 2-bicyclo[2.1.1]hexanamine (**10**). This result excludes stereoselective reactions of diazonium ions **12**, such as inverting displacement or retentive

Scheme III



collapse of diazonium–hydroxide ion pairs.

In contrast, the nitrous acid deamination of [2-^{2}H]-**10** produced a 6% excess of [2-^{2}H]-**8** (Table II). The photolysis of 2-bicyclo[2.1.1]hexanone tosylhydrazone (**11**) in D_2O/DONa gave identical results. Light-induced elimination of sulfinate from sulfonylhydrazone anions generates diazo compounds[18] which are protonated by hydroxylic solvents to give diazonium ions and products derived therefrom.[19] This convenient procedure was also adopted for the generation of [3-^{13}C]-**12** and [3-^{2}H]-**12**. The results with different labels are in good agreement (Table II), excluding systematic errors. The label distribution of [^{13}C]-**8** thus obtained (49:43:8) is far from the 33:33:33 distribution expected for equilibrating open ions $\mathbf{1a}_3 \rightleftarrows \mathbf{1a}_4$ and close to the 50:50:0 distribution predicted for the bridged ion $\mathbf{1b}_2$. Although the major portion of the product apparently originates from $\mathbf{1b}_2$, the occurrence of some 6-^{13}C and the excess of 3-^{13}C over 5-^{13}C point to the intervention of additional intermediates. The less polar solvent methanol lowers the fraction of 6-^{13}C but enhances the excess of 3-^{13}C and, analogously, that of 2-^{2}H (Table II).

Our data may be discussed in terms of alternative reaction schemes. The less likely one (Scheme III) assumes that dediazoniation of **12** leads directly (k_Δ) to the bridged ion $\mathbf{1b}_2$ which is captured by solvent competitively with opening to the classical ions $\mathbf{1a}_3$ and $\mathbf{1a}_4$ (1:1). Ignoring the reversal of these reactions in a first approximation, the observed distribution of the label may be reproduced numerically, as shown in Scheme III. Alternatively, Scheme IV suggests initial formation and partial trapping of the open ion $\mathbf{1a}_3$. The bridged ion $\mathbf{1b}_2$ is thought to arise from $\mathbf{1a}_3$ and, eventually, also from **12**. Most of $\mathbf{1b}_2$ would undergo substitution, while a minor fraction rearranges to the isotopomer $\mathbf{1b}_3$, presumably by way of $\mathbf{1a}_4$. Scheme IV is in accordance with ample precedent for unassisted decomposition (k_c) of aliphatic diazonium ions, *followed* by alkyl bridging (the stereochemical result being partial racemization at the migration terminus along with complete inversion at the migration origin).[20] Scheme IV readily explains the solvent effect on label redistribution, while Scheme III incorrectly predicts that the excess of 3-^{13}C (2-^{2}H) should decrease

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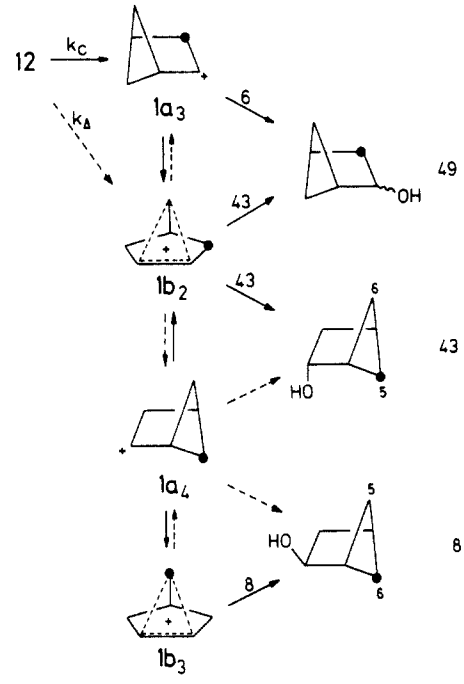
Scheme IV



with increasing nucleophilicity of the medium. Scheme IV has the additional advantage of being applicable to the solvolysis of [3-^{13}C]-**9** as well as to the dediazoniation of [3-^{13}C]-**12**. The solvolysis reaction accentuates k_Δ at the expense of k_c and enhances the $\mathbf{1b}_2 \rightarrow \mathbf{1b}_3$ rearrangement, due to the higher temperature. In terms of Scheme III, the formation of [6-^{13}C]-**8** is invariably associated with an excess of [3-^{13}C]-**8** over [5-^{13}C]-**8**. Thus, Scheme III does not account for the solvolytic data (41:43:16, if corrected for internal return and inverting displacement).

Relative Stabilities of Open and Bridged 2-Bicyclo[2.1.1]hexyl Cations. Schemes III and IV agree in attributing a major role to the bridged ion **1b**. The schemes disagree, however, as to the relative stabilities of the open (**1a**) and bridged (**1b**) structures of **1**. Although we have argued in favor of Scheme IV, more conclusive evidence would be gratifying. The key to the assignment of relative stabilities is provided by the small fraction of [6-^{13}C]-**8**, necessarily derived from the less energetic isomer of **1**.

The origin of [6-^{13}C]-**8** was probed in a double-labeling experiment. Photolysis of [3-^{13}C]-**11** in D_2O/DONa generated the diazonium ion **12** with ^{2}H at position 2 and ^{13}C at position 3. All isotopomeric cations that may evolve successively from [2-^{2}H,3-^{13}C]-**12** are shown in Scheme V (enantiomers have been omitted). If open ions were the more stable species, [6-^{13}C]-**8** would derive predominantly from $\mathbf{1a}_6$, with the deuterium at C-1. In contrast, the bridged ion $\mathbf{1b}_5$ gives rise to equimolar quantities of [1-^{2}H,6-^{13}C]-**8** and [2-^{2}H,6-^{13}C]-**8**. The open ion $\mathbf{1a}_7$ must not be considered as a significant source of [2-^{2}H,6-^{13}C]-**8**. The ^{13}C-distribution excludes rapid equilibration of $\mathbf{1a}_5$ and $\mathbf{1a}_6$; consequently, $\mathbf{1a}_6$ and $\mathbf{1a}_7$ cannot equilibrate either. Thus, the deuterium distribution of [^{2}H,6-^{13}C]-**8** defines its origin unequivocally.

The isotopomers of [^{2}H,6-^{13}C]-**8** are readily distinguished by the β-deuterium isotopic effect on the chemical shift of 6-^{13}C.[21,22] Two signals ($\Delta\delta$ = 0.11 ppm) were observed for C-6 in the ^{13}C NMR spectrum of [^{2}H, ^{13}C]-**8**, corresponding to 4.5% [1-^{2}H,6-^{13}C]-**8** and 4.2% [2-^{2}H,6-^{13}C]-**8**. Since only 9% $\mathbf{1b}_4$ rearranges to $\mathbf{1b}_5$, further interconversion of $\mathbf{1b}_5$ with $\mathbf{1b}_6$ should be scarcely

Scheme V

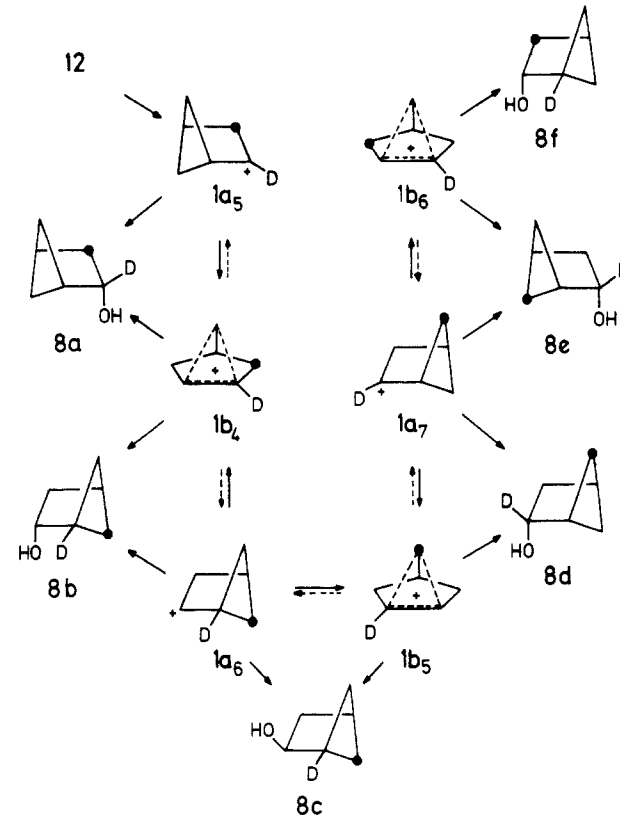


Table III. Isotopomer Distribution of [^{2}H,^{13}C]-**8**

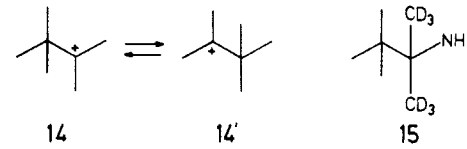
compd[a]	position of ^{2}H	position of ^{13}C	%
8a	2	3	48.5
8b	1	5	42.0
8c	1	6	4.5
8d	2	6	4.2
8e	2	5	<1
8f	1	3	<1

[a] Scheme V.

detectable. The ^{13}C NMR signals of C-3 and C-5 support this notion, showing very minor contributions, if any, of [1-^{2}H,3-^{13}C]-**8** and [2-^{2}H,5-^{13}C]-**8**, respectively (Table III).

Our data provide conclusive evidence for the bridged structure (**1b**) of solvated 2-bicyclo[2.1.1]hexyl cations. The barrier to the interconversion of isotopomers of **1b** should approximate the energy separation of bridged and open ions. The ratio of capture and rearrangement, 91:9, yields $\Delta\Delta G^\ddagger$ = 1.4 kcal·mol^{-1} (25 °C). We add the apparent $\Delta G^\ddagger$ for diffusion-controlled capture, 1.7 kcal·mol^{-1} (H_2O, 25 °C), and arrive at an estimated barrier to interconversion of ca. 3 kcal·mol^{-1}. This value is compatible with the spectroscopic properties of **1** under stable ion conditions[1,2] and with the energy separation between secondary and tertiary 2-bicyclo[2.1.1]hexyl cations.[4]

The confidence in such considerations may be strengthened by comparison with an acyclic case. The spectroscopic properties of the 2,3,3-trimethyl-2-butyl cation (**14**) are those of a classical



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ion undergoing rapid 1,2-methyl shifts. The activation barrier, $\Delta G^\ddagger$ = 3.5 kcal·mol^{-1} (SO_2ClF–SO_2F_2, −136 °C), has been estimated from line broadening in the ^{13}C NMR spectra.[23] Nitrous acid deamination of the labeled amine **15** in water proceeded with

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(22) In the natural-abundance ^{13}C NMR spectrum of a 47:53 mixture of [1-^{2}H]- and [2-^{2}H]-**8**, we observed splitting (ca. 1:1) of the signals of C-3, C-5, and C-6, due to a high-field shift of ca. 0.11 ppm caused by β-D. The isotopic shifts caused by γ-D are smaller by 1 order of magnitude[21] and were not resolved under our operating conditions.

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7% rearrangement.[24] Argumentation as above leads to an estimated barrier, $\Delta G^{\ddagger}$ (H_2O, 25 °C), of 3.2 kcal·mol^{-1}. The agreement with the NMR data suggests that the entropy term and the solvent effect are small or fortuitously cancel. The reaction profiles of **1** and **14** are quantitatively similar but differ in the relative stabilities of open and bridged ions.

1,2-Dimethyl-2-bicyclo[2.1.1]hexyl Cations. For further insight, we compare **1** with **16**, a tertiary bicyclo[2.1.1]hexyl cation of analogous symmetry. The labeled 4-nitrobenzoate [2-$^2H_3$C]-**17** was obtained by conventional methods from 1-methylbicyclo-[2.1.1]hexan-2-one (**19**).[4,25] Solvolysis of [2-$^2H_3$C]-**17** in 55% aqueous acetone at 100 °C led to a 43:57 distribution of the labeled methyl group between positions 1 and 2 of 1,2-dimethylbicyclo-[2.1.1]hexan-2-ol (**18**) (Scheme VI). Scheme II was followed for the preparation of [3-^{13}C]-**19**, replacing acrolein with methacrolein. The nitrobenzoate [3-^{13}C]-**17** was solvolyzed to give a 45:27:28 distribution of ^{13}C between positions 3, 5, and 6 of [^{13}C]-**18**. In contrast to **1**, substitution at C-1 of **16** is not stereoselective. The labeling pattern of [^{13}C]-**18** is consistent with equilibrating open ions **16a**[4] and excludes a significant contribution of the bridged structure **16b**. The excess of [3-^{13}C]-**18**, as well as the excess of [2-$^2H_3$C]-**18**, indicates that nucleophilic capture of the initially formed ion competes with rearrangement. However, the Wagner–Meerwein rearrangement of **16** proceeds faster than that of the 2,3,3-trimethyl-2-butyl cation (**14**). The behavior of **16** is closely analogous to that of the 1,2-dimethyl-2-norbornyl cation.[26]

Conclusion

We found the 2-bicyclo[2.1.1]hexyl system to be well suited for probing the structure (i.e., geometry) of short-lived, solvated ions. In this regard, **1** compares favorably with the 2-norbornyl cation whose intrinsic exo selectivity defies clear-cut answers. Competitive nucleophilic capture dissects the degenerate rearrangement(s) of **1** into two distinct processes. Equivalence of C-1 and C-2 and also C-3 and C-5 is attributed to bridging (**1b**), as the pattern of label redistribution excludes rapidly equilibrating open ions (**1a**). The results of a double-labeling experiment identify the slower process, leading to exchange of all CH_2 groups, as an interconversion of bridged ions. The estimated barrier to interconversion, approximating the energy separation of bridged and open ions, is ca. 3 kcal·mol^{-1}. It should be possible to "freeze" the exchange of C-3,5 with C-6 by very low temperature solid-state NMR techniques.[27] The application of advanced computational methods to **1** might reconcile the divergent results of previous treatments (MINDO/3,[28] ab initio STO-3G[29]).

In contrast to **1**, the 1,2-dimethyl-2-bicyclo[2.1.1]hexyl cation (**16**) behaves as a classical ion, equilibrating faster than the acyclic 2,3,3-trimethyl-2-butyl cation (**14**). The energy profiles of both secondary and tertiary carbocations in aqueous solution resemble those observed in nonbasic media. Nucleophilic solvation does not appreciably affect, or even reverse, the relative stabilities of bridged and open ions.

Experimental Section

General Methods. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Specific rotations were obtained on a Perkin-Elmer 141 polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker WP-80, WM-250, and AM-400 instruments. ^{2}H (61.42-MHz) and ^{13}C (100.61-MHz) NMR spectra were recorded on the Bruker AM-400 spectrometer. For quantitative measurements of ^{13}C-distributions, a pulse spacing of 270 s (ca. 10 times the longest relaxation time) was used to eliminate saturation effects. Gating off the proton decoupler just after data acquisition served to eliminate Overhauser enhancements. The spectral width was kept to 5000 Hz. High-pressure liquid chromatography (HPLC) was performed on a LDC instrument with 25 × 1.5 cm silica gel columns (Si 60, 5 μm, Macherey and Nagel). Gas chromatography (GC) was performed on a Siemens Sichromat equipped with glass capillary columns. The preparation and operation of glass capillaries coated with optically active PPG has been described previously.[14]

[3-^{13}C]Bicyclo[2.1.1]hexan-2-one. To a stirred suspension of lithium aluminum hydride (4.0 g, 105 mmol) in 100 mL of anhydrous ether was added a solution of [1-^{13}C]methyl propiolate (**2**)[10] (8.2 g, 96.5 mmol) in 30 mL of anhydrous ether. The mixture was warmed to room temperature and stirred for 40 h while 1.7 g (45 mmol) of lithium aluminum hydride was added in small portions. The progress of the reduction was monitred by GC analysis of aliquots. Water (250 mL) was added with caution, and the resulting suspension was continuously extracted with ether for 48 h. The extracts were dried over $MgSO_4$ and concentrated to 50 mL. Short-path distillation of the residue afforded a fraction consisting largely (63%) of [1-^{13}C]-2-propen-1-ol (**3**) contaminated with ether (18%), [1-^{13}C]propan-1-ol (6%), and [1-^{13}C]-2-propin-1-ol (9%).

To a mixture of crude **3**, tri-*n*-butylamine (13.7 g), and di-*n*-butyl ether (32.0 g) was added dropwise at −15 °C thionyl chloride (5.4 mL). After the mixture warmed to room temperature, the volatile products were isolated by short-path distillation in vacuo. The distillate was washed twice with 20 mL of 2% aqueous sodium hydroxide, dried over $MgSO_4$, and purified by fractionation (concentric-tube column, Fischer MMS 255) to give 3.6 g (48%) of [3-^{13}C]-3-chloropropene (**4**): bp 43–47 °C; ^{13}C NMR δ 45.2 (>96%, all other signals <4%).

The allylation of 2-(1-ethoxyethoxy)-3-butenenitrile (**5**)[30] was performed according to the general procedure given by Stork[12] (ca. 50% yield). Five and one-half grams of the crude product (80% pure, ca. 23 mmol) was stirred for 1 h with 15 mL of methanol and 5 mL of 5% aqueous sulfuric acid. Extracting with ether, washing (saturated brine), drying ($MgSO_4$), concentrating in vacuo, and short-path distilling afforded the crude cyanohydrin (80–90% yield). Ether solutions of the crude cyanohydrin (0.5 g, ca. 3.4 mmol) were stirred for 1 h with 10 mL of 2 M sodium carbonate. The organic layer was separated, and the aqueous phase was extracted with 5 mL of ether. The combined ether solutions were washed (saturated brine) and dried ($MgSO_4$). Pentane (10 mL) was added, and the solution of [4-^{13}C]penta-1,5-dien-3-one (**6**) was irradiated for ca. 1 h (medium-pressure mercury arc, 150 W, quartz vessel). The progress of the photocycloaddition was monitored by GC. Six runs were combined and fractionally distilled to yield 53% of [3-^{13}C]-**7**: ^{13}C NMR δ 40.8 (C-3, 96%), 40.9 (C-5,6, 4%), no enhancement of the remaining signals at δ 214.0 (C-2), 56.0 (C-1), and 35.8 (C-4) was observed.

The labeled ketone (202 mg, 2.1 mmol) was added to a hot solution of *p*-toluenesulfonylhydrazine (0.6 g) in methanol (3 mL). The mixture was heated at reflux for 2 h and cooled to 0 °C. The crystals were filtered with suction and washed with cold methanol to give 0.42 g (77%) of the tosylhydrazone [3-^{13}C]-**11**: mp 183–185 °C [lit. mp 184–185 °C].[31]

Bicyclo[2.1.1]hexan-2-ol. To a suspension of lithium aluminum hydride (1.0 g, 25 mmol) in ether (50 mL) was added dropwise a solution of **7** (2.4 g, 25 mmol) in ether (30 mL). The mixture was heated at reflux for 1 h and hydrolyzed in the conventional manner. Sublimation in vacuo afforded 2.0 g (80%) of pure **8**; mp 82–84 °C (84 °C[8]). [2-^{2}H]-**8** was obtained analogously from **7** and $LiAlD_4$. Lithium aluminum hydride reduction of [3-^{13}C]-**7** provided [3-^{13}C]-**8**: ^{13}C NMR δ 38.3 (C-2, 96%), 34.7 (C-5, 2%), 39.2 (C-6, 2%). The spectra of [3-^{13}C]-**8** identify the signal of C-3. The remaining ^{13}C NMR signals of **8** were assigned on the basis of multiplicities and LIS values, Δδ [**8**]/[Pr(DPM)$_3$] (given in parentheses): ^{13}C NMR δ 34.7 (15.6, t, C-5), 38.3 (21.2, t, C-3), 38.8 (12.4, d, C-4), 39.2 (10.2, t, C-6), 46.3 (21.2, d, C-1), 72.2 (54.0, d, C-2).

(−)-Bicyclo[2.1.1]hexan-2-ol. Sucrose (100 g), Baker's yeast (40 g), and water (200 mL) were stirred for 30 min. Bicyclo[2.1.1]hexan-2-one (2.0 g, 20.8 mmol) was then added. Stirring was continued for 6 days with addition of more saccharose (20 g) and water (50 mL) after 2 and 4 days. The conversion of **7** and the optical activity of **8** were monitored by GC. The mixture was separated by centrifugation (ca. 40 min at 4000 rpm) and continuous extraction of the viscous liquid with pentane (48 h). The extracts were dried over $MgSO_4$ and evaporated. Short-path

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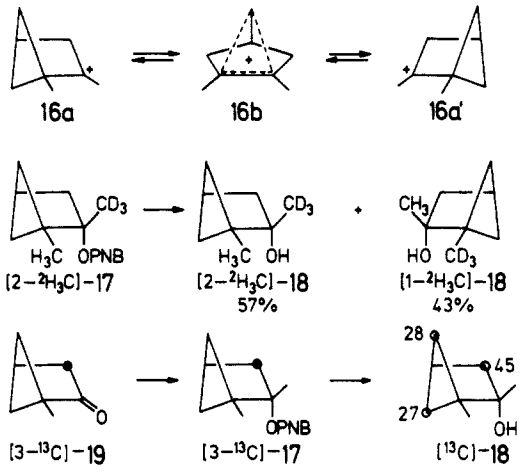
Scheme VI



distillation afforded a mixture of **8** (70%) and **7** (30%) from which pure (−)-**8** (0.28 g, 14%) was isolated by preparative GC and sublimation in vacuo: $[\alpha]^{23}_D$ −13.7° (*c* 0.073 in pentane); ee 82 ± 1% (by GC on optically active PPG[14]).

2-Bicyclo[2.1.1]hexyl Brosylate (9). To a solution of **8** (0.22 g, 2.25 mmol) in anhydrous pyridine (3 mL) was added at 0 °C *p*-bromobenzenesulfonyl chloride (0.60 g, 2.35 mmol). The mixture was stirred at 0 °C for 2 h, kept in the refrigerator for 2 days, poured into ice–water (10 mL), and extracted with ether (4 × 10 mL). The extracts were washed with dilute sulfuric acid, aqueous $NaHCO_3$, and water. Drying ($MgSO_4$) and evaporating the ether solution afforded **9** (0.52 g, 73%) as a solid which was recrystallized from hexane: mp 65 °C; ^{1}H NMR δ 0.93 (6s-H, dd, $J_{6s,6a}$ = 7, $J_{6s,5s}$ = 9.7 Hz), 1.15–1.85 (m, 5 H), 2.07 (3a-H, dddd, $J_{3a,3s}$ = 11.5, $J_{2,3a}$ = 7.2, $J_{3a,5a}$ = 2.5, $J_{3a,4}$ = 1.6 Hz), 2.54 (m, 1-H, 4-H), 5.05 (2-H, ddd, $J_{2,3a}$ = 7.2, $J_{2,3s}$ = 3.2, $J_{2,5a}$ = 1.6 Hz), 7.75 (m, 4 H). Anal. Calcd for $C_{12}H_{13}BrO_3S$: C, 45.43; H, 4.13. Found: C, 45.56; H, 4.09. [2-^{2}H]-**9**, [3-^{13}C]-**9**, and (−)-**9** [$[\alpha]^{20}_D$ −5.5° (*c* 0.157, $CHCl_3$)] were prepared analogously.

2-Bicyclo[2.1.1]hexanamine (10). Bicyclo[2.1.1]hexan-2-one (**7**) (2.0 g, 20.8 mmol), hydroxylamine hydrochloride (1.7 g, 24.5 mmol), ethanol (30 mL), and pyridine (20 mL) were heated at reflux for 2 h. After evaporation of the solvents in vacuo, water (100 mL) was added. Extraction with ether and the usual workup provided 1.8 g (78%) of 2-bicyclo[2.1.1]hexanone oxime: mp 49–51 °C (from *n*-pentane); ^{1}H NMR δ 1.38 (dd, 2 H), 2.0 (m, 2 H), 2.3 (m, 0.3 H), 2.4 (m, 1.7 H), 2.6 (m, 1 H), 3.0 (dt, 0.85 H), 3.7 (dt, 0.15 H), 7.9 (1 H); this NMR data indicated a syn–anti (15:85) mixture. Anal. Calcd for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.15; N, 12.57.

2-Bicyclo[2.1.1]hexanone oxime (0.6 g, 5.4 mmol), lithium aluminum hydride (0.5 g), and ether (40 mL) were heated at reflux for 2 h. Excess $LiAlH_4$ was hydrolyzed by dropwise addition of water. The solution was filtered, dried over K_2CO_3, and concentrated to ca. 15 mL. Anhydrous hydrogen chloride was introduced, and the precipitate of **10**·HCl (0.47 g, 65%) was recrystallized from ethyl acetate–methanol: mp (sublimation) 295 °C; ^{1}H NMR of **10** (C_6D_6) δ 0.8–1.25 (m, 3 H), 1.30 (s, NH_2), 1.45–1.7 (m, 2 H), 2.0 (dddd, *J* = 11.1, 7.7, 2.4, 1.45 Hz, 1 H), 2.15–2.5 (m, 2 H), 3.27 (ddt, *J* = 7.7, 2.9, 1.45 Hz, 1 H). Anal. Calcd for $C_6H_{12}ClN$: C, 53.93; H, 9.05; N, 10.48. Found: C, 54.07; H, 9.09; N, 10.40. [2-^{2}H]-**10** was obtained analogously by $LiAlD_4$ reduction of the oxime.

For the preparation of optically active **10**, 3.0 g of (−)-**9**, 2.0 g of sodium azide, and 30 mL of dimethyl sulfoxide were stirred for 68 h at 80 °C. Partitioning between water and ether afforded a solution of the azide (ν_{N_3} 2100 cm^{-1}) which was heated at reflux with 1.5 g of lithium aluminum hydride. After 3 h the mixture was hydrolyzed and partitioned between ether and aqueous hydrochloric acid. The acid solutions were made alkaline with concentrated sodium hydroxide and extracted with ether. Introduction of anhydrous HCl into the dried (K_2CO_3) and concentrated ether solution precipitated 0.65 g (51%) of **10**·HCl: ee 76 ± 2% (by GC of the *N*-(trifluoroacetyl)-(*S*)-prolyl amide[15]).

Solvolytic Reactions of 9 (Table I). Trifluoro acetolyses of labeled brosylates (1 mmol in 15 mL of TFA) were performed in the presence of 10 equiv of sodium trifluoroacetate (25 °C, 16 h). Water (40 mL) and aqueous potassium hydroxide (50 mL) were added to obtain pH >12. The mixture was stirred for 2 h at room temperature and extracted with ether. The extracts were dried ($MgSO_4$) and concentrated by distillation (Vigreux column) at normal pressure. Preparative GC of the residue afforded bicyclo[2.1.1]hexan-2-ol (**8**) of >99% purity for NMR analysis.

Labeled brosylate (0.33 g, 1 mmol), 2,6-lutidine (0.2 mL), acetone (25 mL), and water (17 mL) were stirred in a pressure bottle at 80 °C for 10–60 min. The conversion was estimated by GC after cyclohexanol was added as an internal standard to 0.5 mL of the mixture. The major portion was diluted with saturated brine (100 mL) and extracted with ether. After the ether was dried ($MgSO_4$) and distilled (as above), short-path distillation in vacuo transferred the volatiles to a cold trap, from which **8** was isolated by preparative GC. HPLC (ether–pentane 1:1) of the residue afforded unreacted **9**. The deuterium distribution of recovered [^{2}H]-**9** from solvolyses of [2-^{2}H]-**9** was as follows (percent conversion, percent 1-^{2}H): 18, 15.7; 69, 35.4; 90, 40.5. The ^{13}C distribution of [^{13}C]-**9**, recovered after 62% conversion, was 55% 3-^{13}C, 44% 5-^{13}C, and ca. 1% for all other carbons. The chemical shift of C-3 (δ 35.7) was derived from the spectra of [3-^{13}C]-**9**, while the signals of C-5 (δ 35.6) and C-6 (δ 38.3) were assigned in analogy to **8**.

Dediazoniation Reactions (Table II). The tosylhydrazones **12** and [3-^{13}C]-**12** (0.8 g, 3 mmol) were photolyzed (medium-pressure mercury arc, quartz vessel) in 35 mL of 0.2 M NaOH (NaOD–D_2O). The evolution of nitrogen (calcd 69 mL, found 65 mL) was monitored to avoid overirradiation. The solution was saturated with sodium chloride and extracted with ether. As above, the alcohol **8** was purified by preparative GC or sublimation. Photolysis mixtures of **12** in 0.2 M methanolic $NaOCH_3$ were diluted with water and extracted with *n*-pentane. Preparative GC provided 2-methoxybicyclo[2.1.1]hexane (**13**): ^{1}H NMR δ 0.88 (dd, *J* = 9.5, 6.8 Hz, 6s-H), 1.35 (dd, *J* = 9.5, 6.8 Hz, 5s-H), 1.2–1.7 (m, 3 H), 1.90 (dddd, *J* = 11.2, 6.8, 2.5, 1.5 Hz, 3a-H), 2.4 (m, 1 H), 2.6 (m, 1 H) 3.32 (s, OCH_3), 3.88 (ddd, *J* = 6.8, 3.0, 1.5 Hz, 2-H); ^{13}C NMR δ 35.1 (C-5), 35.2 (C-3), 38.4 (C-4), 38.5 (C-6), 42.9 (C-1), 58.2 (C-2), 81.1 (OCH_3). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.04; H, 10.66.

A solution of **10**·HCl (0.27 g) in water (50 mL) was adjusted to pH 3.5 (glass electrode) with dilute perchloric acid. Solutions of sodium nitrite (1.1 g in 15 mL of water) and of perchloric acid (0.1 M) were concurrently added to keep the pH constant. Stirring was continued for 16 h at room temperature. The products were extracted with ether and isolated by preparative GC ([2-^{2}H]-**10**) or analyzed on capillaries coated with optically active PPG.[14] For the enantiomers of **8**, the separation factor and the resolution were α = 1.009 and R_S = 1.26, respectively. The ratio of enantiomers observed for the deamination product, 49.1:50.8, agreed with that of racemic **8**, 49.5:50.5 (the latter value indicating a small systematic error). Deaminations of [2-^{2}H]-**10** and optically active **10** were also performed in a water (50 mL)–ether (20 mL) biphasic system. Such conditions have occasionally been found to enhance ion pairing (diazo hydroxide collapse).[17,32] In the case of **10**, the results of homogeneous and heterogeneous deaminations were identical.

1,2-Dimethyl-2-bicyclo[2.1.1]hexyl *p*-Nitrobenzoate (17). 2-(1-Ethoxyethoxy)-3-methyl-3-butenenitrile[30] was reacted with [3-^{13}C]-3-chloropropene (see above) according to the general procedure given by Stork[12] (ca. 50% yield). The product was processed to [3-^{13}C]-**19** (overall yield ca. 45%), as described for [3-^{13}C]-**7**. The directions of Sorensen[4] for the synthesis of [2-^{2}H$_3$C]-**18** (**19** + CD_3MgI) were applied analogously to the preparation of [3-^{13}C]-**18**. ^{13}C NMR of **18** (multiplicities and LIS values, Δδ [**18**]/[Pr(DPM)$_3$], in parentheses): δ 13.5 (q, 12.4, 1-CH_3), 23.3 (q, 23.0, 2-CH_3), 33.6 (d, 11.5, C-4), 42.2 (t, 15.0, C-5), 43.9 (t, 9.7, C-6), 46.2 (t, 22.1, C-3), 55.5 (s, 17.7, C-1), 77.6 (s, 43.4, C-2). With [3-^{13}C]-**18**, 96% of the label was located at C-3.

Following the literature procedure,[33] a THF solution of **18** was successively treated with *n*-butyllithium and *p*-nitrobenzoyl chloride. The *p*-nitrobenzoate **17** (68% yield) was recrystallized from *n*-hexane: mp 139–141 °C. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.55; H, 6.27; N, 5.05. [2-^{2}H$_3$C]-**17** and [3-^{13}C]-**17** were prepared analogously. $LiAlH_4$ reduction of [3-^{13}C]-**17** and ^{13}C NMR spectroscopy of [3-^{13}C]-**18** proved that no redistribution of the label had occurred.

The labeled *p*-nitrobenzoates (0.3 g, 1.1 mmol), calcium carbonate (2.5 g), acetone (50 mL), and water (40 mL) were stirred for 96 h at 100 °C in a pressure bottle. Water (100 mL) was added, and the mixture was extracted with ether (4 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to 5 mL. Short-path distillation and preparative GC afforded **18** (purity >99%) whose isotopic distribution was estimated by NMR spectroscopy (see Scheme VI).

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