^{13}C NMR Chemical Shifts and Transfer of ^{13}C Spin Saturation and the Structures and Rearrangements of 9-Barbaralyl Cations, Protonated Barbaralone, and Barbaralone

Carin Engdahl and Per Ahlberg*

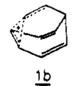
Contribution from the Institute of Chemistry, University of Uppsala, S-751 21 Uppsala, Sweden. *Received October 2, 1978*

Abstract: The usefulness of a recently developed technique for detection and quantitative study of exchange reactions, ^{13}C spin-transfer saturation, is demonstrated. It has been used to measure rates and elucidate reaction mechanisms for the degenerate rearrangements of 1,9-dimethyltricyclo[3.3.1.$0^{2,8}$]nona-3,6-dien-9-yl cation (1,9-dimethyl-9-barbaralyl cation) (**2**), 9-methyltricyclo[3.3.1.$0^{2,8}$]nona-3,6-dien-9-yl cation (9-methyl-9-barbaralyl cation) (**3**), protonated tricyclo[3.3.1.$0^{2,8}$]nona-3,6-dien-9-one (protonated barbaralone) (**4**), and tricyclo[3.3.1.$0^{2,8}$]nona-3,6-dien-9-one (barbaralone) (**5**). The ions were synthesized in superacid using an ion generation apparatus for low-temperature synthesis (ca. 0 to ca. −155 °C). The ^{13}C chemical shifts of the ions show that they contain cyclopropylcarbinyl cation like structural elements. No significant charge delocalization into the double bonds was detected. Some of the ^{13}C spin relaxation times (T_1) are also reported. Ion **3** is shown to undergo a 4 + 2 carbon scrambling through divinylcyclopropylcarbinyl cation–divinylcyclopropylcarbinyl cation rearrangements rather than through a regular Cope mechanism. This was inferred from the small rearrangement barrier, 7.63 + 0.21 (−0.18) kcal mol^{-1} (−128.6 °C) of **3** compared with those of **4** (13.4 + 0.3 (−0.2) kcal mol^{-1} at −43.5 °C) and **5** (10.2 ± 0.1 kcal mol^{-1} at −93.2 °C). The ^{13}C spin-transfer experiments with **2** show that this ion undergoes more extensive rearrangements than **3**. The bridge constituted by C-1, -5, and -9 rotates in a stepwise fashion around the pseudoring made up by the six carbons C-2, -3, -4, -6, -7, and -8. The barrier for exchange of C-3,C-7 with C-2,C-8 and C-4,C-6 was 7.58 + 0.33 (−0.28) kcal mol^{-1} at −128.0 °C. Microscopic mechanisms for the "rotation" are discussed. The totally degenerate parent barbaralyl cation (**1**) is found to have a ^{13}C NMR spectrum at −136 °C that shows essentially no signal at the S/N ratio of ca. 6 expected if there was no exchange. The NMR probe temperature was calibrated using a chemical reaction whose rate was determined in the probe as well as outside in a low-temperature thermostat (the ion generation apparatus).

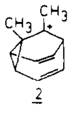
Structure **1a**, the 9-barbaralyl cation, contains as structural elements the cyclopropylcarbinyl cation and two homoallylic cations partially superimposed on each other. The stereoelectronic composition of these elements suggests that the ion is very reactive and has access to several interesting pathways that are either degenerate or nondegenerate in nature. Barbaralyl cations have been synthesized in superacid media at ca. −130 °C and directly observed in ^1H NMR.[1] These studies have indeed revealed rapid and extensive degenerate rearrangements as well as nondegenerate reactions to 1,4-bishomotropylium ions,[1-3] the bishomoaromatic character of which has recently been confirmed by ^{13}C NMR studies.[3,4]

The ^1H NMR chemical shifts of the barbaralyl cations indicated the 9-barbaralyl cationic structure with the positive charge delocalized into the cyclopropane ring (**1b**). The spectrum of the unsubstituted barbaralyl cation, assigned structure **1**, was observed as a sharp singlet at ca. −125 °C.

1a



1b



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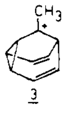

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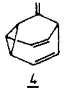

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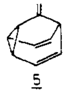

5

This indicates the presence of rapid scrambling of all nine carbons.[1b,d] The temperature dependence of the band shapes of the 1,9-dimethyl-9-barbaralyl cation (**2**) showed the presence of a 6-carbon scrambling,[1c,d] and the behavior of 9-methyl-9-barbaralyl cation (**3**) established 4 + 2 carbon scramblings.[1a,d] It was concluded that the degenerate rearrangement of ion **3** does not proceed by an ordinary Cope mechanism but by a divinylcyclopropylcarbinyl cation–divinylcyclopropylcarbinyl cation rearrangement (see Scheme II). This conclusion was based upon the observation that protonated barbaralone has a much larger Cope rearrangement barrier than barbaralone, which in turn has a much larger barrier toward rearrangement than ion **3**. The positive charge was considered to retard the rearrangement by the ordinary Cope mechanism. Therefore, the above-mentioned mechanism is suggested to operate in the rearrangements of **3**.[1] Such a mechanism has also been proposed as an explanation of the scrambling results obtained with the 9-barbaralyl cation (**1**) generated under solvolytic conditions.[5]

In order to firmly establish the structures of the barbaralyl cations and to study their rearrangements in detail, we have investigated ions **1**, **2**, and **3**, protonated barbaralone (**4**), and barbaralone (**5**) by ^{13}C NMR, thereby also hoping to resolve some controversy about their structures and their mechanisms of rearrangement.[6]

The degenerate rearrangements have been investigated with a new technique, *transfer of ^{13}C spin saturation*,[7,8] for quantitative investigation of exchange phenomena.[8] In this method, an extra ^{13}C frequency is used for saturation of a selected ^{13}C band, while the ^{13}C spectrum (proton noise decoupled) is observed. Transfer of spin saturation is observed when the saturated carbon is exchanging with another carbon at a rate comparable with or faster than the rate at which the latter carbon undergoes relaxation (T_1). At comparable rates the exchange rate can be calculated from the amount of spin saturation transferred and the measured T_1 value for the partially saturated nonirradiated carbon.[8a,b] If the exchange rate is much slower than the relaxation process, no such transfer is observed.

This new tool makes it possible to elucidate reaction mechanisms for systems in which three or more magnetically different carbons exchange, i.e., it can show whether some carbons are exchanging preferentially with each other or not and consequently make it possible to exclude mechanistic alternatives.[8d,f,9]

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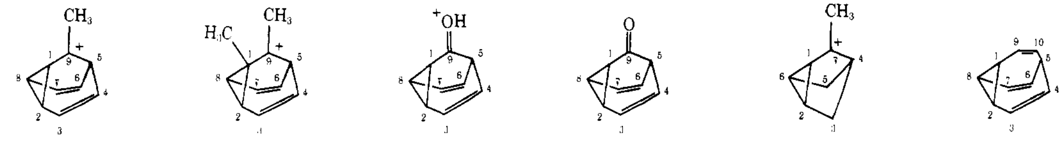
Table I. ^{13}C Chemical Shifts in Parts per Million of **2–4**, **11**, and **12**



carbon atom	**3**[a]	**2**[b]	**4**[c]	**5**[d]	**11**[e]	**12**[f]
C-1	72.5	81.2	38.3	26.8	67.5	20.5
C-2	86.2	94.3	53.8	33.1	83.7	20.5
C-3	116.2	116.6	119.5	121.5	43.7	127.2
C-4	130.2	129.7	127.6	128.3	47.0	128.1
C-5	59.2	59.3	48.6	49.9	43.7	30.0
C-6	130.2	129.7	127.6	128.3	83.7	128.1
C-7	116.2	116.6	119.5	121.5	293.2	127.2
C-8	86.2	94.3	53.8	33.1		20.5
C-9	260.0	252.4	238.7	214.0[g]		127.2
C-10						128.1
Me-9	33.2	31.7				
Me-7					33.7	
Me-1		18.3				

[a] At ca −132 °C; internal standard CD_2Cl_2; δ_C 53.8; solvent, FSO_3H-SO_2ClF-SO_2F_2. [b] At −130 °C; internal standard CD_2Cl_2; solvent, FSO_3H-SO_2ClF-SO_2F_2. [c] At −128 °C; internal standard CD_2Cl_2; solvent FSO_3H-SO_2ClF-SO_2F_2. [d] At −103 °C; internal standard CD_2Cl_2; solvent, $CHCl_2F$. [e] At −80 °C; external standard Me_4Si; solvent FSO_3H-SbF_5-SO_2ClF or SbF_5-SO_2ClF.[11] [f] At −62 °C; internal standard Me_4Si; solvent, $CDCl_3$.[12a] [g] 211.1 ppm at ca. −82 °C; internal standard CS_2; δ_C 192.8; solvent, CS_2-CD_2Cl_2-$(CD_3)_2CO$.

Results and Discussion

^{13}C Chemical Shifts and Structures of the Ions. The barbaralyl cations were synthesized from related alcohols, and barbaralone was the precursor of protonated barbaralone. A CD_2Cl_2 solution of the precursor was mixed into a mixture of FSO_3H-SO_2ClF-SO_2F_2 in a 5-mm NMR tube at ca. −130 °C using the ion generation machine shown in the Experimental Section (Figure 3).[10] Usually, it was not possible to prepare the ionic solutions free from other carbocations at barbaralyl cationic concentrations > 0.2 M. The barbaralyl cations rearrange rapidly to 1,4-bishomotropylium ions at ca. −115 °C, and, therefore, the ions could only be studied in a narrow temperature interval, i.e., ca. 30 °C below −115 °C.[2]

The NMR spectra were obtained with a JEOL-FX100 NMR pulse spectrometer equipped with a 5-mm variable temperature $^1H/^{13}C$ dual probe. Complete noise-decoupled ^{13}C spectra of ions **2–5** could be obtained with an acceptable *S*/*N* ratio in less than 10 min (Figure 1), despite the low concentrations of the ions. The reason for this is mainly the short ^{13}C relaxation times (<0.1 s) (Table II) at the low observation temperatures (ca. −130 °C), which allows the repetition times to be kept short.

In contrast to the ^1H spectra, which showed broad, nonstructured, and overlapping bands, caused by ^1H-^1H coupling, the exchange reactions, and small shift differences, the ^{13}C spectra exhibited well-resolved singlets (Figure 1a). The structural evidence presented below fully confirms earlier conclusions based upon the ^1H NMR data.[1]

Protonated Barbaralone (4) and Barbaralone (5). The ^{13}C spectrum of **5** in $CHCl_2F$ was obtained at −103 °C. At this temperature the carbon exchanges due to the Cope rearrangements of both **4** and **5** are slow on the ^{13}C NMR time scale and frozen spectra of barbaralone (**5**) and protonated barbaralone (**4**) were obtained. The chemical shifts are summarized in Table I. The assignments were made with the aid of off-resonance decoupling experiments with **5** and comparison with other ions (Table I).

The data of **5** agree, except for the carbonyl carbon, with those obtained by Nakanishi and Yamamoto[14b] (Table I). Comparison of the data from **5** and **4** shows that the charge in **4** is delocalized onto C-1, -2, -8, and -9, since these are shifted downfield relative to the corresponding carbons in **5**. Thus, **4** contains a cyclopropylcarbinyl cation like structural element. The chemical shifts of the other carbons do not suggest that they carry significant charge.

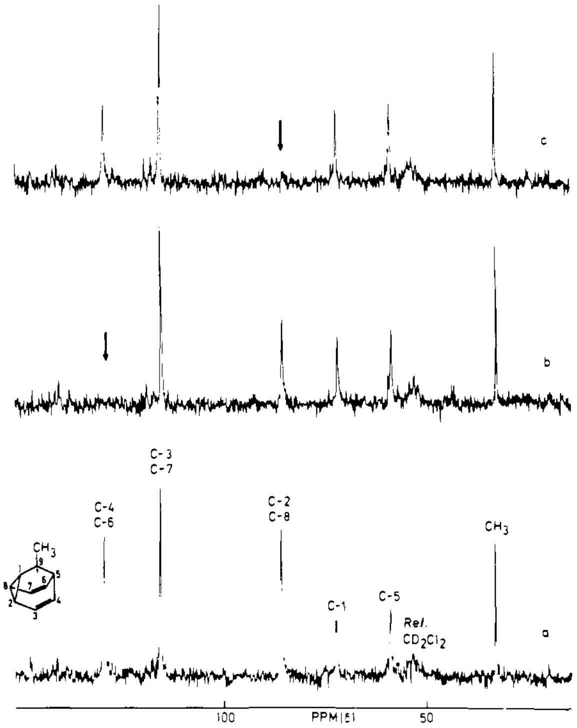


Figure 1. ^{13}C NMR spectra of cation **3** at −128.6 °C: (a) without saturation of any of the carbon atoms; (b) with saturation of carbon atoms C-4, C-6; (c) with saturation of carbon atoms C-2, C-8.

9-Methyl-9-barbaralyl Cation (3) and 1,9-Dimethyl-9-barbaralyl Cation (2). In this work, ion **3** was also prepared from the new precursor 3-methylbicyclo[3.2.2]nona-3,6,8-trien-2-ol (**6**) (Scheme I). Other precursors used were 2-methylbicyclo[3.2.2]nona-3,6,8-trien-2-ol (**7**) and 9-methyltricyclo-[3.3.1.0^{2,8}]nona-3,6-dien-9-ol (**8**). The first ion observed from all these precursors was **3**. Ion **2** was made either from the new precursor 2,3-dimethylbicyclo[3.2.2]nona-3,6,8-trien-2-ol (**9**) or 1,9-dimethyltricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-ol (**10**) (Scheme I).

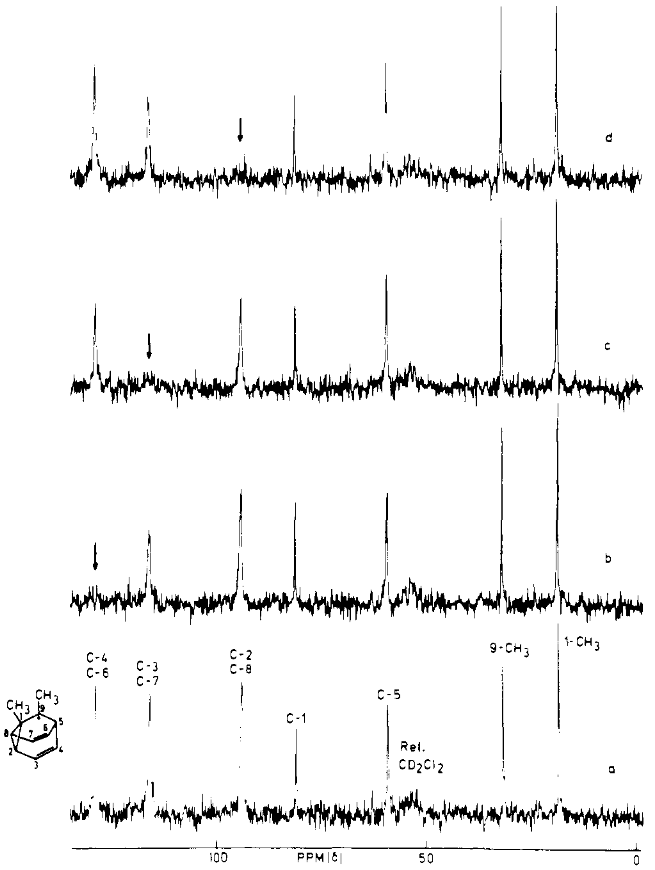
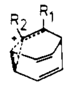


Figure 2. ^{13}C NMR spectra of cation **2** at −130.1 °C: (a) without saturation of any of the carbon atoms; (b) with saturation of carbon atoms C-4, C-6; (c) with saturation of carbon atoms C-3, C-7; (d) with saturation of carbon atoms C-2, C-8.

Figures 1a and 2a show the spectra of **2** and **3** and Table I the chemical shifts of **2** and **3** at ca. −130 °C. Comparison of their shifts with those of **4**, **5**, 3-methyl-3-nortricyclyl cation (**11**),[11] and bullvalene (**12**),[9,12] together with the results of the ^{13}C spin-transfer saturation experiments described below, clearly show the 9-barbaralyl cationic structure of the ions. Even more charge is distributed over C-1, -2, -8, and -9, constituting the skeleton of the cyclopropylcarbinyl cationic structural element of **2** and **3** than in **4**, but the olefinic carbons are essentially unperturbed as concluded from the constancy of the chemical shifts of these carbons in species **2–5** and **12** (Table I). The data show that the two methyl groups of **2** occupy the 1 and 9 carbons. No trace of the ion with methyl groups in the 5 and 9 positions could be detected.

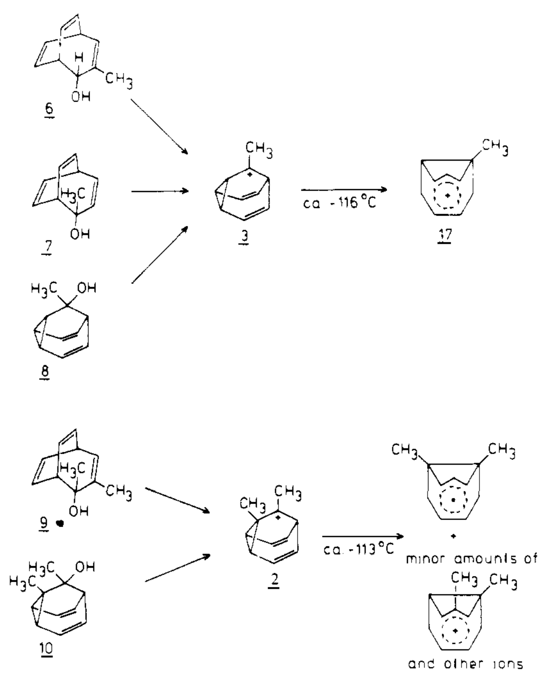
Our data confirm that the structures shown below (**2–4**) are proper representations of the ions.[1]

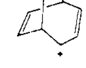


2 $R_1 = R_2 = CH_3$
3 $R_1 = CH_3, R_2 = H$
4 $R_1 = -OH, R_2 = H$

The 9-Barbaralyl Cation (1). When a dilute CD_2Cl_2 solution of bicyclo[3.2.2]nona-3,6,8-trien-2-ol (**13**) was mixed into superacid in the usual way, a carbocation was formed.[1b,d] ^{1}H NMR showed a sharp singlet at −121 °C, which indicated the presence of fast, totally degenerate, rearrangements. An upper limit for the barrier of the total degenerate rearrangement was estimated to be 6 kcal mol^{-1}. It was not possible to observe the frozen structure of the ion. However, the chemical shift of the singlet compared with ^{1}H shifts of model compounds indicated the 9-barbaralyl cation structure **1b** rather than the bicyclo[3.2.2]nona-3,6,8-trienyl cation (**14**) structure for ion **1**. Another structure suggested for the ion is **15**, which is not easily excluded on the basis of the proton NMR data.[5,6] The ^{13}C NMR spectrum of **1** is most interesting in this context,

Scheme I





14

15

since it could potentially allow one to distinguish between the proposed structures. However, the spectrum of **1** at −136 °C showed only a noisy base line with insinuation of a broad band instead of signals with $S/N \simeq 6$ expected if the exchange was slow at the ^{13}C NMR time scale. A substantially increased S/N ratio could not be obtained before a considerable fraction of the ion had rearranged to the parent 1,4-bishomotropylium ion (**16**). Obviously the degenerate rearrangements are only moderately fast on the ^{13}C NMR time scale, yielding such broad signals that they essentially disappear in the noise. It is possible that the information required may be obtained with a ^{13}C-enriched ion.

Transfer of ^{13}C Spin Saturation by Rearrangements. Exchange reactions in which magnetically different carbon nuclei exchange can be investigated by transfer of ^{13}C spin saturation. This new tool may not only be used for detection of exchange reactions, but also to measure the rate of exchange and sometimes for elucidation of reaction mechanisms.[7,8] The transfer of spin saturation technique was originally invented by Forsen and Hoffman for ^{1}H nuclei.[13] However, with the latter the method for various reasons has had limited application; when applied to exchanging ^{13}C nuclei it seems to have a bright future.

Selected carbons in the molecule under study are saturated with an extra radiofrequency magnetic field while the whole ^{13}C spectrum is observed. If the saturated carbons exchange with magnetically different carbons, the saturation could be transferred if the lifetime for chemical exchange (τ) is smaller or comparable to the relaxation time (T_1) of the nonirradiated exchanging carbons. When $\tau \ll T_1$, the nonirradiated exchanging carbons will be completely saturated by the transfer. On the other hand, when $\tau \simeq T_1$ only partial saturation will be obtained. In the latter circumstances, τ could be determined from T_1 and the amount of partial saturation found using eq 2 of the Experimental Section.[8a,b] If $\tau \gg T_1$ no transfer of spin saturation will be observed (cf. eq 2).

Table II. Results of Spin Transfer Saturation and Relaxation Time Measurements with **2–5** (C-2,C-8 Are Observed, while C-3,C-7 in **2** and C-4,C-6 in **3–5** Are Saturated)

molecule	temp, °C	rel inten with satn/ rel inten with out satn	T_1, s, of obsd C	k, s^{-1}	$\Delta G^{\ddagger}$ kJ mol^{-1}	$\Delta G^{\ddagger}$ kcal mol^{-1}
2^a	−128.0 ± 0.4	0.60 ± 0.18	0.058 + 0.011 − 0.009	12^b + 17 − 8	31.7 + 1.4 − 1.1	7.58^c + 0.33 − 0.28
3^a	−128.6 ± 0.4	0.60 ± 0.13	0.077 + 0.005 − 0.003	8.7^d + 6.5 − 4.2	31.9 + 0.9 − 0.7	7.63^e + 0.21 − 0.18
4^a	−43.5 ± 1	0.63 ± 0.08	0.74 + 0.11 − 0.03	0.79^d + 0.36 − 0.31	56.2 + 1.2 − 1.0	13.4^f + 0.3 − 0.2
5^g	−93.2 ± 0.4	0.48 ± 0.03	0.76^h + 0.13 − 0.09	1.4^d ± 0.4	42.8 ± 0.5	10.2^i ± 0.1

[a] Solvent FSO_3H–SO_2ClF–SO_2F_2. [b] The same rate constant within the experimental error was obtained from the spin-saturation transfer to C-4,C-6 upon saturation of C-3,C-7. [c] Lit. 7.3 kcal mol^{-1} at ca. −121 °C.[1c] [d] The same rate, but with smaller precision, was obtained from spin-saturation transfer experiments employing exchanging C-1 and C-5. [e] Lit. 7.3 kcal mol^{-1} at ca. −121 °C.[1a] [f] Lit. >13.8 kcal mol^{-1} at −5 °C.[1a] [g] Solvent $(CD_3)_2CO$. [h] Lit. T_1 = 0.13 s at −94.8 °C in CS_2–CD_2Cl_2–$(CD_3)_2CO$ (14:3:1) solvent system.[14b] [i] Lit. 10.5 kcal mol^{-1} at −41 °C;[14a] 10.1 kcal mol^{-1} at 25.0 °C.[14b]

With the present cations, τ increases and T_1 decreases when the temperature is lowered and, fortunately, the situation where $\tau \simeq T_1$ can be reached is at temperatures at which the nondegenerate reactions of the ions are slow. The experimental temperatures were determined with an accuracy better than ±0.4 °C using a chemical-shift difference thermometer calibrated with a temperature-sensitive reaction at one temperature run in the NMR probe and in a low-temperature thermostat (the ion generation apparatus) as described in the Experimental Section.[10] The results of ^{13}C spin-transfer saturation experiments with barbaralone (**5**) and ions **2–4** are presented in detail below. The rearrangement barriers and their mechanistic implications are discussed and a phenomenological mechanism for the rearrangement of **2** is uniquely selected (see Scheme III).

Barbaralone (5) and Protonated Barbaralone (4). In the Cope rearrangement of **5**, C-2 and -8 exchange with C-4 and C-6, and C-1 exchanges with C-5 at the same rate, i.e., 2,8 ⇄ 4,6 and 1 ⇄ 5, respectively. At −93.2 °C, τ for the rearrangement is approximately equal to T_1 for the relevant carbons of **5**, and, consequently, when C-4, C-6 or C-5 is saturated, the spin saturation is transferred to C-2, C-8 and C-1, respectively, but only partially. The intensity drop of the signal from C-2,C-8 is 52%. This value, together with the T_1 value of C-2,C-8, which was determined separately immediately after the spin-transfer experiments, and eq 2, gave the rate constant k ($\equiv 1\tau$) shown in Table II. Eyring's equation was used to calculate the free energy of activation. The k value obtained with C-1 and C-5 did not deviate significantly from that obtained with C-2,C-8 and C-4,C-6, but it was less accurate because of the smaller absolute drop in intensity upon transfer of saturation. Our value of 10.2 ± 0.1 kcal mol^{-1} (−93.2 °C) for the rearrangement barrier agrees, within the experimental error, with 10.1 ± 0.1 kcal mol^{-1} ($\Delta H^{\ddagger}$ = 10.9 ± 0.1 kcal mol^{-1}, $\Delta S^{\ddagger}$ = 2.7 ± 0.7 cal K^{-1} mol^{-1} at 25.0 °C) obtained with complete lineshape analysis of ^{13}C spectra,[14b] if compensation for the difference in temperature is made. However, these values differ significantly from values obtained earlier with the coalescence temperature method.[14a,15]

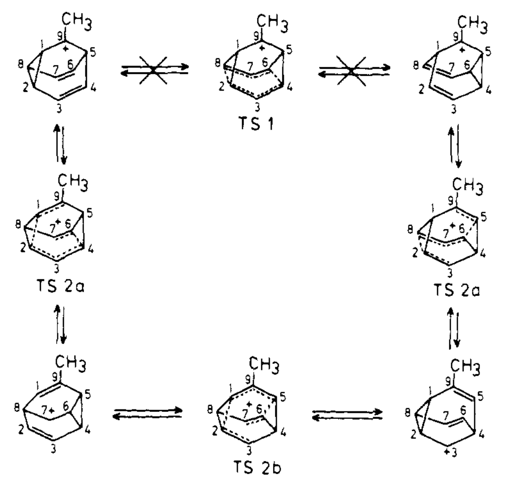
Protonated barbaralone (**4**) has been reported to have a Cope rearrangement barrier > 13.8 kcal mol^{-1} in FSO_3H at −5 °C.[1a] No averaging process was observed with ^{1}H NMR when the temperature was changed over a large temperature interval. At −5 °C the decomposition rate became too large and the above lower limit for the barrier was estimated. This value has recently been questioned.[16] We have now detected the Cope rearrangement (2,8 ⇄ 4,6 and 1 ⇄ 5) of **4** and also measured the barrier with the ^{13}C spin-transfer technique in the same way as for **5** (Table II). The barrier of 13.4 kcal mol^{-1} obtained in FSO_3H–SO_2ClF–SO_2F_2 at −43.5 °C is close to the above lower limit (13.8 kcal mol^{-1}) obtained at −5 °C. The difference may result from an entropy of activation and/or temperature inaccuracy in earlier experiments.[1a] The barrier for the rearrangement of **4** in pure FSO_3H was found not to deviate significantly from the above value, but the measurements were disturbed by some decomposition of **4**.

Obviously the Cope barrier for barbaralone is increased by ca. 3 kcal mol^{-1} upon protonation, and it is clear that the positive charge retards the rearrangement. However, ions **2** and **3** behaved entirely differently.

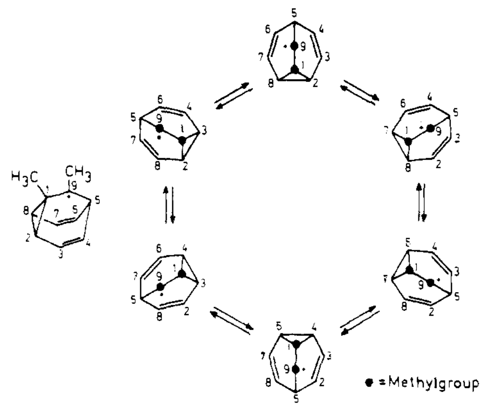
9-Methyl-9-barbaralyl Cation (3) and 1,9-Dimethyl-9-barbaralyl Cation (2). At −128.6 °C the complete saturation of C-4,C-6 in ion **3** is partially transferred to C-2,C-8 and vice versa (Figure 1). Also, complete saturation of C-1 yields partial saturation of C-5 and vice versa. Thus, the behavior of the barbaralyl cation **3** is similar to that of **4** and **5** (2,8 ⇄ 4,6 and 1 ⇄ 5), but the rearrangement takes place with a barrier of only 7.63 kcal mol^{-1}, which is even smaller than that of uncharged **5** (10.2 kcal mol^{-1}). Since more charge is delocalized into the cyclopropane ring of **3** than of **4**, it was expected that **3** should show an even larger barrier than **4**, which shows a substantially larger barrier than **5**. That **3** has a barrier which is ca. 6 kcal mol^{-1} lower than **4** indicates that ion **3** does not use an ordinary Cope mechanism for its rapid rearrangement, but rather that a new route is made available to the ion. By saturating C-3, -7, and -9 in turn and the methyl carbon, it was shown that none of these are involved in any rapid exchange reaction (i.e., no evidence for C-methyl bond breaking in the rearrangement process), since no significant transfer of spin saturation to the nonirradiated carbons could be detected (i.e., $\tau \gg T_1$). The above results strongly support the previously reported mechanism shown in Scheme II, which involves a series of divinylcyclopropylcarbinyl cation–divinylcyclopropylcarbinyl cation rearrangements, and makes other suggested mechanisms, such as that using TS **1** in Scheme II[1a,d] and those involving the intermediacy of bicyclo[3.2.2]nonatrienyl cations, unlikely.

In the discussion on structures earlier, it was mentioned that ion **2** has a structure in which the second methyl group occupies the 1 position. No trace of an ion with the extra methyl group in the 5 position could be detected.[1c,d] Consequently, rearrangement of **2** according to Scheme II should have the ^{1}H NMR unchanged and transfer of ^{13}C spin saturation should not be detectable. However, as previously reported, the ^{1}H NMR shows considerable temperature dependence, indicating a six-carbon scrambling, and the phenomenological mechanism

Scheme II



Scheme III

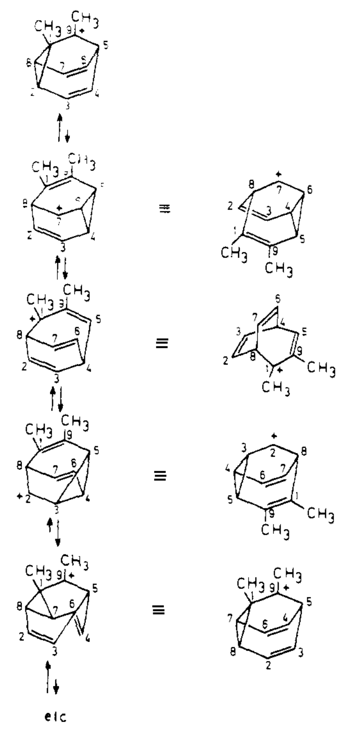


shown in Scheme III has been suggested but not firmly established by these results.[1c,d]

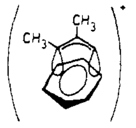
We have now studied the rearrangements of ion **2** with the new technique presented above, and the results are shown in Figure 2. At −128.0 °C complete saturation of the C-2,C-8 band yields partial saturation of C-3,C-7, but C-4 and -6 are also saturated to a minor extent in sharp contrast to the behavior of ion **3**. Saturation of C-4,C-6 results in partial and minor saturation of the bands from C-3,C-7 and C-2,C-8, respectively. Furthermore, saturation of C-3,C-7 gives partial saturation of the bands of C-2,C-8 and C-4,C-6 and to the same extent as the C-3,C-7 band was saturated when either C-2,C-8 or C-4,C-6 was completely saturated. Saturation, in turn, of C-1, C-5, C-9, and the methyl carbons shows that these carbons neither exchange rapidly with each other nor with the six carbons that exchange with each other, i.e., there is no evidence for C-methyl bond breaking in the rearrangement process. Obviously, C-2,C-8 exchange preferentially with C-3,C-7 as do C-4,C-6. C-3 and -7 show no preference in their exchange with C-2,C-8 and C-4,C-6. These results (2,8 ⇄ 3,7 ⇄ 4,6) prove the mechanism shown in Scheme III, in which the bridge constituted by C-1,C-9 and C-5 rotates in a stepwise fashion around the pseudoring made up by C-2, C-3, C-4, C-6, C-7, and C-8.

The barrier calculated for the exchange of C-3, C-7 with C-2,C-8 or C-4,C-6 was 7.58 kcal mol^{-1}, which is not significantly different from the value obtained for the Cope-mimicking rearrangement of **3**. This similarity suggests a connection between their mechanisms of rearrangement. Therefore, for any one step of the phenomenological mechanism (Scheme III), the microscopic mechanism of Scheme IV is suggested, which is fully consistent with all results obtained so far.

Scheme IV



Mechanisms involving direct ring opening to 6,7-dimethylbicyclo[3.2.2]nonatrienyl cation predict more extensive carbon scrambling than observed. The results could also be explained by involving structure **18** as a transition state, in which a dehydroallyl cation interacts with a benzene molecule, for a step in the Scheme III phenomenological mechanism.



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Experimental Section

Preparation of Ions. All ions were synthesized directly in 5-mm NMR tubes using the ion generation apparatus shown in Figure 3. This reactor and thermostat and its use are carefully described in ref 10. In this work, alcohols were precursors of the barbaralyl cations. Typically, solutions of the alcohols (ca. 25 mg of alcohol in ca. 10 mg of CD_2Cl_2) were mixed into ca. 0.4 mL of superacid, FSO_3H-SO_2ClF-SO_2F_2 (1:6:1, v/v/v), at ca. −135 °C yielding ionic solutions ca. 0.3 M in cation. The manufacturers of the compounds used were: CD_2Cl_2 (Ciba Geigy), FSO_3H, SO_2ClF (Research, Organic/Inorganic Chemical Corp.), and SO_2F_2 (Matheson Gas Products).

Ion **3**, 9-methyltricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-yl cation (9-methyl-9-barbaralyl cation),[1a,d] was prepared either from the new precursor 3-methylbicyclo[3.2.2]nona-3,6,8-trien-2-ol (**7**)[17] or from 2-methylbicyclo[3.2.2]nona-3,6,8-trien-2-ol (**6**)[1a,d] or 9-methyltricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-ol (9-methyl-9-barbaralol) (**8**),[1a,d] cf. Scheme I.

The 1,9-dimethyltricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-yl cation (1,9-dimethyl-9-barbaralyl cation) (**2**)[1c,d] was synthesized either from the new precursor 2,3-dimethylbicyclo[3.2.2]nona-3,6,8-trien-2-ol (**9**)[17] or 1,9-dimethyltricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-ol (1,9-dimethyl-9-barbaralol) (**10**).[1c,d]

The generation of the totally degenerate $C_9H_9^+$ cation from bicyclo[3.2.2]nona-3,6,8-trien-2-ol (**13**) has previously been described.[1b,d]

Protonated barbaralone (**4**)[1a,d] was prepared either by mixing a CD_2Cl_2 solution of barbaralone (**5**)[1a,d] into FSO_3H-SO_2ClF-SO_2F_2 (1:6:1, v/v/v) as above or into pure FSO_3H. The final solutions were ca. 0.3 M in **4**.

The barbaralone (**5**) solution was prepared by condensing $CHCl_2F$

(Matheson Gas Products) at −80 °C into a NMR tube with **5** dissolved in CD_2Cl_2. The final solution was ca. 0.6 M in **5**. For the spin-transfer experiments, a solution of barbaralone (**5**) dissolved in acetone-d_6 (Ciba Geigy) was also used which was ca. 0.7 M in **5**.

Spectra and ^{13}C Spin-Transfer Saturation Experiments. The ^1H and ^{13}C NMR spectra were obtained with a JEOL-FX100 pulse spectrometer equipped with a 5-mm, variable-temperature $^1H/^{13}C$ dual probe, external ^7Li lock, quadrature phase detection, and a multi-irradiation unit. Data autostacking programs FAFT 20/21/22 were used.

As internal standards, $CHDCl_2$ (δ_H 5.30) and CD_2Cl_2 (δ_C 53.8) were used unless otherwise stated.

During the multiple irradiation experiments, the multi-irradiation unit supplied the noise-modulated ^1H irradiation frequency, while the ^{13}C irradiation frequency was fed through the homonuclear gated decoupling unit of the instrument. The power level used for saturation was set at: high, 5–6. In the transfer of spin saturation spectra, a spectral width of 4–6 kHz, 8192 data points were used with a pulse flip angle of 90°, pulse repetition time > $5T_1$, 1200 scans (for **2** and **3**) and 100 scans (for **4** and **5**), and data acquisition times of 0.35, 0.35, 1.02, and 0.68 s, respectively, for **2–5.** When processing data, we used the following positive exponential and trapezoidal window: exp = 5, $T_1 = T_2 = 0$, $T_3 = 0.9 \times T_4$, and T_4 chosen as the end of the data acquisition time.

A reduced spectral width was sometimes used to increase the resolution. The observation frequency was then chosen in such a way that folded lines, if any, did not coincide with other lines.

The measurements of the spin-lattice relaxation times (T_1) for the carbons in **2, 3,** and **5** have been made with the inversion recovery method using the pulse sequence (180°, τ, 90°), while the progressive saturation method with the pulse sequence (τ, 90°) was applied to ion **4**. These methods could be applied, since the spin-lattice relaxation times of the exchanging carbons are not significantly different. This conclusion is based on the fact that the intensity decrease of the bands from the exchanging carbons is independent of the carbon that was saturated.[8b]

In every spectrum the heights of the resonance lines from exchanging carbon atoms have been measured and related to a reference consisting of the arithmetic mean of the heights of resonance lines from the nonexchanging carbons.

Table II shows the ratio between the relative intensities with and without saturating irradiation. The above ratio error limits are based on propagated maximal errors obtained from several experiments.

It was earlier shown that for a two-site exchange problem involving sites A and B, the change of the magnetization at site A with time can be written:[8a,b,13]

$$\frac{dM_z^A(t)}{dt} = \frac{M_z^A(0) - M_z^A(t)}{T_{1A}} - k_A M_z^A(t) + k_B M_z^B(t) \qquad (1)$$

where $k_A^{-1} \equiv \tau_A$ is the lifetime at site A, T_{1A} is the corresponding spin-lattice relaxation time, and $k_B^{-1} \equiv \tau_B$ is the lifetime at site B. For a spin-transfer saturation experiment with complete saturation of site B, i.e., $M_z^B(t) = 0$, eq 1 can be solved to give:

$$k_A = \frac{1}{\tau_A} = \frac{M_z^A(0) - M_z^A(\infty)}{M_z^A(\infty)} \frac{1}{T_{1A}} \qquad (2)$$

where $M_z^A(0)$ and $M_z^A(\infty)$ are the magnetizations (i.e., intensities) at site A in the absence and presence of irradiation at site B, respectively.

For the exchange reactions of **2–5**, eq 2 has been applied to give the relevant rate constants which in combination with Eyring's equation yield $\Delta G^{\ddagger}$ (Table II).

Calibration and Measurement of Reaction Temperatures. The temperature of the reaction mixture in the probe has been measured using a nondegenerate reaction, i.e., the rearrangement of ion **3** to 1-methylbicyclo[4.3.0]nonatrienyl cation (**17**) as reported above. The rate constant of this first-order reaction increases 30% per °C at ca. −120 °C.

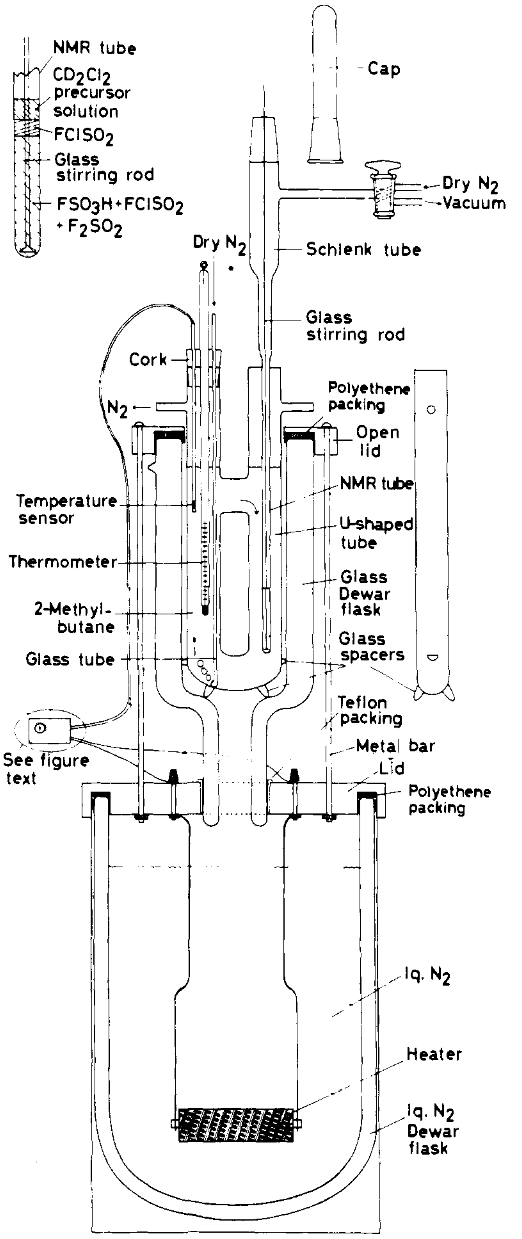

Figure 3. Ion generation apparatus used for synthesis of carbocations in the temperature interval 0 °C to ca. −155 °C. The apparatus has also been used as a thermostat in kinetic experiments. The ellipse circumvents the temperature control unit. The lower part of the NMR tube is shown enlarged in the upper left corner of the figure.

An ionic solution of **3**, free from **17**, was prepared in the usual way. The rate of rearrangement of **3** was measured using the ion generation apparatus (Figure 3) as thermostat.[10] The temperature during a kinetic run which lasted for ca. 1 h did not vary more than ±0.15 °C, as measured with a digital voltmeter and three copper-constantan thermocouples plasma welded together in series. The junctions of the thermocouples were immersed in the right-hand shank of the thermostat (Figure 3), together with the 5-mm NMR tube containing the reaction mixture, and also into a mixture of ice and water. The thermocouple battery was calibrated at several temperatures.[18] After ca. 1 h at ca. −119 °C, the reaction had proceeded ca. $1.5t_{1/2}$ and was stopped by transferring the tube to liquid N_2. The sample was then studied in the spectrometer at ca. −135 °C. At this temperature the reaction rate is negligible compared with the observation time. The extent of reaction was determined, and the rate constant (k) was calculated to be $2.49 \pm 0.14 \times 10^{-4}$ s^{-1}; the free energy of activation ($\Delta G^{\ddagger}$) was calculated to be 47.6 kJ mol^{-1} (11.4 kcal mol^{-1}).

Then the reaction (using the same reaction mixture as above or a new one free from **17**) was studied in the NMR probe, the temperature of which had been set using the chemical-shift thermometer described below. The amount of reaction as a function of time was measured. The reaction was shown to be first order and the rate constant obtained was $2.46 \pm 0.14 \times 10^{-4}$ s^{-1}. Using this k value and the above $\Delta G^{\ddagger}$ value, the temperature was calculated to be −118.78 + 0.18 (−0.22) °C.

The proton noise decoupling (20 W) was applied for ca. $t_{1/2}$, but no significant change of the above k value was observed, and the temperature of the sample could therefore at most be increased ca. 0.3 °C by the noise decoupling. In this way, the calibration of the chemical-shift thermometer was improved (CH_3OH in a mixture of $CHCl_2F$-$CDClF_2$, 1:1, v/v)[1d,2b] at one temperature. Most of the spin-transfer experiments were performed at ca. −128 °C, and, therefore, the above careful temperature calibration at one temperature of the shift thermometer automatically gave accurate temperature estimates over a large interval around −119 °C.

The maximal error estimates shown in Table II are conservative, since they have been obtained through propagation of maximal errors.

The higher temperatures used were not calibrated in the way described above and therefore the estimated error limits are much larger. The separation of the CH_3 and OH proton bands of the shift thermometer was measured before and after each NMR experiment. Since these separations were usually found to vary <~0.1 Hz (i.e., <0.1 °C) from the average value, the temperature stability during the kinetic experiments was concluded to be within ±0.1 °C.

All spin-transfer experiments showed reproducibility within the limits shown in Table II. If there is any temperature gradient over the sample part of the NMR tube, it cannot be subtracted from the above measurements, but can probably be neglected as if diffusion of molecules is significant (which is unlikely at this low temperature); the number of molecules of a certain kind diffusing into the central part used for the observation is probably similar to that diffusing away.

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Elucidation of the Stereochemistry of the Carboxypeptidase A Catalyzed Enolization of 2-Benzyl-3-*p*-methoxybenzoylpropionate, a Ketone Substrate

Takuji Sugimoto and E. T. Kaiser*

Searle Chemistry Laboratory, University of Chicago,
Chicago, Illinois 60637.
Received February 1, 1979

Abstract: Carboxypeptidase A_γ catalyzes hydrogen–deuterium exchange with retention of configuration at the activated methylene group of (−)-2-benzyl-3-*p*-methoxybenzoylpropionic acid, (−)-**1**, a ketonic analogue of the enzyme's ester and peptide substrates. However, (+)-**1** does not undergo the corresponding exchange process even though it is bound to the enzyme slightly more tightly than the − isomer. ^1H NMR measurements at 270 MHz show that the signals for the diastereotopic protons on the activated methylene group of **1** appear separately at 2.98 (H_a) and 3.33 ppm (H_b) and that exchange occurs only at the H_a position of (−)-**1**. Degradation of the enantiomers of **1** by Baeyer–Villiger oxidation and subsequent hydrolysis to give the corresponding isomers of 2-benzylsuccinic acid showed that (−)-**1** has the *R* configuration at the chiral methine group. *cis*- and *trans*-2-benzyl-4-*p*-methoxyphenyl-γ-butyrolactones containing hydrogen and/or deuterium at the 3-methylene position were prepared by sodium borohydride reduction of **1** and various of its deuterated forms, followed by cyclization using dicyclohexylcarbodiimide. Comparison of the ^1H NMR spectra of the lactones with those of the *cis*-2-benzyl-4-*p*-methoxyphenyl-γ-butyrolactones produced by the cyclization of **1** and **1**-d_2 (substituted with deuterium at the 3 position) with acetic anhydride, followed by reduction with hydrogen over platinum oxide, showed that the H_a proton on the activated methylene group is in the *pro-R* configuration. The stereochemical results obtained are consistent with the hypothesis that (−)-**1** binds in a manner similar to that which has already been postulated for reactive peptide and ester substrates and that the γ-carboxylate moiety of Glu-270 is the functional group in the enzyme which abstracts the H_a hydrogen from the 3 position of the ketone substrate.

Potent nucleophiles are known to be present at the active sites of many enzymes involved in acyl- and phosphoryl-transfer processes. While kinetic studies and chemical modification experiments have been powerful mechanistic tools, often the multiplicity of reaction intermediates, the possibility of a change in what is the rate-determining step as the pH is changed, and other factors can combine to make it exceedingly difficult, even with these techniques, to discern clearly the catalytic behavior of the crucial enzyme-bound nucleophiles. Recently, we undertook experiments to test whether a relatively

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