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Author's Review

Secondary Deuterium Isotope Effects and Neighboring Group Participation Revisited*

Dionis E. Sunko

Department of Chemistry, Faculty of Science, University of Zagreb, 10000 Zagreb, Croatia

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Studies on solvolytic reactions proceeding *via* neighboring group participation by means of secondary deuterium isotope effects are reviewed. The changes in magnitude of secondary KIEs are related to the degree of participation in the reaction transition state and these data are compared with other experimental evidence. Supporting information on the structure of carbocations is obtained by high level *ab initio* calculations. Isotope effect studies turned out to be among the most powerful tools available to chemists for elucidating the nature and structure of reaction transition states.

> *»For progress there is no cure«*
>
> J. von Neumann, 1955

INTRODUCTION

Twenty five years ago, Stanko Borčić and I published a review article under the above title in Collins and Bowman's ACS Monograph on Isotope Effects in Chemical Reactions.[1] Until today our review retained its position as principal reference on this subject in spite of the fact that it is obviously in many aspects outdated. This issue of Croatica Chemica Acta commemorating the untimely death of my friend and long time collaborator appears to be the appropriate place to publish a brief update describing the present state of our knowledge of a field to which Stanko and I devoted most of our active lives.

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* Dedicated to the memory of Stanko Borčić.

In the period between 1970 and 1995 many new techniques for the study of reaction mechanisms have been developed and applied in concert with the earlier known methods. This has proved to be of fundamental importance for the refinement of our knowledge of potential energy surfaces (PES) and the structure of transient species involved in the energetically preferable pathway separating the reactants from the product(s).

Great improvements have been made in the application of high level *ab initio* MO calculations for the investigation of potential energy surfaces,[2] and a number of computer programs became available to the practicing chemist. This strengthened the previously rather weak link between experimental and theoretical chemistry and rendered more confidence to computational chemistry while at the same time enabling the study of structures inaccessible by experiment.

The application of isotope effects in physical organic chemistry has from its very beginning been characterised by a fruitful interaction of theory and experiment. The fundamental work of Bigeleisen and Mayer,[3] and by Melander[4] laid the theoretical foundation of our knowledge about the origin of these effects, while the elegant experiments of Westheimer,[5] and others[6–9] demonstrated the usefulness of isotope effects for the elucidation of organic reaction mechanisms. These investigations coincided with the flourishing of mechanistic studies on solvolytic nucleophilic displacement reactions extensively reviewed by Streitwieser in 1956.[10] At the same time the existence of nonclassical ions was suggested by Saul Winstein[11] and John D. Roberts.[12] This hypothesis was strongly challenged by H. C. Brown[13] which resulted in a long lasting debate among physical organic chemists and the publication of hundreds of papers and review articles some of doubtful value. The nonclassical ion problem which addressed the structure of transition states in solvolytic reactions allegedly proceeding by neighboring carbon-carbon σ-bond participation became *inter alia* a promising field for the application of isotope effects.

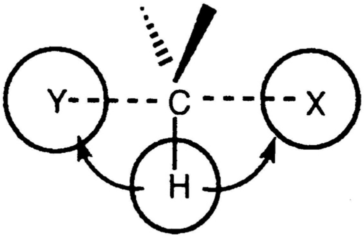
Since, in Winstein's view,[11,14] nonclassical ions arise from neighboring carbon-carbon π as well as σ bond participation in the rate determining step of a solvolytic reaction and thus are related to participation by other potential internal nucleophiles such as multiple bonds and/or lone pair electrons, these reactions became the main target of our mechanistic studies. Depending on the position of the deuterium label relative to the reacting center, α-, β-, γ-, and even more remote kinetic isotope effects (KIEs) were investigated. Relating these effects to changes of the force field involving the labeled atom(s), conclusions could be drawn of the structure of the respective transition states, and, by extrapolation, on the structure of the resulting reactive intermediate(s). Much of our reasoning has been based on analogies and comparisons with closely related structures and reactions and was whenever possible compared with the results of high level quantum mechanical calculations.[15]

In this account, I will review what we know today how changes in the magnitude secondary deuterium KIEs relate to the degree of neighboring group participation in the reaction transition state and how these data can be brought in line with theoretical and experimental studies of the structure of carbocations. Rather than following a chronological order, I will review some recent work related to topics which are logically connected and where the application of secondary deuterium isotope effect studies provided better insight into the mechanism of organic chemical reactions. Since our work dealt mostly with reactions proceeding *via* carbocationic intermediates generated under solvolytic conditions and consequently involve positively charged transition states most of the examples will cover this field. A small digression will be made by discussing the relevance of our early work on the Cope rearrangement[16a–c] to more recent theoretical and experimental results.

Where possible, the presentation will follow the sequence of the 1970 review and emphasis will be given to the work published in collaboration with S. Borčić or independently by our two groups between 1970 and 1994. This review does not pretend to be comprehensive and some important work by other authors will be, because of space limitations, only briefly covered or not mentioned at all. I am taking the responsibility for making this selection which by no means reflects the relative importance or the order of priorities of the topics which will or will not be covered.

α-SECONDARY DEUTERIUM KIE'S IN SOLVOLYSIS AND DIRECT DISPLACEMENT REACTIONS

Streitwieser and coworkers in their classical paper[7a] related the origin of α-secondary deuterium KIEs to the change of the out of plane C-H(D) bending frequency in going from an sp^3 hybridized carbon atom in the ground state to the sp^2 hybridized transition state. This vibration is severely hindered in the trigonal bipyramid which has been the accepted structure for the S_N2 transition state encountered in nucleophilic direct displacement reactions (Scheme 1).



Scheme 1.

Calculations taking the carbonyl group as a suitable model for the sp^2 hybridized carbocation seemed to support this hypothesis. This simple model offered the rationalization for the absence of any significant α-KIE in S_N2 reactions. The hypothesis of steric hindrance of the out of plane bending vibration by the entering (participating) group as the main factor in reducing the α-KIE was recently challenged by Wolfe and Kim.[17] They pointed out that inverse α-effects in degenerate S_N2 reactions calculated at *ab initio* level of theory arise from an increase in the α-CH bond stretching force constant in the transition state relative to the tetrahedral reactant (Table I).

TABLE I

Unscaled C-H stretching and bending frequencies computed at the MP2/6-31+G* level for the ground (sp^3) and transition (sp^2) state for the $Cl^- + CH_3Cl$ reaction[17]

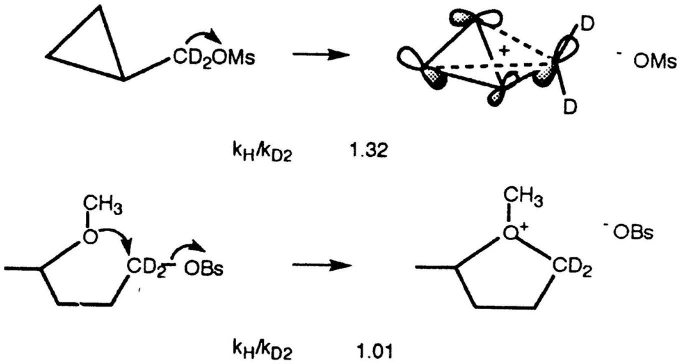
	C-H(sp^3)	C-H(sp^2)
ν(str)/cm^{-1}	3144; 3255	3273; 3483
ν(bend)/cm^{-1}	1078; 1464	992; 1110

This alternative interpretation meant that, contrary to the accepted view, smaller α-KIEs are associated with looser rather than tighter transition state. Westaway and coworkers[18a] calculated reactant and transition state structures for several S_N2 reactions at the HF/6-31+G* level of theory and concluded that the bending vibration contributions to the KIE are much more sensitive to a change in the nucleophile than the stretching vibration. Thus, with the essentially constant contribution from the stretching mode, the $(k_H/k_D)_{bend}$ and the magnitude of the total effect in displacement reactions is determined by the looseness of the transition state. Barnes and Williams[18b] reported that α-methyl and/or α-methoxy substitution in the reaction of chloromethane with chloride ion shows that the inverse inductive contribution is approximately constant while the calculated α-KIE is determined by changes in the bending force constant as originally postulated. Truhlar and Hu[19] performed model experiments at the correlated *ab initio* level of S_N2 reactions of gas-phase microsolvated clusters and demonstrated that both low- and high-frequency modes contribute significantly to the inverse KIE. The issue is further complicated by the fact that the calculated harmonic frequencies give a better fit of the temperature dependence of k_H/k_D isotope effects then if anharmonic frequencies are used. They also pointed out that we still do not unterstand why the calculated KIEs are by up to 26% larger than the experimental values. Simple models of transition states are evidently not adequate for calculating rate (and isotope) effects in S_N2 reactions.[20]

The S_N2 transition state model can be extended to neighboring group participation reactions. Depending on the character of the participating internal nucleophile a more or less tight transition structure could be envisioned. Consequently, the magnitude of α-KIEs should reflect the degree of participation (bridging) in the solvolysis transition state. This was indeed observed in some n-participating systems,[21] but was much less pronounced in reactions where π- or σ-participation was anticipated. Therefore, it seems that the use of α-effects as a probe for π- or σ-neighboring group participation is of doubtful value. As repeatedy stated by Winstein,[22] participation, which implies bridging, may not occur in concert with the departure of the leaving group, and, while anchimeric assistance may be observed, the transition structure can still resemble the reactant. The extent of bridging depends largely on the relative stability of the bridged *vs.* open structure of the intermediate and only in cases where bridging is pronounced in the transition state, a decrease in magnitude of the α-effect might be observed.

The following two examples substantiate this argument. The solvolysis of α-deuterated cyclopropylcarbinyl mesylate is retarded by 32% relative to the unlabeled derivative (20 °C, 60% aq. diglyme),[23] while 4-methoxy-1,1-d_2-pentyl brosylate solvolyzes at the same rate as the undeuterated compound.[21] Both systems show considerable anchimeric assistance and the intermediate has a bridged (in the first case delocalized) structure. However, the degree of bridging in the transition state differs substantially from being very pronounced in the methoxy compound but much less so in the cylopropylcarbinyl derivative (Scheme 2). Another example where the bridged transition structure affords the same α-effect as the classical structure will be discussed later in connection with the norbornyl cation problem.

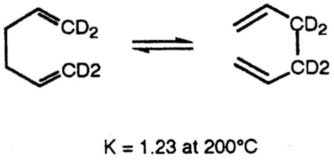
The rationalization of α-effects in neighboring group participating reactions is further complicated by the occurence of tight and/or solvent separated ion pairs in the rate determining step of the reaction and also the



Scheme 2.

often present internal return. α-KIEs in solvolytic reactions have been the subject of elaborate investigations by Shiner and coworkers who suggested that α-effects are reduced by σ- but not π-bonds. For more detailed discussion the reader is referred to recent papers by this author.[24a,b]

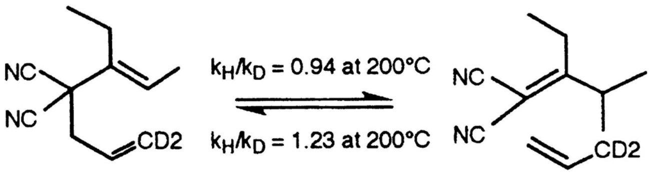
A special case is the Cope rearrangement where only carbon-carbon bonds are involved. We determined both, kinetic and thermodynamic isotope effects in two such rearrangements (Scheme 3).[16a–c]



Scheme 3.

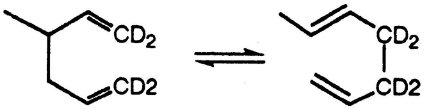
The equilibrium isotope effect, $K = 1.23$ at 200 °C, (calculated to be 1.41 at 25 °C) gives the measure of the isotopic fractionation factor between an sp^3 and sp^2 hybridized carbon and is consistent with the notion that deuterium prefers the more sterically congested sp^3 position. Recent calculations at the RHF/6-31G* level are in good agreement ($K = 1.24$ at 200 °C) with the experimental value.[16d]

The kinetic effect on the bond breaking side is similar to solvolytic α-KIEs, which shows that charge development plays no role and that the effect is a manifestation of the degree of rehybridization and of the tightness of the transition state (Scheme 4).



Scheme 4.

In the meantime much experimental and theoretical work has been reported on this and other pericylic reactions.[16d–g] Notably, the experiments by Joe Gajewski's group at Indiana University,[16e,f] and supporting theoretical



k_H/k_D = 0.885 at 248°C[16d]

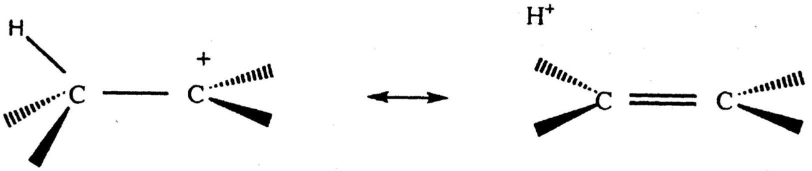
k_H/k_D = 0.885 at 248°C; RHF/6-31G*[16f]

Scheme 5.

calculations by Houk and coworkers,[16d,g] confirmed our initial results (Scheme 5).

β-DEUTERIUM KINETIC ISOTOPE EFFECTS

The hyperconjugative origin of β-deuterium KIEs has been firmly established[25] but the simple scheme describing hyperconjugation by resonance of two canonic structures[26] is not adequate (Scheme 6).

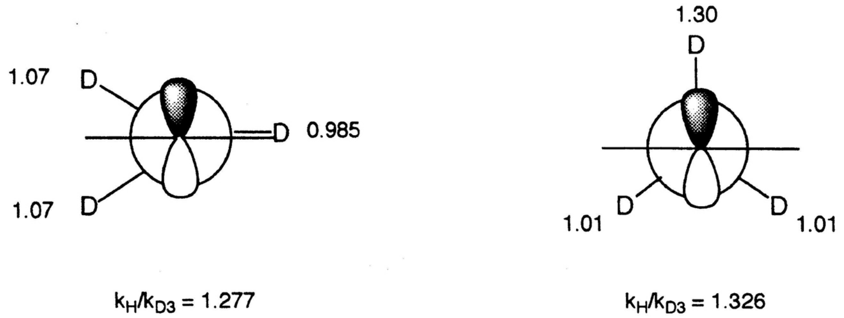


Scheme 6.

It does not take into account at least three additional factors, *i.e.* (1) the conformational dependence of hyperconjugative stabilization and consequently of the magnitude of the β-effects, (2) the opposing inductive effect of deuterium in the β-position, and (3) the intimate connection between hyperconjugation, hydrogen participation and rate determining β-elimination.

Neighbornig group participation can be a significant factor in reducing β-effects and the effectiveness of such groups parallels their ability to stabilize the positive charge in the transition state.[1,15a,b]

The conformational dependence of the maginitude of these effects was first demonstrated by Shiner and coworkers in 1963,[27] but conclusions derived from the observed effects in partially deuterated *tert*-butyl chlorides raised some questions. Namely, the hyperconjugative interaction of a freely rotating methyl group with the p-function at the reacting center, should be independent of conformation (Scheme 7).



found: $k_H/k_{D3} = 1.356^a$

[a] in TFE, ref. 15[a], p. 146

Scheme 7.

In other words, the two extreme conformations *A* and *B* should afford the same d_3-effect which is evidently not the case.

Since β-KIE has its origin in two phenomena, hyperconjugation and the inductve effect, the following relationship should hold (Eq. 1):

$$\log (k_H/k_D) = \cos^2\alpha \log (k_H/k_D)_{max} + \log (k_H/k_D)_{ind} \tag{1}$$

where $\log(k_H/k_D)_{max}$ is the maximal hyperconjugative effect obtained when the C-D bond is eclipsing the p-orbital. As we have shown,[28] methyl-d_3-isotope effects are also linearly correlated with methyl-group rate effects (Eq. 2),

$$\log k(CH_3/CD_3) = 0.02024 \log k(CH_3/H) \tag{2}$$

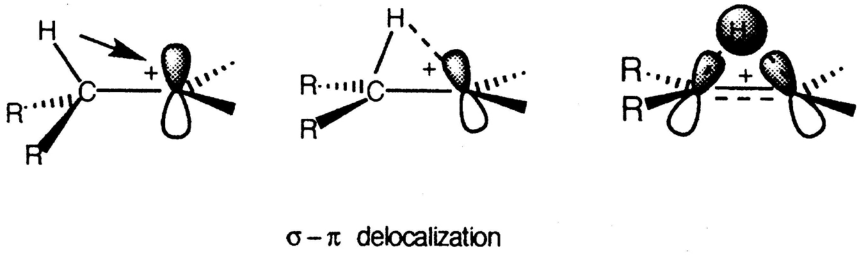
These two relationships have been used to formulate an equation for the conformational dependence of β-deuterium KIEs[29a] (Eq. 3).

$$\log k(H/D)\alpha = 0.666 \cos^2\alpha\ [0.0195 + 0.02024 \log k(CH_3/H)] - 0.00656 \tag{3}$$

Theoretical *ab initio* calculations performed by Hehre and collaborators and published in a joint paper[29b] conformed this relationship. A review published in 1983 [29c] provides examples of its application. Further examples can be found in recent literature.[24a,c,d]

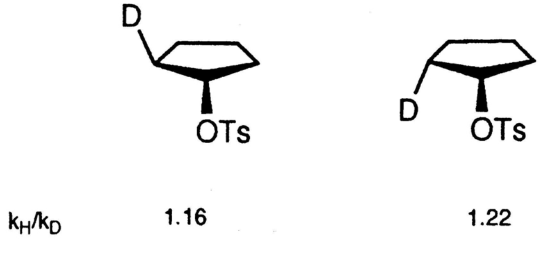
HYPERCONJUGATION *vs.* HYDROGEN PARTICIPATION

Hyperconjugation, or σ–π interaction can be regarded as a continuum between no distortion and bridging (Scheme 8).



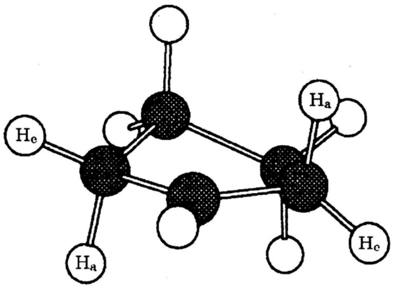
Scheme 8.

Isotope effect studies by Jewett and Shiner on specifically deuterated 4-*tert.*-butylcyclohexyl derivatives demonstrated the asserted intimate connection between these two phenomena.[30] In 1972 Humski and Shiner[31] reported an elaborate study of secondary KIEs for a series of specifically deuterated cyclopentyl derivatives. In a detailed analysis of the rates and the stereochemistry of E1 and S_N1 reactions they estimated the isotope effects for each of the individual steps in the reaction. The observed effects for the two isotopomeres are different from and higher than the β-KIEs estimated for the product formation from the tight ion pair (k_{5s}) because of a rate determining elimination of the *cis*-β-proton by the leaving group (Scheme 9).



Scheme 9.

The most stable structure of the cyclopentyl cation was recently calculated on the MP2(FU)/6-31G** level of theory by Schleyer, Koch and coworkers.[32]



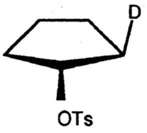
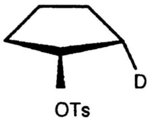
Scheme 10.

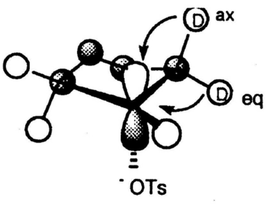
This structure favors strong hyperconjugative interaction from both (pseudo) axial hydrogens in the twisted conformation. The corresponding hydrogen bridged structure was found to be only slightly higher in energy.

From the calculated most stable structure of the cyclopentyl cation it was possible by applying our equation for the angular relationship to reproduce the observed isotope effects for the different isotopomers (Table II).

TABLE II

The cyclopentyl cation.
Experimental[a] and calculated[b] β-deuterium isotope effects

	 *trans*-2d	 *cis*-2d
k_H/k_D obs.[a]	1.16	1.22
k_H/k_D on k_{5s}[a]	1.13	1.10
k_H/k_D calc.[b]	1.16	1.03



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[a] Brosylates in EtOH at 40°; effect on k_{5s} (Ref. 31).

[b] For twisted conformation of C_s symmetry (this work).

The difference between the calculated and experimental values for the β-effect of the equatorial hydrogen probably arises from a difference between the twisted (calculated) C_2 structure of the free cation and the more planar transition structure in the solvolysis reaction.

The hyperconjugative interaction of β-hydrogen atoms was directly observed in the 1-methylcyclopentyl cation by IR spectroscopy in the antimony pentafluoride matrix using the technique developed by Vančik in our laboratory.[33] The intense absorption at 2775 cm^{-1} which amounts to a shift to lower frequencies of about 300 cm^{-1} can be assigned to the (weakened) C-H bond adjacent to the cationic center which is properly aligned for hyperconjugation (Figure 1).

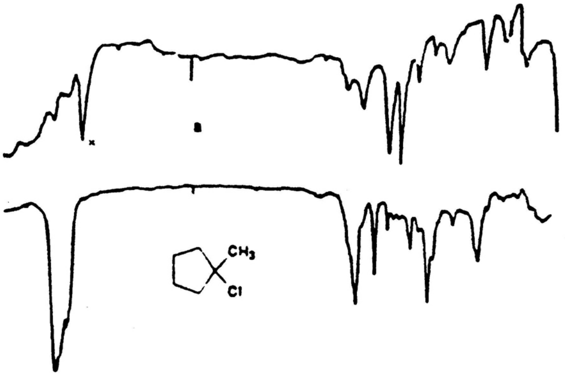
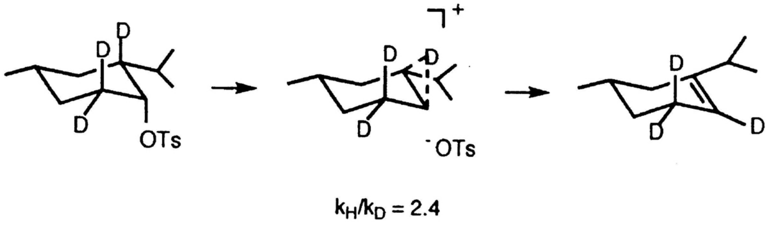


Figure 1. IR spectra of the 1-methylcyclopentyl cation (a) generated in the matrix from 1-methylcyclopentyl chloride.

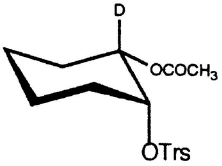
Our studies of β-effects in rigid cyclohexyl system offer further examples.[34a]The antiperiplanar arrangement of the leaving group and the axial tertiary β-hydrogen in neomenthyl tosylate offer an ideal geometry for hyperconjugation and participation.[34a] The magnitude of the β-effect is typical for systems where 1,2-hydride migration occurs in the rate determining step.[34b] The observed effect (k_H/k_D = 2.4) in the β-d_3 neomenthyl tosylate is composed of the effect of the migrating deuterium ($k_H/k_D \approx 2$) and the effect of the two nonmigrating deuterium atoms (Scheme 11).



Scheme 11.

The relatively large effect of the migrating hydrogen (deuterium) arises from the superposition of primary (participating) and secondary (hyperconjugative) effects. In this system the elimination products still retain the participating hydrogen (deuterium). Thus, the migrating hydrogen is, contrary to the prevailing opinion, not involved in the elimination reaction which is the main product forming path.

The problem of distinguishing between hyperconjugation and participation by means of kinetic deuterium isotope effects is subject to limitations on theoretical grounds because, as already mentioned, there is no dichotomy between these two interactions[35a] One example where hyperconjugation is the dominant interaction is the solvolysis of *cis*-2-acetoxycyclohexyl-2*d* tresylate (Scheme 12).[35b]



k_H/k_D = 1.34, 95 °C; 97% TFE

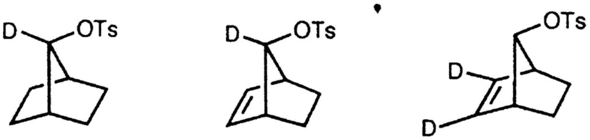
Scheme 12.

Here, the axial hydrogen does not migrate, but some stretching and bending of the C-H(D) bond towards the cationic center still occurs which explains the magnitude of the effect.

Schleyer and collaborators calculated IGLO $\delta(^1H)$ chemical shifts and the natural as well as Mulliken charges at the MP2/6-31* level for the symmetrically hydrogen bridged 2-butyl[36] and the cyclooctyl cation[37] and found no charge-chemical shift correlation. The bridging hydrogens are positively (not negatively) charged, but to a different degree. Matrix isolation experiments confirmed the intermediacy of hydrogen bridged structures; the characteristic C-H frequencies of the bridging hydrogen atom are 2175 and 1845 cm^{-1} respectively.

NEIGHBORING π- AND σ-BONDS. ON THE CONCERTEDNESS OF π-CYCLIZATION REACTIONS

Rate enhancements due to participation of a neighboring double bond are quite common in carbocation reactions. Probably the most dramatic example is the 10^{11} rate increase in the solvolysis of 7-norbornenyl tosylate relative to the saturated analog.[38–40] The bridged, two electron-three center structure of the intermediate cation has been established beyond doubt.[41] However, the α-KIEs differ only slightly in both derivatives,[21a,28b] (k_H/k_D = 1.13 and 1.15 resp.) demonstrating, as mentioned before, the insensitivity of the α-effect to neighboring double bond participation. Deuterium labeling on the double bond carbon atoms gives rise to inverse effects as anticipated and confirmed in other systems (Scheme 13).[1,42]

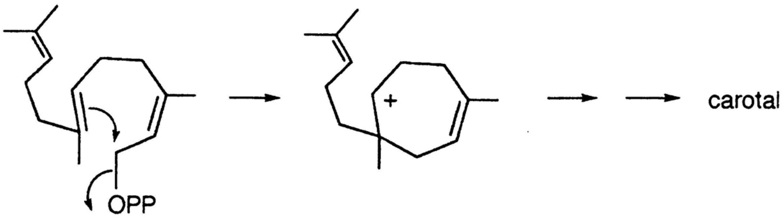


k_{rel}	1	10^{11}	
k_H/k_D	1.15	1.13	0.93

Scheme 13.

π-Participation is often accompanied by cyclization which is an important step in numerous biosynthetic pathways in particular in terpene and steroid chemistry.[43] The classic example is the squalene cyclization reaction leading to lanosterol and other steroids.[44] Here multiple double bonds are involved and it was questionable whether the cyclization reaction involving multiple double bonds is a concerted or a stepwise process.

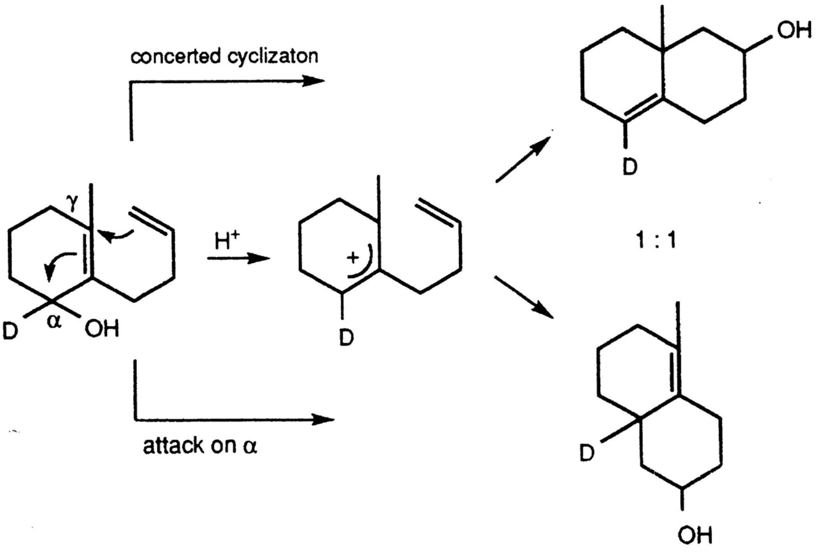
Attempting to solve this problem we took two different approaches, both making use of deuterium labeling. Allylic cations are known to be *inter alia* intermediates in the biosynthesis of carotal (Scheme 14)[45] and in the 1',4-coupling reaction of isopentenyl pyrophosphate with dimethylallyl pyrophosphate.[46]



Scheme 14.

For this last reaction it was established that it proceeds by an ionization-condensation-elimination mechanism.[47] This was not established for the first named cyclization reaction where the allylic moiety and the double bond are parts of the same molecule.

As a model system we chose a cyclohexanol derivative which under acidic conditions easily undergoes cyclization.[48a] Deuterium labeling perturbs the system, and product analysis should answer the question of the concertednes or nonconcertedness of the cyclization reaction (Scheme 15).[48b]

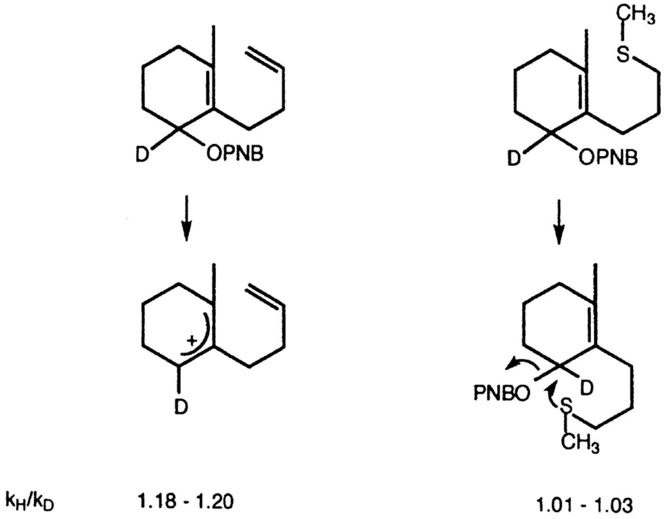


Scheme 15.

The products consisted of equal parts of both isomers which proved that under the applied conditions this reaction proceeds in a stepwise fashion.

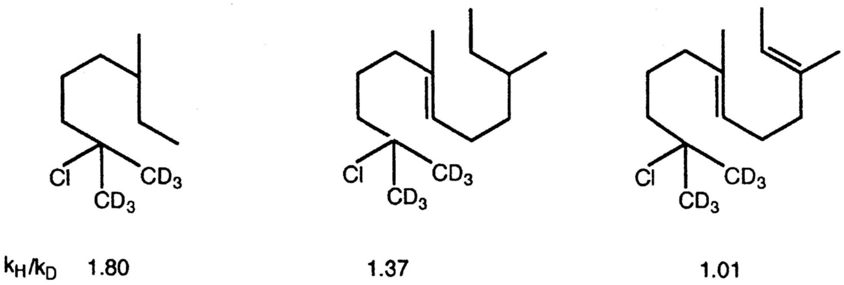
Further experiments have shown that in allylic substrates such as 3-substituted 2-cyclohexenyl esters pronounced neighboring group participation occurs only with very strong nucleophiles (*e.g.* sulfur) and in solvents which cannot form strong hydrogen bonds with the participating atom. While the α-deuterium isotope effect in the rate determining formation of the cyclic allyl cation is 1.18–1.20, sulfur participation reduces this efect in ethanol to 1.01–1.03 (Scheme 16).[49]

A different approach was taken by Borčić and coworkers.[50a] They used methyl-d_3-labeled derivatives and looked at β-KIEs as probes for double bond participation in the rate determining step. The observed significantly



Scheme 16.

reduced *gem*-dimethyl-d_6 isotope effects have been interpreted as indicative for extended π-participation involving even remote double bonds (Scheme 17).



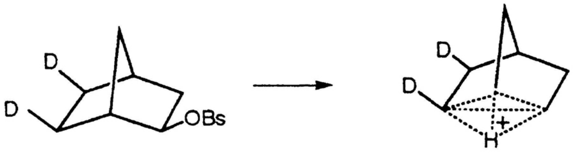
Scheme 17.

This work has been reviewed in one of Borčić's last papers[50b] and more recent results are reported by Humski *et al.* in this memorial issue. New light on the problem of the mechanism of the cyclization reaction in sterol biosynthesis was thrown by a recent paper by Corey *et al.*[50c] They presented clear evidence against a concerted mechanism for the enzymic cyclization of 2,3-oxidosqualene favoring a stepwise reaction *via* discrete carbocationic intermediates.

σ-PARTICIPATION: THE 2-NORBORNYL CATION, THE CLASSIC OF NONCLASSICAL IONS

The controversy surrounding the question of carbon-carbon single bond participation centered around the 2-norbornyl cation problem[13c] and the work contributing to its solution will be briefly reviewed.

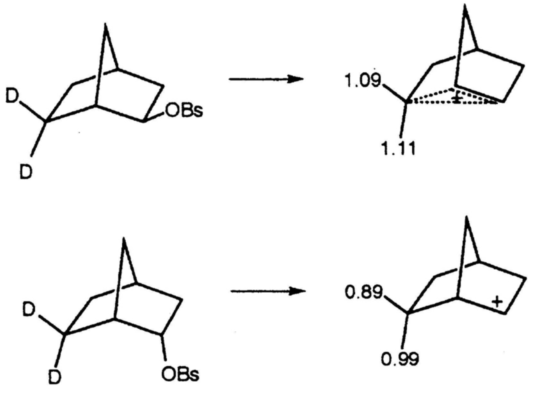
Our first paper dealing with isotope effects in solvolyses of *exo*- and *endo*-2-norbornyl brosylates deuterated in the 5,6-*exo*-position appeared in 1961 and remained almost unnoticed.[51] The observed effect in the *exo*-derivative was erroneously ascribed to a 1,3-hydride shift in the nortricyclyl cation supposedly formed in the rate determining step (Scheme 18).



$k_H/k_D = 1.09$ (25°. AcOH)

Scheme 18.

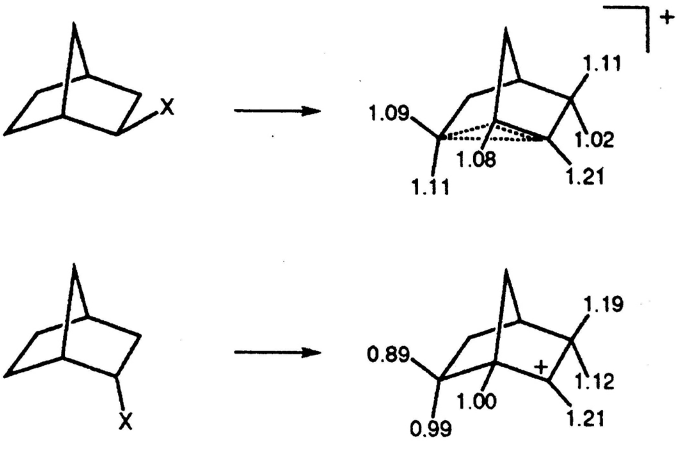
This interpretation was rectified six years later in a paper[52a] independently published back to back with a communication by Brown Murr, Alex Nickon and collaborators[52b] reporting identical KIEs in the solvolysis of 6-*exo*- and *endo*-*d*-2-*exo*- and *endo*-norbornyl brosylates (Scheme 19).



Scheme 19.

The results spoke strongly in favor of a nonclassical structure of the ion formed in the rate determining step in solvolysis of the *exo*-brosylate. Winstein referred to this work in his Centeniary lecture presented before the Chemical Society (London):[14] »....the norbornyl cation was discussed in Sheffield by H. C. Brown. His paper has been published in *Chem. in Britain*,[13b]... While this article will undoubtedly prove to be of historical interest, I would recommend reading the actual older and more recent literature for conclusive evidence that the secondary norborn-2-yl cation prefers a nonclassical structure.«

Maskill[53] redetermined the effects in the 2-position and incorporated a second deuterium in position 1 in order to avoid problems involving label scrambling during the internal return reaction. He concluded that the results are incompatible with a mechanism involving direct ionization to interconverting *classical* cations. The isotope effects determined in the solvolysis of specifically deuterated 2-*exo*- and 2-*endo*-norbornyl brosylates are summarily shown in Scheme 20.



Scheme 20.

While the α-KIE is practically the same for both isomers, all other effects differ significantly. This difference is most pronounced in the 6-deuterated 2-norbornyl esters supporting the nonclassical structure for the ion generated in the solvolysis of the *exo*-derivative. These results elegantly demostrate the usefulness of KIEs in studies of solvolytic reaction mechanisms.

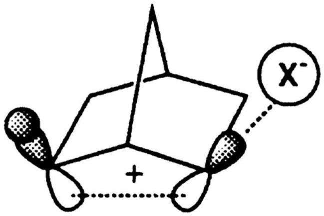
In numerous papers on this subject[13c,54] one of the principal participants of this debate, which continued long after Winstein's death, minimized our interpretation. In his book on the 2-norbornyl cation problem published in 1977, H. C. Brown gives the following commentary of the isotope effect studies: »It is evident that the effects of deuterium substitution are interesting. However, the interpretation of secondary isotope effects in solvolysis becomes increasingly complex. Until we have a full understanding of such secondary isotope effects, it would appear highly dangereous to attempt to rationalize them to resolve the question of the structure of the 2-norbornyl cation«.[13c]

Fortunately today we know a lot more about the origin of these effects and it is generally accepted that »kinetic isotope effects (KIEs) are among the most powerful tools available to chemists for elucidating the nature and structure of transition states of chemical reactions.«[55]

The nonclassical structure of the 2-norbornyl cation gained further support from spectroscopic studies of this cation formed under stable ion conditions. The nonclassical structure could be inferred from ^{13}C cross-polarization magic angle spinning (CP-MAS) spectra of a fluoroantimonate[56] as well as from the X-ray structure by Laube[57] of the 1,2,4,7-tetramethylnorborn-2-yl cation and by Montgomery *et al.*[58] of the 2-methoxy-1,7,7-trimethylbicyclo[2.2.1]heptylium fluoroborate. Finally, the vibrational spectrum of the most stable structure of the cation calculated at high level of theory by Koch *et al.*[59] agrees with the IR spectrum of the cation generated in the solid antimony pentafluoride matrix at 150 K[60] using the method of Vančik and Sunko.[33]

HOMOHYPERCONJUGATION AND REMOTE ISOTOPE EFFECTS

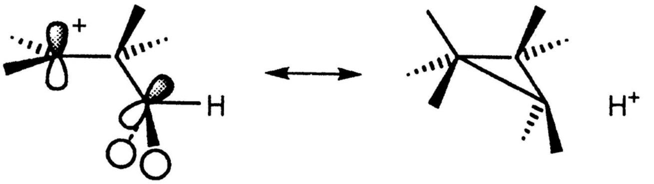
Only few examples of homohyperconjugation can be found in carbocation chemistry. The most dramatic manifestation of a remote secondary KIE is the already discussed rate retardation caused by deuterium substitution at the γ-position in *exo*-2-norbornyl derivatives.[52] The hypothesis that this effect might have been caused by a through space »backlobe effect« of the *exo*-C_6-H(D) bond *i.e.* homohyperconjugation[61] does not hold because the same effect was observed with the *endo*-deuterated derivative where such interaction is not present (Scheme 21).[52]



Scheme 21.

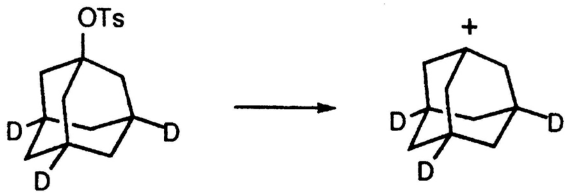
A few other remote KIEs have been studied in some detail and these were mostly inverse and rather small.[62] Homohyperconjugation was not invoked as a possible cause of these effects.

Long range through space interactions implied in homohyperconjugation rapidly fall off at distances greater than 250 pm or more than three carbon atoms apart and are critically dependent on the proper orientation of the interacting orbitals (Scheme 22).



Scheme 22.

The rigid skeleton of adamantane provided a suitable system for studying such interactions. The γ-effects measured in the solvolysis of 1-adamantyl-3-*d* tosylate and 1-adamantyl-3,5,7-d_3 tosylate turned out to be k_H/k_D = 1.041 and 1.073, respectively (Scheme 23).

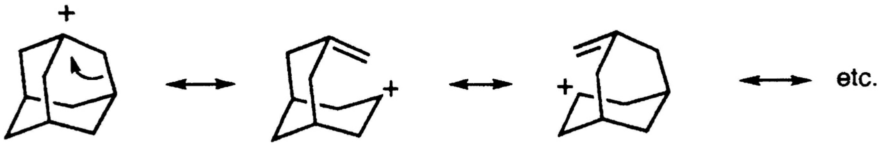


k_H/k_D = 1.07

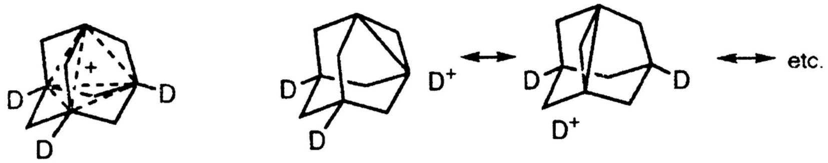
Scheme 23.

These effects could be rationalized by either carbon-carbon hyperconjugation or carbon-hydrogen homohyperconjugation (or a combination of both) (Scheme 24).[63]

Calculations of structural parameters of the 1-adamantyl cation[64] and crystal structure data for the 3,5,7-trimethyl-1-adamantyl cation[65] show an elongation of the C_β-C_γ bonds which is consistent with the hyperconjugative model. The shortening of the C_α-C_β bonds agrees with the partial double



C - C hyperconjugation



C - H (D) homohyperconjugation

Scheme 24.

bond character indicated in the canonic resonance structures of the cation. Since it is not possible to obtain precise data for the C-H bond lenghts from X-ray diffraction measurements, the question of a possible superimposed C_γ-H homohyperconjugative interaction in the 1-adamantyl cation remains open.

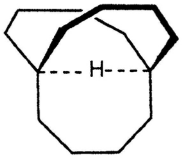
Remote hydrogen participation has been invoked as possible cause for rate enhancements in the solvolysis of medium-sized ring derivatives relative to cyclohexyl and alicyclic compondes. These transannular hydride shifts were first investigated by Prelog and collaborators[66] who argued that anchimeric assistance of a remote hydrogen atom should be accompanied by a significant deuterium isotope effect. In his dissertation Borčić reported a value of 1.01 for k_H/k_D in solvolysis of 5,5,6,6-d_4 cyclodecyl tosylate which supported the hypothesis that I-strain is responsible for the rate effects and that the hydride shift occurs after the rate determining step. Subsequent careful studies by Parker and Watt[67] of the solvolysis of *cis-* and *trans-*(5-*d*) cylooctyl brosylates revealed a significant effect (k_H/k_D = 1.12) in the *trans* isomer in keeping with the proposed μ-hydrido bridged structure for the cationic transition state (Scheme 25).

This structure was confirmed by NMR and IR studies on the cyclooctyl cation generated under stable ion conditions. In agreement with NMR data and IGLO chemical shifts calculated with MP2/6-31 G* geometry of the C_s conformation (Figure 1) the broad signal at 1845 cm^{-1} observed in the IR spectrum of the matrix isolated cation was assigned to the C-H-C stretching vibration of the bridged hydrogen.[37] It remains to be seen if similar isotope

$k_H/k_D = 1.12$; ν(C–H–C) = 1845 cm^{-1}

Scheme 25.

effects could be observed in other *μ*-hydrido bridged ions such as McMurry's *in*-bicyclo[4.4.4]-1-tetradecyl cation.[68]

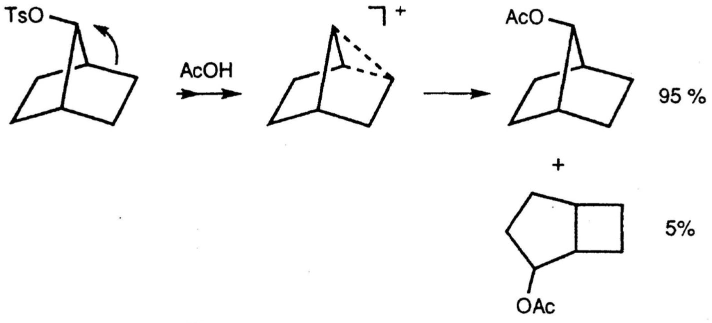


ν(C--H--C) = 2113 cm^{-1}

Scheme 25a.

THE 7-NORBORNYL CATION PUZZLE

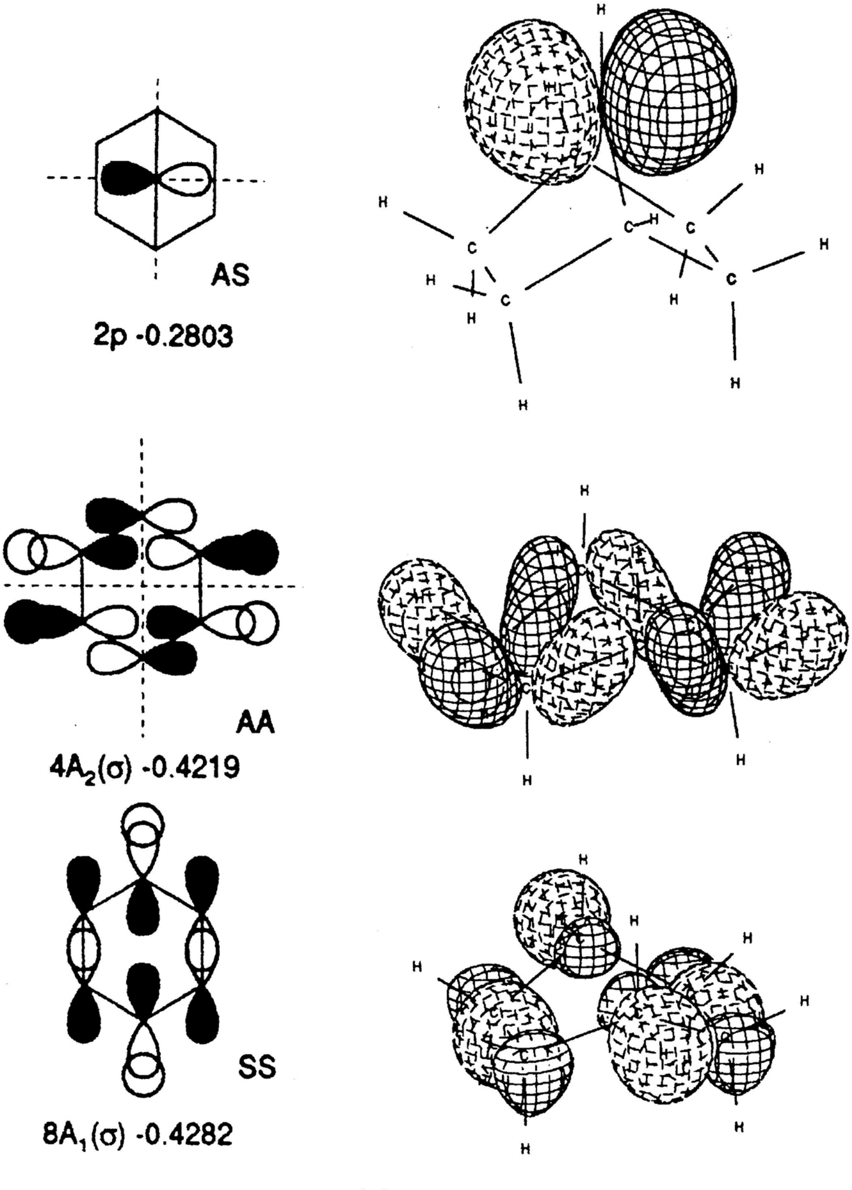
In the wake of the 2-norbornyl cation controversy, another nonclassical structure proposed by Winstein in 1955[38] remained almost unnoticed. 7-Norbornyl derivatives while of proper geometry for C_2-C_3 or C_1-C_2 sigma bond participation hold the record of unreactivity among secondary systems. The tosylate in acetic acid has at 25 °C an extrapolated half-live of more than 3×10^6 years (Scheme 26).



$k = 6.36 \times 10^{-15}$; AcOH, 25° (extrap.); $t/2 = 3455200$ years!

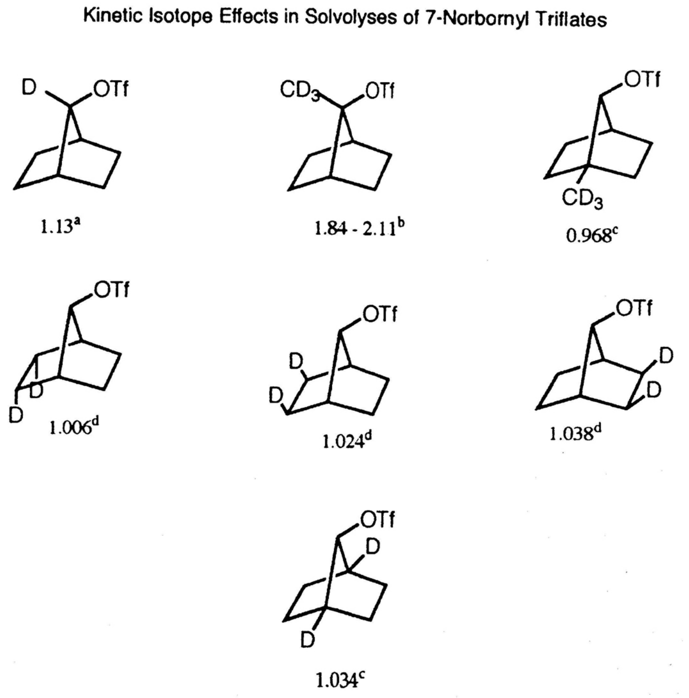
Scheme 26.

In 1973, Hoffmann, Mollere and Heilbronner[69] suggested that the cause for this extreme unreactivity is probably the symmetry forbidden interaction of the developing p-orbital at the 7-position with the ribbon orbitals of the underlying six-membered ring (Scheme 27).



Scheme 27.

This proposal prompted us to systematically investigate substituent effects and the effects of deuterium substitution at different position in the 7-norbornyl system.[70] The results are shown in Scheme 28.

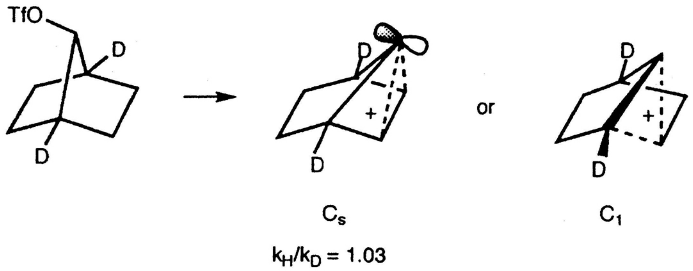

Kinetic Isotope Effects in Solvolyses of 7-Norbornyl Triflates

[a]ref. 21a; [b]ref. 28b; [c]ref. 70b; [d] ref. 70a

Scheme 28.

From the first isotope effects determined in the seventies on the 7-methyl derivative[27b] to the observation of remote effects in the parent system and other substituent effects[70] practically all available tools of modern physical organic chemistry have been used in order to determine the structure of this elusive cation. The precise determination of β-effects conducted by Toby Wilgis in Shiner's group[70b] provided a strong indication for a tilted transition structure of C_s or C_1 symmetry (Scheme 29).

This structure was later confirmed by theoretical work of Schleyer *et al.*[71a,b] using high level *ab initio* methods. The matrix isolation of the cation and the comparison of calculated and observed IR spectra[71a,c] solved the problem of the structure of the 7-norbornyl cation. Thus, the structure pro-



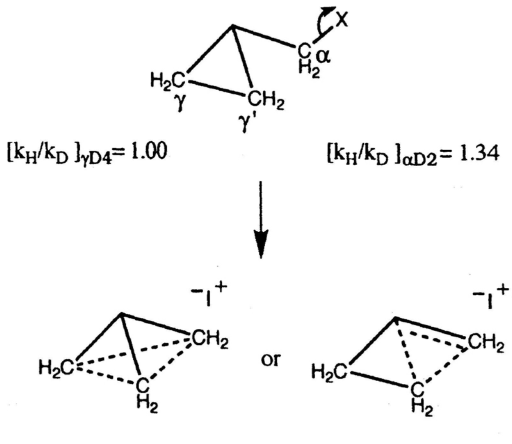
Scheme 29.

posed by Winstein in the fifties was shown to be correct. The whole complexity of the $C_7H_{11}^+$ potential energy surface has been disclosed in recent papers by Schleyer and collaborators[71a,b] and by Szabo and Cremer.[72]

THE »BICYCLOBUTONIUM ION CONTROVERSY«[73]

The term »nonclassical ion« was first introduced by Roberts,[12,74] who proposed a delocalized structure for the ion formed in the solvolysis of cyclopropylcarbinyl and cyclobutyl derivatives.[75] Our working hypothesis was that if the intermediate has the tricyclonium ion structure as proposed by Bergstrom and Siegel[76] or a "bicyclobutonium" like structure as suggested by Roberts,[72] then labeling at α- and γ-positions should show similar effects (Scheme 30).[74]

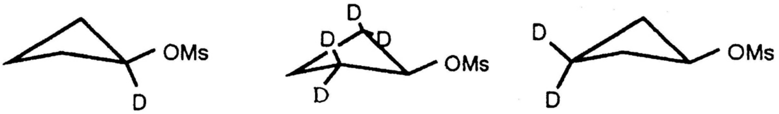
This was found not to be the case and we published this result challenging the proposed structure. What followed was a rebuttal by Roberts[78] who stated quite correctly that the two methylene groups in the cyclopropyl ring



Scheme 30.

differ in hybridization from the α-methylene group. Had we been aware of this, we would, most probably, never have started this project. Nevertheless, our *Chem. & Ind.* paper stirred a lively discussion which resulted in more papers from our laboratory and others on the same subject.[79] At the same time this marked our entry into physical organic chemistry, a field which was at that time poorly represented in Europe.

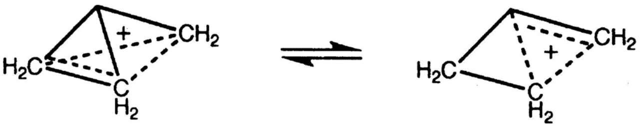
In the seventies, the cyclopropylcarbinyl system was found to be involved in the biosynthesis of squalene from farnesyl pyrophosphate[80] and a graduate course organized by Jack Shiner and myself in 1973 reviewed this field.[81] In the meantime, the problem of the structure of the $C_4H_7^+$ ion was approached by a combination of theoretical and experimental methods. Based on label scrambling results and borohydride trapping experiments we suggested in 1970, that the solvolysis of cyclopropylcarbinyl and of cyclobutyl derivatives seems to proceed *via* two equilibrating delocalized ions.[82] Our early work on isotope effects in this system was reinvestigated in 1973 and with cyclobutyl mesylate a reduced α-effect, an inverse β-effect and a rather large but normal γ-effect were observed (Scheme 31).[23]



$[k_H/k_D]_\alpha = 1.10$ $[k_H/k_D]_{\gamma D4} = 1.00$ $[k_H/k_D]_{\gamma D2} = 1.08$

Scheme 31.

These results indicated a strong 1–3 interaction in the transition state. The isotope effects observed in the solvolysis of cyclopropylcarbinyl mesylate were inconclusive with respect to possible bridging in the transition state. Support for the presence of two delocalized equilibrating ions as explicitly suggested by Saunders and Siehl on the basis of isotope fractionation measurements[83] and IGLO calculations of chemical shifts[84] came much later from CP MAS experiments of Myhre and Yannoni[85] on solid samples of the stable ion complex with antimony pentafluoride at 5 K. These results indicate the presence of two isomers of nearly equal energy, the bicyclobutonium ion and the cyclopropylcarbinyl cation which are in rapid equilibrium (Scheme 32).



Scheme 32.

Our final paper on this subject,[86] published 33 years after the first (!), reported the vibrational spectra of these two ions in the cryogenic SbF_5 matrix which are in accord with the superimposed spectra for the two equilibrating cations calculated at the MP2/6-31G* level of theory[84] and observed in the CP MAS spectra.[85]

CONCLUDING REMARKS

With the results discussed in this review, which only partly covers the past twenty five years of research, the final chapter of the fascinating story of the nonclassical ion problem seems to be written. Seldom has an academic question as this one engaged for so long so many scientists and contributed so much to the development of modern physical organic chemistry. Isotope effects contributed to the solution of this problem and in return much was learned about the origin and application of secondary KIEs in reaction mechanism studies. Kinetic isotope effects are today a standard tool of physical organic chemistry and this updated review should help the coming generation to remember how this field of chemistry unfolded.

Acknowledgment. – The work reviewed in this paper would not have been possible without the involvement and support of many talented students and postdoctoral co-workers whose names are quoted in the references. I enjoyed the privilege of a long lasting friendship and collaboration with the late Stanko Borčić and also with many other colleagues and friends whose numerous stimulating and clarifying discussions contributed much to the advance of physical organic chemistry in Croatia. On a personal note, I take pleasure in the friendship, collaboration and fruitful exchange of ideas with Jack Shiner spanning over more than 30 years.

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SAŽETAK

Sekundarni deuterijski izotopni efekti pri sudjelovanju susjedne skupine

Dionis E. Sunko

Dan je pregled istraživanja solvolitskih reakcija koje teku uz sudjelovanje susjednih skupina primjenom sekundarnih deuterijskih izotopnih efekata. Promjene u veličini tih efekata odražavaju stupanj participacije u prijelaznom stanju reakcije. Ti su podaci uspoređeni s drugim eksperimentalnim dokazima. Dodatnu potvrdu strukture karbokationa dali su najnoviji kvanto-mehanički računi visoke *ab initio* razine. Studij izotopnih efekata jedno je od najmoćnijih pomagala za objašnjenje prirode i strukture reakcijskih prijelaznih stanja.