Ab Initio MO Calculations of Isotope Effects in Model Processes of Neopentyl Ester Solvolysis

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Received January 28, 1983

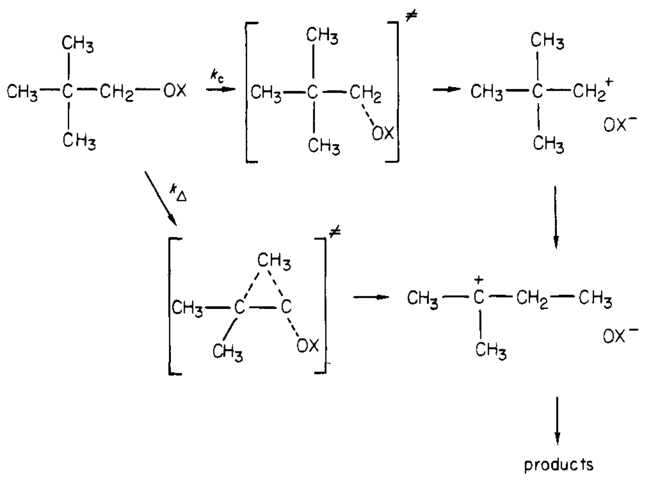
Ab initio molecular orbital calculations were carried out for the isotope effects on ionizations of 1-propanol to a series of propyl cations, model reactions of the neighboring group assisted (k_Δ) and nonassisted (k_c) processes of neopentyl ester solvolysis. Calculated carbon-14 isotope effects of the migrating methyl group were normal (larger than unity) for all the model processes, suggesting that the experimentally observed normal carbon isotope effect at the position cannot be decisive evidence supporting the k_Δ mechanism for the neopentyl solvolysis. On the other hand, deuterium isotope effects of the methyl group were calculated to be normal for the k_Δ process, as expected, but inverse (smaller than unity) for the k_c model process; the inverse effect is incompatible with experiment. The results are consistent with our earlier conclusion that the mechanism of the neopentyl solvolysis is k_Δ.

Neopentyl esters solvolyze through either of two possible pathways (Scheme I); one is a stepwise process via a primary ion-pair intermediate (designated k_c, S_N1) and the other is a concerted process in which one of the neighboring methyl groups migrates in the rate-determining ionization step (designated k_Δ, σ participation).[2]

Kinetic isotope effects are believed to be the most decisive means to determine whether the mechanism of such a 1,2-molecular rearrangement is concerted or stepwise.[3] Basic strategy of the isotope effect technique is that if we observe a normal isotope effect for the migrating carbon atom, the reaction is assumed to proceed via a concerted process, and if, on the other hand, no measurable isotope effect is detected for the atom, the reaction is concluded to proceed via a stepwise process. Many examples of this technique have been reported for a variety of reactions.[3,4]

We have previously measured the carbon-14 and deuterium kinetic isotope effects of the migrating γ-methyl group in the acetolysis of neopentyl arenesulfonates and observed normal effects.[2] These isotope effects as well as the normal α-^{14}C, β-^{14}C, and α-D_2 isotope effects observed in the reaction have suggested that the reaction proceeds via the k_Δ mechanism. However, in contrast to the case of solvolysis with π participation[4] and other molecular rearrangements,[3] the interpretation of the observed isotope effect data is not straightforward for this solvolysis with σ participation. Although the data are apparently consistent with the concerted k_Δ process, they may not be conclusive enough to completely eliminate the possibility that the reaction proceeds via the k_c process whose transition state is stabilized by the extensive C_β–C_γ hyperconjugation. In such a transition state, bonding at the γ-position must differ from that in the reactant, and this bonding change may result in the normal isotope effects as observed. If it is really the case, we have to abandon the above simple strategy on the use of the isotope effect technique. Thus, it is now very important, not only for the elucidation of the solvolysis mechanism but also for further use of the isotope effect technique, to investigate the possibility that the k_c process yields the normal isotope effects at the γ-position to the experimentally observed magnitudes.

Scheme I



In the present investigation, we calculated the isotope effects on the model k_c and k_Δ processes of neopentyl solvolysis by use of the ab initio SCF MO method and examined the above possibility by comparing the calculated isotope effects for the model processes with the experimental values.

Calculations and Results

As Scheme I shows, one of the γ-methyl groups migrates to the α-position after the rate-determining C–O bond breaking in the k_c process, whereas ionization and methyl migration occur synchronously in the rate-determining step of the k_Δ process. Accordingly, the two processes may be characterized in terms of the position of the migrating methyl group measured, for example, by the C_α–C_β–C_γ angle in the transition state. In the present investigation, the reactant neopentyl arenesulfonate was modeled by

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[2] Ando, T.; Yamataka, H.; Morisaki, H.; Yamawaki, J.; Yukawa, Y. *J. Am. Chem. Soc.* **1981**, *103*, 430–436 and references cited therein.

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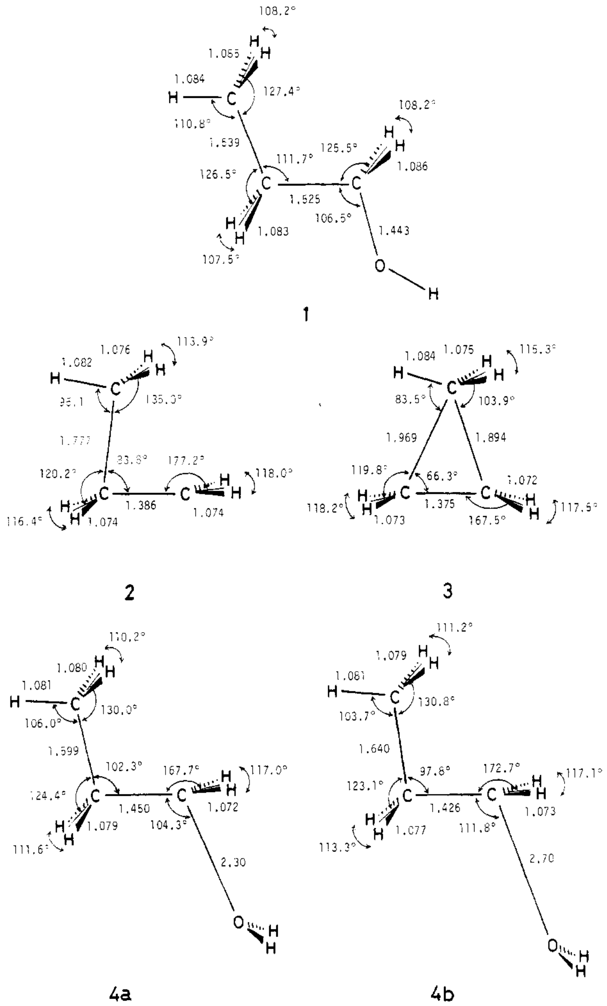


Figure 1. Optimized geometries of 1–4 with the 3-21G basis set.

1-propanol (**1**), and the isotope effects on its ionization to a series of propyl cations of different C_α–C_β–C_γ angles were calculated by the ab initio SCF MO method. All calculations were carried out with the 3-21G basis set[5,6] unless otherwise noted. Geometries and vibrational frequencies were determined by using an energy gradient method.[7,8]

We observed two cations (**2** and **3**) having the same type of symmetry as **1** (Figure 1). These are quite similar in energy; **3** is less stable than **2** by only 0.08 kcal/mol. Cations **4a** and **4b** were calculated by placing a water molecule at fixed distances (2.4 Å for **4a** and 2.7 Å for **4b**) from the α-carbon of **2**. The water molecule serves as a perturbation that holds the C_α–C_β–C_γ angle in between those of **1** and **2**. Thus, we obtained four cations that were different in the position of the methyl group (Figure 1).

Table I. Theoretical Isotope Effects in the Ionization of 1-Propanol to Various Propyl Cations[a]

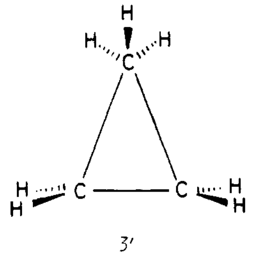
	cations				exptl isotope effect[b]
	4a	4b	2	3	
α-^{14}C	1.039	1.039	1.033	1.029	1.074
β-^{14}C	1.022	1.026	1.027	1.028	1.019
γ-^{14}C	1.016	1.025	1.043	1.047	1.037
α-D_2	1.288	1.392	1.268	1.036	1.187
β-D_2	0.969	0.972	1.000	1.058	
γ-D_3	0.955	0.940	0.995	1.033	1.123

[a] Values at 100 °C. [b] Experimental isotope effects in the solvolysis of neopentyl esters. Data taken from ref 2.

Table II. Kinetic Isotope Effects in the Heterolysis of Protonated Neopentyl Alcohol

position	α-^{14}C	β-^{14}C	γ-^{14}C	α-D_2	γ-D_3
$k/{}^*k$	1.079	1.049	1.062	1.248	1.304

For cations **1** and **2** 3N-6 normal frequencies were obtained, showing that these compounds are at local minima on the potential energy surface. On the other hand, normal coordinate analysis of cation **3** showed that the cation has one imaginary frequency that corresponds to the rotation of the transfering methyl group; cation **3′**, a protonated cyclopropane of a different type of symmetry, was found to be lower in energy than **3** by 0.08 kcal/mol. However, the difference in energy between **3** and **3′** is small enough to assume free rotation of the methyl group. Isotope effects were calculated for both cations, **3** and **3′**; in the case of **3**, the imaginary frequency was simply neglected because the frequency was little affected by isotopic substitution. Calculated isotope effects for both cations were found to be quite similar with each other. Since it is desirable to compare the isotope effects for cations of the same molecular symmetry throughout the series, the isotope effects for cation **3** rather than **3′** were used for the discussion below. For cations **4a** and **4b**, normal coordinate calculations were carried out by using a force-constant matrix constructed with 3N-7 internal coordinates; one internal coordinate corresponding to the C_α–O bond stretch was excluded because the C_α–O bond length was kept constant during the geometry optimization.



3′

Isotope effects were calculated by Bigeleisen's equation (eq 1) from the calculated frequencies, where u stands for

$$k_1/k_2 = \left[\frac{\nu^{\ddagger}_{L1}}{\nu^{\ddagger}_{L2}}\right]\left[\prod_i^{3n^{\ddagger}-7}\left(\frac{u_{1i^{\ddagger}}}{u_{2i^{\ddagger}}}\times\frac{e^{-u_{1i}^{\ddagger}/2}}{e^{-u_{2i}^{\ddagger}/2}}\times\frac{1-e^{-u_{2i}^{\ddagger}}}{1-e^{-u_{1i}^{\ddagger}}}\right)\prod_i^{3n-6}\left(\frac{u_{2i}}{u_{1i}}\times\frac{e^{-u_{2i}/2}}{e^{-u_{1i}/2}}\times\frac{1-e^{-u_{1i}}}{1-e^{-u_{2i}}}\right)\right] \quad (1)$$

$h\nu/kT$ and $\nu^{\ddagger}_L$ is the reaction coordinate frequency.[9] Because the reaction coordinate term ($\nu^{\ddagger}_{L1}/\nu^{\ddagger}_{L2}$) in eq 1 cannot be determined in the present calculations, it was set equal to unity for all cases. The magnitude of the reaction coordinate term is usually small except for primary isotope effects such as the α-carbon isotope effect for the present case[10] and can be neglected in the following

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(5) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939–946.

(6) An IMSPACK program was used: Morokuma, K.; Kato, S.; Kitaura, K.; Ohmine, I.; Sakai, S.; Obara, S. IMS Computer Library Program, No. 0372, 1982.

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(9) Bigeleisen, J. *J. Chem. Phys.* **1949**, *17*, 675–678.

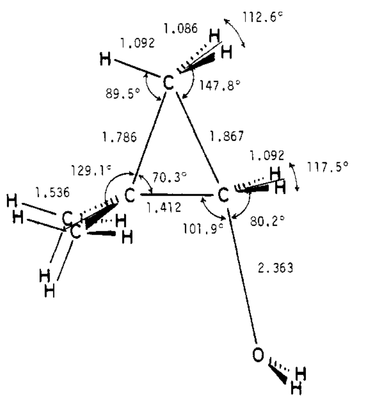
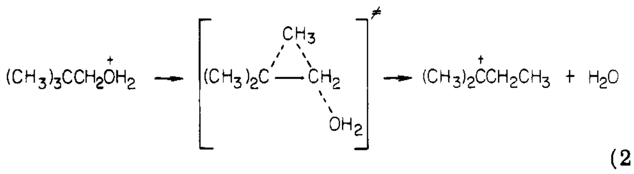


Figure 2. Geometries of the transition state of reaction 2.

discussion. Calculated isotope effects are summarized in Table I together with the experimental values.

Isotope effects were also calculated for the k_Δ-type reaction of protonated neopentyl alcohol (eq 2), where the



$$(CH_3)_3CCH_2\overset{+}{O}H_2 \rightarrow \left[(CH_3)_2\overset{+}{C}\overset{CH_3}{\text{—}}CH_2\cdots OH_2\right]^{\neq} \rightarrow (CH_3)_2\overset{+}{C}CH_2CH_3 + H_2O \qquad (2)$$

original neopentyl moiety was retained but the sulfonate leaving group was replaced by water. Since this system was too large to perform isotope effect calculations with the 3-21G basis set, the calculations were carried out at the STO-3G level of approximation. The calculation yielded a transition state that lies 67.6 kcal/mol above the reactant. The mode of the reaction coordinate was mainly the migration of the methyl group that lay at the *s*-trans position to the H_2O group.[11] The geometry of the transition state is shown in Figure 2, and the calculated isotope effects are listed in Table II.

Discussion

Before going into a discussion of the results, it may be important to assess the reliability of the isotope effects calculated by the present method. There are some precedents for the quantum mechanical calculations of isotope effects both by the semiempirical[12] and the ab initio schemes.[13] Among them is a series of Hehre–Wolfsberg's papers that are relevant here, in which equilibrium isotope effects were calculated by the ab initio MO method and compared with those determined experimentally.[13a,b]

One example is the equilibrium constants for isotopic exchange reactions, eq 3 and 4.[13b] The equilibrium con-

$$HD + XH \rightleftharpoons H_2 + XD$$
$$XH = LiH,\ CH_4,\ NH_3,\ H_2O,\ HF \qquad (3)$$
$$CH_3D + HX \rightleftharpoons CH_4 + XD$$
$$XH = C_2H_6,\ CH_3F,\ C_2H_4,\ C_2H_2,\ HCN \qquad (4)$$

stants were calculated at three levels of approximation, HF/3-21G, HF/6-31G*, and MP2/6-31G*, and compared with spectroscopic values obtained from the experimentally observed frequencies. Agreement between the theoretical and experimental equilibrium constants was reasonably good for all levels of theory; the average error for the ten reactions was 10%. Another system is proton-transfer reactions between CH_3NH_2 and CD_3NH^-, CH_3OH and CD_3O^-, and CH_3NH_2 and $CD_3NH_3^+$.[13a] The equilibrium constants for these reactions were calculated with the HF/4-31G basis set, and the experimental values were determined by ion cyclotron resonance spectroscopy. For these reactions, agreement between theory and experiment was reasonable. In particular, agreement was excellent for the cationic species (the third reaction); anionic species are known to be less satisfactorily computable at this level of theory as compared with cationic ones.

It is unlikely that the uncertainty in the calculated isotope effects in the present study is much larger than that reported by Hehre–Wolfsberg, namely, ca. 10%. We believe that the uncertainty of this magnitude is sufficiently small to allow qualitative comparison between the calculated and observed isotope effects.

Since primary carbocations are known to be very unstable, it is expected that the transition state of the k_c (S_N1) process of the neopentyl solvolysis should resemble the intermediate primary neopentyl cation (the Hammond postulate[14]). Therefore, cations **2** and **4** were expected to be good models for the k_c transition state. This expectation was supported by the fact that the calculated isotope effects for **2** and **4** are in good agreement with experimental values for typical S_N1 reactions where comparable data are available. For example, the calculated α-^{14}C isotope effects for **2** and **4** ($^{12}k/^{14}k$ = 1.035–1.039) are only slightly larger than that (1.027) observed for the solvolysis of 2-chloro-2-methylpropane at 25 °C,[15] and the α-deuterium isotope effect ($^{H}k/^{D}k = 1.18 = (1.39)^{1/2}$, per D_1 for **4a**) is smaller only slightly than the experimental limiting value (1.22 for a sulfonate leaving group at 25 °C) for S_N1 reactions of various substrates.[16] These differences between the calculated and observed isotope effects become still smaller when the temperature effect is considered; α-carbon isotope effects are larger while α-deuterium isotope effects are smaller at higher temperature in S_N1 reactions.[17]

The most important result in Table I is that the γ-^{14}C isotope effects are normal for all the cations **2**–**4**. The result suggests that the γ-^{14}C effect can be normal for both the k_c and k_Δ processes. Thus, the experimental observation of the normal γ-^{14}C isotope effect cannot be decisive

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(10) The magnitude of the reaction coordinate term can be as large as 1.04 for the α-carbon isotope effect in the k_Δ solvolysis of neopentyl esters: Yamataka, H.; Ando, T. *J. Am. Chem. Soc.* **1982**, *104*, 1808–1813.

(11) We have previously carried out the MINDO/3 calculations on reaction 2. Interestingly, the reaction coordinate motion determined by the MINDO method is different from the present ab initio results; the MINDO reaction coordinate motion is essentially the C_α–O bond cleavage. This seems to show that the ab initio method even with the minimal basis set describes more adequately the concerted nature of the reaction than the MINDO/3 method: Ando, T.; Yamataka, H.; Yabushita, S.; Yamaguchi, K.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3613–3614.

(12) (a) Wilcox, C. F., Jr. *Tetrahedron Lett.* **1975**, 4457–4460. (b) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 8343–8344. (c) Brown, S. B.; Dewar, M. J. S.; Ford, G. P.; Nelson, D. J.; Rzepa, H. S. *Ibid.* **1978**, *100*, 7832–7836. (d) Gabbay, S.; Rzepa, H. *J. Chem. Soc., Faraday Trans. 2* **1982**, *78*, 671–677.

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(15) Bender, M. L.; Buist, G. I. *J. Am. Chem. Soc.* **1958**, *80*, 4304–4307.

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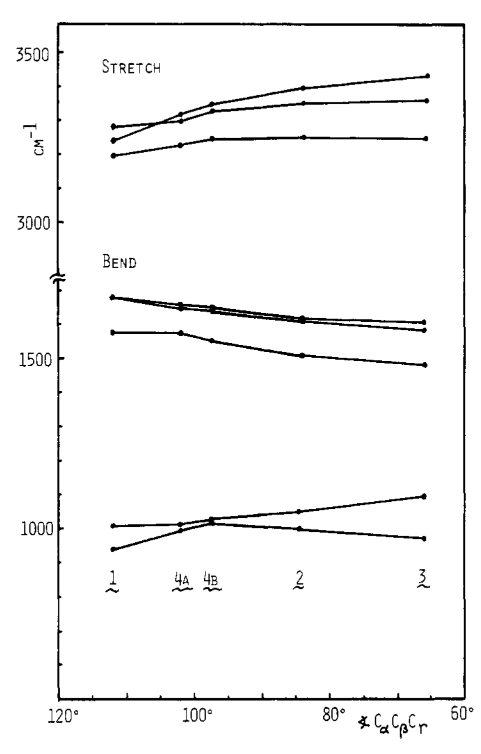

Figure 3. Variations of stretching and bending frequencies at the C_γ–H bonds against the $C_\alpha C_\beta C_\gamma$ angle.

evidence for the concerted mechanism contrary to the usual expectation. In contrast, the γ-D_3 isotope effect seems to be more informative in this respect; it varies from inverse for **2** and **4** to normal for **3**. The comparison of the calculated γ-D_3 isotope effects with the experimental value shows that the neopentyl solvolysis does not proceed via the k_c process and that the k_Δ process is the only possible pathway for the solvolysis.

Then what causes such a difference in the response of the γ-^{14}C and D_3 isotope effects to the structural variation? It is apparent that the origin of the γ-^{14}C isotope effect is the hyperconjugative C_β–C_γ bond weakening. This C–C bond weakening leads to a decrease in the C_β–C_γ bond-stretching frequency, resulting in the normal isotope effects at the carbon. The increasing trend of the magnitude of the effect, **4a** < **4b** < **2**, is consistent with the higher extent of hyperconjugation in this order.

In contrast, the magnitude of the γ-D_3 isotope effect appears to depend on the frequencies of both stretching and bending modes about the C_γ–H bonds. Figure 3 illustrates the variations of these frequencies as functions of the C_α–C_β–C_γ angle. Among these frequencies the higher six (three stretches and three bends) are highly dependent on the isotopic substitution of the γ-hydrogen and important for the γ-D_3 isotope effect; these frequencies are reduced by 26–28% upon deuterium substitution. The lower three frequencies are much less important for the isotope effect because the reduction of the frequencies upon deuterium substitution is small. As Figure 3 shows, the stretching frequencies increase while the higher bending frequencies decrease on going from **1** to **3**. This means that the former frequencies act to decrease the γ-D_3 isotope effect to the inverse direction while the latter act to increase the effect to the normal direction on the ionization process of **1**. Calculated magnitude of the γ-D_3 isotope effects suggests that the isotope effect is governed by the changes in the stretching frequencies for cations of a larger C–C–C angle and that the bending frequencies become progressively important when the angle becomes smaller. The net results are that the γ-D_3 isotope effect is inverse for **2** and **4** and normal for **3**.

Recently, Hehre et al. have carried out ab initio calculations of β-deuterium isotope effects for the hypothetical ionization of isobutane to *tert*-butyl cations[13e] and found that the cation formation not only leads to lengthening of the C–H bonds that can interact hyperconjugatively with the reaction center but also results in significant shortening of the bonds that are orthogonal to the vacant p orbital. This C–H bond shortening was shown to decrease the deuterium isotope effects to the inverse direction as in the case of the C_γ–H bond shortening in our system.[18]

Calculations on reaction 2 support the above conclusion that the reaction proceeds via the k_Δ process. The STO-3G calculations yielded a k_Δ transition state (Figure 2) and normal kinetic isotope effects (Table II), which are qualitatively consistent with the experimental observations. Although the calculated isotope effects are uniformly larger than the observed values, the differences can be explained in terms of the following two factors. The first is the accuracy of force constants. It is known that the force constants calculated with the STO-3G basis set are overestimated[19] and that the errors in the vibrational frequencies are as large as 20%.[20] Although isotope effects reflect changes in frequencies at the position of isotopic substitution rather than the absolute values of the frequencies, this low accuracy may cause large uncertainties in the calculated isotope effects. Second, a part of the difference may be attributable to the possible difference in the position of the transition state along the reaction coordinate; absence of solvent molecules makes the product carbocation unstable and may shift the transition state to be more reactant-like (the Leffler–Hammond postulate[14,21]). A poorer leaving group (H_2O) used in the calculations compared with the arenesulfonate group in the actual solvolysis also has the same effect.

Conclusion

In contrast to a number of successful studies using molecular orbital calculations on reaction mechanism in the gas phase, theoretical studies on reactions in solution are so far quite limited. This is obviously due to large solvent effects on activation and reaction energy in solution. In view of the established usefulness of the molecular orbital calculations, it is important to find a practical and useful way of applying the MO calculations to reactions in solution. The present study is one of such applications, in which isotope effects on model processes were theoretically determined and compared with experimental observations. The results are consistent with the earlier conclusion that the mechanism of the neopentyl solvolysis is k_Δ. Furthermore, it was suggested that the measurement of isotope effect of the participating carbon alone is mis-

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(18) This inverse deuterium isotope effect can be regarded as "inductive origin". In the physical organic language, C–D bonds are inductively more electron donating and capable of stabilizing carbocations compared with C–H bonds. However, it should be recognized that the usual interpretation of the inductive origin of the isotope effect is not correct. In the Bohn–Oppenheimer approximation, nuclear mass has no effect on the electronic wave function, and therefore C–D bonds cannot be more or less electron donating or accepting than C–H bonds. The inverse deuterium isotope effect arises because inductive effects shorten the C–H and C–D bonds and the resulting increase in vibrational frequencies associated with the bonds is larger for C–H bonds than C–D bonds because of the mass difference.

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leading in determining whether the reaction is concerted or stepwise. Successive labeling at various positions of a single substrate is desirable to obtain a firm conclusion.

Acknowledgment. Numerical calculations were carried out at the Computer Center of the Institute for Molecular Science and the Osaka University Computation Center.

Registry No. 1, 71-23-8; 2, 19252-52-9; 3, 17806-70-1; 4a, 17456-36-9; protonated neopentyl alcohol, 18682-92-3.

Structure of the Pseudoaglycon of Actaplanin

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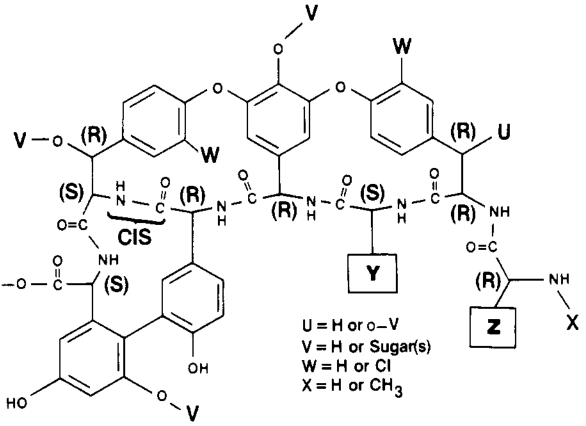
Received September 16, 1983

The structure of the pseudoaglycon of actaplanin is described. The proposed structure is based on ^{1}H NMR studies of the ψ-aglycon in dimethyl sulfoxide solution (including observation of negative nuclear Overhauser effects), analogies with the structures of other glycopeptides, and the products of oxidative degradation of the actaplanin aglycon. The actaplanin ψ-aglycon differs from that of ristocetin by the absence of a benzylic OH and the presence of an aromatic Cl.

Introduction

Actaplanin (A4696) is a complex of glycopeptide antibiotics produced by *Actinoplanes missouriensis*;[1] other antibiotics of this class include vancomycin,[2] ristocetin (ristomycin),[3,4] avoparcin,[5] and A35512B.[6] The general structure 1 is shared by all the glycopeptides for which structures have been reported;[2–6] they may be divided into three subclasses, on the basis of the structures of the groups Y and Z in 1.



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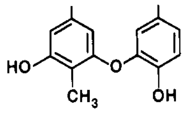
(1) Y, Z = Aliphatic. The only reported example of this glycopeptide type is vancomycin, where Y and Z are the side chains of L-asparagine and D-*N*-methylleucine, respectively.[7] The absolute configurations shown in 1 have been determined for a vancomycin degradation product, CDP-I, by X-ray crystallography (based on the known configurations of asparagine and *N*-methylleucine);[2a] the relationship between CDP-I and vancomycin has recently been described by Harris and Harris.[2b] The cis amide linkage shown in 1 is present in the CDP-I crystal structure, and NMR results have supported such a linkage in all other glycopeptides for which spectra have been described.[3a,5c,6c,8]

(2) Y, Z = Aromatic. Two glycopeptide families of this type have been reported, where Y and Z may be a phenylalanine or a *p*-hydroxyphenylglycine side chain: α- and β-avoparcin[5] and actinoidin A and B.[9]

(3) Y, Z = a Diphenyl Ether. The glycopeptide antibiotic that has been studied the most extensively (after vancomycin) is ristocetin A; the ristocetins A and B differ only in the nature of the sugars attached to 1.[10] In the ristocetins[3,4] and in A35512B,[6] the groups Y and Z in structure 1 are linked together by an ether bond; in ristocetin the substituent has the structure 2.[4]



2

The actaplanins are glycopeptides of the ristocetin type; they each contain the diphenyl ether linkage 2. The A4696 complex differs from all previously reported glycopeptides in having only one benzylic hydroxyl group on the aglycon; i.e., U = H in structure 1 for the actaplanins. The actaplanins differ from each other in the nature and distribution of sugars attached to the peptide core;[11] appropriate

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