The acid-catalyzed rearrangement of deuterium-labeled 2,3-dimethylbutan-2-ol; the concentration of the intermediate cation

Olga Kronja,*[a] Mladen Biruš[a] and Martin Saunders*[b]

[a] *Faculty of Pharmacy and Biochemistry, University of Zagreb, Ante Kovačića 1, 10000 Zagreb, Croatia. E-mail: kronja@rudjer.irb.hr; Fax: +385 1 48-56-201*
[b] *Department of Chemistry, Yale University, New Haven, CT, 06511, USA. E-mail: ms@gaus90.chem.yale.edu*

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The rate of rearrangement of hexadeuterated 2,3-dimethylbutan-2-ol **1A** in sulfuric acid solution in D_2O was measured by means of ^2H NMR. Kinetic data revealed that after the acid-induced formation of the carbocation intermediate, it rearranges through two parallel paths: (*a*) by way of a 1,2-hydride shift, and (*b*) by way of elimination of the methine proton and readdition of water. The elimination/addition reaction is approximately seven times slower than the rearrangement *via* the hydride shift, which is the major reaction pathway. In an experiment carried out with 2,3-dimethylbutan-2-ol-2-[^{13}C] as a substrate in $H_2{}^{18}O$, the ratio of the rearrangement rate and the rate of the exchange of the hydroxy oxygen was found to be $k_{-1}/k_2 = 9.5$. Consequently, the highest point on the energy surface in the overall rearrangement reaction presented in Scheme 1 is the hydrido-bridged 2,3-dimethylbutyl cation. The $K_{R^+} = [ROH][H^+]/[R^+] = 2.2 \times 10^{15}$ was obtained. The concentration of the carbocation **2** obtained under experimental conditions (20 vol% H_2SO_4 in D_2O at 40 °C) was calculated to be $[R^+] = 6 \times 10^{-15}$ M.

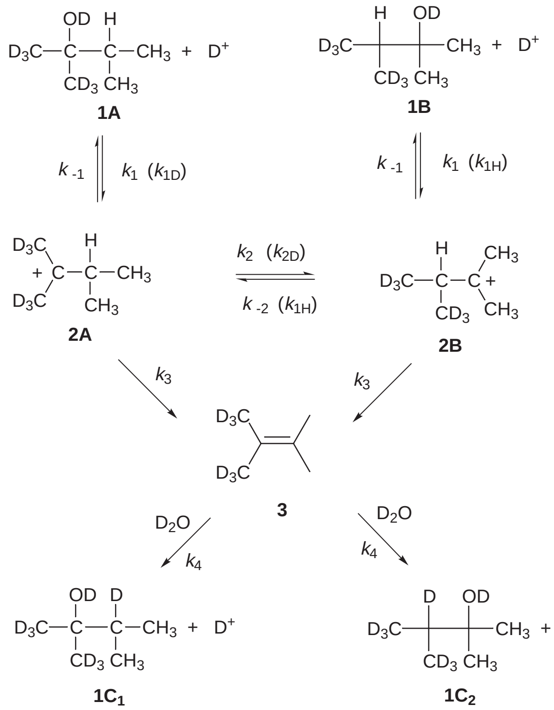
Introduction

It has been well established that a number of rearrangement reactions, such as the Wagner–Meerwein, pinacol, *etc.*, begin with the protonation of an hydroxy group, followed by its loss as water. A carbocation is produced which can rearrange before its reaction with nucleophiles to yield products.[1] Thus, when an alcohol is treated with an acid, besides substitution and elimination, products can also result from Wagner–Meerwein rearrangement.[2] The reaction proceeds through a carbocation intermediate[3] which can either (*a*) rearrange by 1,2-sigmatropic shift of a β-hydrogen, β-alkyl or β-aryl group, respectively, or (*b*) undergo loss of the β-hydrogen to a base and produce an olefin. Subsequent acid-catalyzed addition of water may occur.[1,2] Uncertainties remain concerning the detailed mechanism of these processes. In particular, the amounts of the cationic intermediates have not previously been determined.

We chose to study the mechanism of the acid-catalyzed degenerate rearrangement of 2,3-dimethylbutan-2-ol **1** in water, and to determine the concentration of the intermediate carbocation. It is an advantage to study alcohol **1**, since its corresponding carbocation **2** (2,3-dimethylbutyl cation) has been intensively examined as a stable ion in superacid media.[4,5] Cation **2** undergoes a rapid degenerate hydride shift (through the hydrido-bridged transition state), with a barrier of 3.1 ± 0.1 kcal mol^{-1}. Our presumption was that if this hydride shift were the rate determining step for the rearrangement of the alcohol in aqueous solution, we would be able to calculate the pK_{R^+} ($K_{R^+} = [ROH][H^+]/[R^+]$) and the concentration of the cation by using the appropriate H_R acidity function of the sulfuric acid. On the other hand, if the formation of the carbocation is the rate determining step, only a limit on the carbocation concentration could be obtained.

Results and discussion

In order to determine the reaction pathway for the rearrangement, we set out to follow the rearrangement of the hexadeuterated isotopomer of 2,3-dimethylbutan-2-ol (**1A** in Scheme 1). Formation of the rearranged product is consistent



Scheme 1

with the mechanism involving two parallel pathways, as is presented in Scheme 1. The common steps in both paths are formation of the carbocation (**2A**) from the protonated carbinol **1A**, and also the addition of water to the rearranged carbocation **2B**, giving the rearranged carbinol **1B**. However, the rearranged intermediate **2B** can be obtained from the carbocation intermediate **2A** by (*a*) degenerate hydride shift

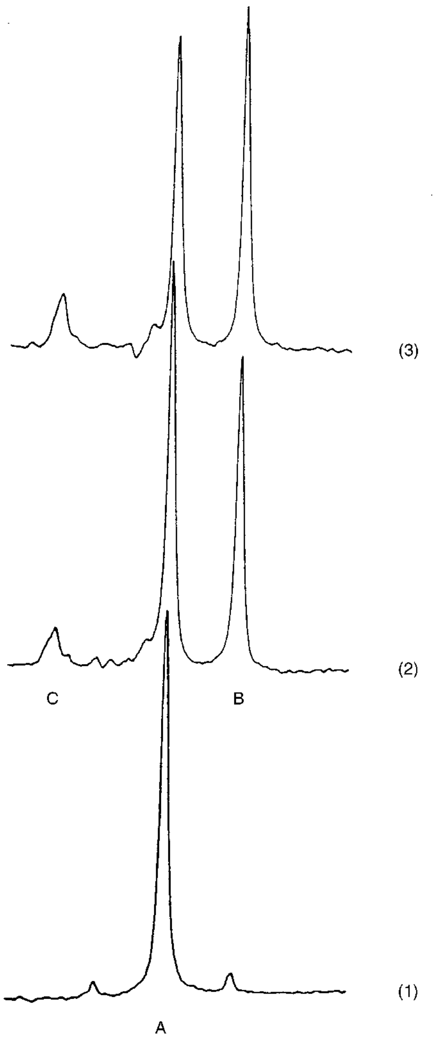


Fig. 1 ^{2}H NMR spectra taken at the start (1), after 20 min (2), and after 40 min (3) of the acid-catalyzed rearrangement of hexadeuterated 2,3-dimethylbutan-2-ol (**1A**) in 20 vol% sulfuric acid in D_2O at 30 °C. Peak A corresponds to **1A**, peak B corresponds to **1B** + **1C**$_2$, and peak C corresponds to **1C**$_1$ + **1C**$_2$ (all presented in Scheme 1).

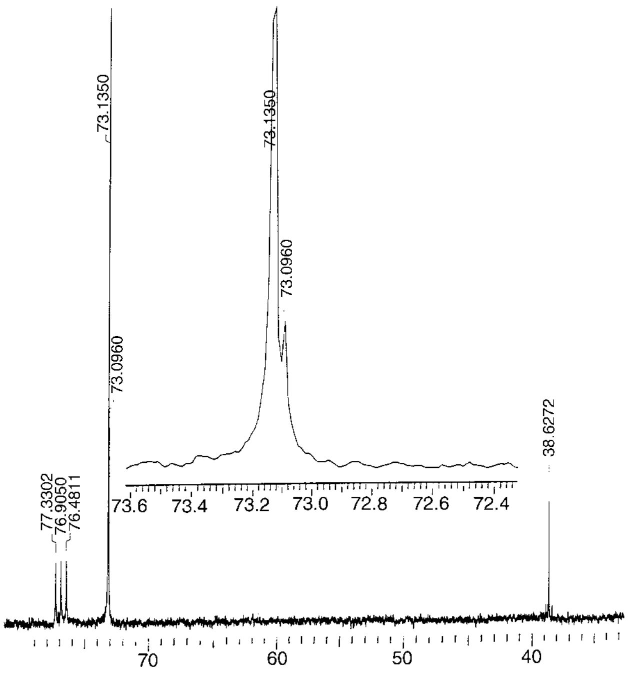


Fig. 2 ^{13}C NMR spectrum of the reaction mixture after 8 min reaction of 2,3-dimethylbutan-2-ol-[^{13}C] (**1D**) in 20 vol% sulfuric acid in $H_2{}^{18}O$ at 40 °C.

(k_2) producing the rearranged carbocation **2B**, followed by addition of water, or by (*b*) elimination of the proton from carbocation **2A** and formation of 2,3-dimethylbut-2-ene (**3**). The product **1B** is then obtained by rate determining protonation to form the intermediate carbocation **2B**, followed by rapid hydrolysis.[6]

The hexadeuterated isotopomer of 2,3-dimethylbutan-2-ol (**1A**) was subjected to acid-catalyzed rearrangement in a solution of sulfuric acid in D_2O. Kinetic data for the rearrangement were obtained by means of ^{2}H NMR, since the deuterium peaks of the starting carbinol **1A** and the rearranged product **1B** differ sufficiently ($\Delta\delta \approx 0.4$ ppm). Therefore measurements of the time dependent disappearance of the deuteromethyl groups attached to C-2 in **1A**, and the appearance of the two deuteromethyl groups attached to C-3 in **1B** (hexadeuterated isopropyl group) are possible. Typical spectra are presented in Fig. 1, representing the start (1) and the reaction mixtures after 20 min (2), and after 40 min (3) of the reaction of **1A** in 20 vol% sulfuric acid in D_2O at 30 °C. Peak A corresponds to starting material, signal B corresponds to the hexadeuterated isopropyl group in the rearranged carbinol, and C is the deuteromethine peak at C-3.

In heavy water as a medium, the two pathways for rearrangement, (*a*) and (*b*), can be distinguished. The rearranged isotopomer obtained through the hydride shift mechanism (*a*) has structure **1B** (hydrogen at the C-3 position). The product obtained through the elimination/addition reaction has deuterium at position C-3 (**1C**$_1$ and **1C**$_2$), introduced in the step of addition of D_2O. The reaction pathways can be distinguished on the basis of the following considerations. If the observed rate of appearance of a deuterium peak corresponding to **1C** at C-3 is twice the observed rate of the appearance of the deuterated isopropyl group (half of the addition product will be rearranged giving **1C**$_2$; whereas the other half will produce **1C**$_1$; the observed rate $k_{e/a} = 2k_4$), then all the signals correspond to products obtained by an elimination/addition process, and mechanism (*b*) is operative. If there is no H/D substitution at C-3, the hydride shift mechanism (*a*) would be demonstrated. The third case is the mixed mechanism, in which both (*a*) and (*b*) occur. The ratio can be decided from the ratio of the rate of rearrangement *vs.* the rate of the elimination/addition process.

The kinetic results are summarized in Table 1, in which k_r stands for the rate of the overall rearrangement (both reaction that proceeds through the hydride shift and reaction proceeding through the elimination/addition process; **1A**→**1B** + **1C**$_2$) and $k_{e/a}$ is the rate of the competitive elimination/addition reaction (**1A**→**1C**$_1$ + **1C**$_2$).

The results presented in Table 1 demonstrate that both processes occur. The observed rate constant for the overall rearrangement k_r is the sum of the hydride shift process rate constant and the rate constant of the elimination/addition that produces rearranged product (**1C**$_2$); $k_r = k_{hy} + k_4$. The overall rearrangement is about 3.5 times faster than the elimination/addition reaction under all conditions used (Table 1). It is easy to calculate that the fraction of the rearranged product obtained by elimination/addition in the overall rearrangement is about 1/7.

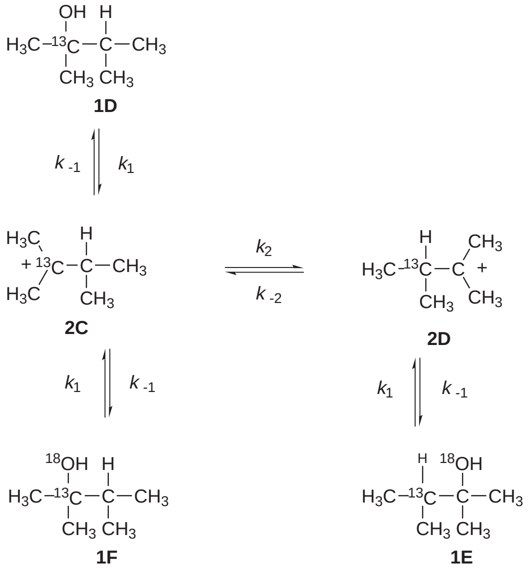
Even though the exact reaction rate of the rearrangement that proceeds through a hydride shift k_{hy} can be obtained as $k_{hy} = k_r - 1/2\ k_{e/a}$, the subtraction is not necessary, since the difference between the observed k_r and k_{hy} is in the range of the experimental error. In other words, the rate of appearance of the signal **B** (Fig. 1) can be attributed only to the major hydride shift path.

Once the major pathway of the rearrangement was clarified, the question of the rate determining step of the overall reaction arose. It is not clear which is the highest point on the energy surface; is it the transition state in the process of the carbo-

Table 1 Reaction rates of the acid-catalyzed rearrangement of 2,3-dimethylbutan-2-ol solution in sulfuric acid–deuterium oxide

t/°C	Concentration of H_2SO_4 in D_2O	H_0[a]	$k_r \times 10^{-4}$ s^{-1}[b]	$k_{e/a} \times 10^{-4}$ s^{-1}[c]	$k_r/k_{e/a}$[d]
40	1.82 M (10 vol.%)	−0.76	5.41 ± 0.69	—	
	2.73 M (15 vol.%)	−1.23	23.9 ± 2.0	6.68 ± 0.99	3.6
	3.64 M (20 vol.%)	−1.69	85.2 ± 4.4	25.4 ± 0.38	3.3
30	20% (vol.)		16.2 ± 0.7	4.10 ± 0.98	3.9

[a] H_0 is the acidity function; values at 40 °C taken from ref. 10. [b] k_r is the rate of the rearrangement reaction obtained as a function of appearance of the deuteroisopropyl group in **1B** and **1C**$_2$ (one peak) in ^{2}H NMR spectra; uncertainties are standard errors. [c] $k_{e/a}$ is the rate of the rearrangement that proceeds through an elimination/addition mechanism obtained as a function of appearance of the methyl peak in **1C**$_1$ and **1C**$_2$ in ^{2}H NMR spectra; uncertainties are standard errors. [d] Relative rates of the overall rearrangement rate (k_r) and the rearrangement that proceeds through an elimination/addition mechanism ($k_{e/a}$).



Scheme 2

cation formation (k_1) or is it the transition state of the hydride shift reaction (k_2)?

2,3-Dimethylbutan-2-ol-2-[^{13}C] **1D** 99% enriched with ^{13}C at C-2 which was used as a substrate for setting the rate determining step, exhibits only one peak in ^{13}C NMR at 73 ppm. The rearranged product **1F** also has one signal in the spectrum at 38 ppm. **1D** was subjected to rearrangement in 20 vol% sulfuric acid in 60–65% $H_2{}^{18}O$, and the products were isolated. According to Scheme 2, the carbocation **2C** can undergo two processes: nucleophilic attack of water (k_{-1}) and a hydride shift (k_2). In the former case, the hydroxy group of the product obtained is labeled with ^{18}O. Compared to the spectrum of the starting alcohol, the C-2 peak of **1E** is shifted upfield in the ^{13}C spectrum, due to an intrinsic isotope shift due to the ^{18}O.[7] At the same time, the signal that corresponds to **1E** also appears in the spectrum at 38 ppm. Fig. 2 presents the ^{13}C NMR spectrum of the reaction mixture obtained after **1D** was subjected to acid-catalyzed rearrangement for 4 min in 20 vol% sulfuric acid in 60–65% $H_2{}^{18}O$ at 40 °C. From the peak areas of **1D** and **1F** in NMR, the relative reaction rate k_{-1}/k_2 was calculated. It is worth emphasizing that this result is reliable, since the comparison of the reaction rates is carried out under exactly the same conditions. The ratio obtained is: $k_{-1}/k_2 = 9.5$, suggesting that the hydride shift is the rate determining step of the overall reaction. On the basis of the former consideration an energy diagram of the overall rearrangement of **1** is described in Fig. 3.

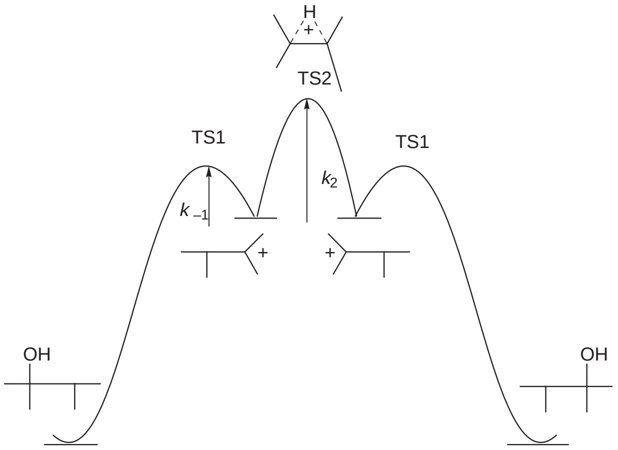


Fig. 3 Energy diagram of the acid-catalyzed rearrangement of 2,3-dimethylbutan-2-ol in aqueous sulfuric acid.

In order to obtain the equation for the observed reaction rate, the β-deuterium isotope effects are taken into account, since the measurements were carried out with the hexadeuterated isotopomer of 2,3-dimethylbutan-2-ol (**1A**). Carbinol **1A** and carbocation **2A** are the deuterated compounds, and **1B** and **2B** can be considered as their protio analogs (no β-deuteriums). Therefore, the corresponding rate constants can be indicated as k_{1D} and k_{2D}, and k_{1H} and k_{2H}, respectively, as is shown in parentheses in Fig. 1. According to Hammond's postulate, the structure of the carbocation **2** and the lower energy transition state (TS1) (Fig. 3) should be closely related. Consequently, their force field differs very little ($k_{-1H} \approx k_{-1D}$), so the nucleophilic attack of water can be approximated by a single rate constant (k_{-1}) in both directions of the rearrangement. By applying the steady state approximation to the concentration of the cationic intermediate, an equation [eqn. (1)] for the reaction constant was obtained, and by taking its logarithm, is transformed to eqn. (2), where H_0 is an acidity function.[8]

$$k_r = [H^+]\,\frac{k_{1H}k_{2H} + k_{1D}k_{2D}}{k_{-1} + k_{2H} + k_{2D}} \qquad (1)$$

$$\log k_{obs} = -H_0 + \log\frac{k_{1H}k_{2H} + k_{1D}k_{2D}}{k_{-1} + k_{2H} + k_{2D}} \qquad (2)$$

According to numerous data from the literature, the β-deuterium kinetic isotope effect in formation of the carbocation with a hexadeuterated tertiary substrate (two deuteromethyl groups) is $k_H/k_D = 1.70$,[9] thus $k_{1D} = k_{1H}/1.70$. The ratio k_{2D}/k_{2H} corresponds to the equilibrium constant of the rearrangement **2A**⇌**2B**. The equilibrium constant of the hexadeuterated carbocation was measured in superacid media in the temperature range −138 to −84 °C.[5] The equilibrium constant at 40 °C obtained after extrapolation was $K_{eq} = k_{2D}/k_{2H} = 1.66$. Substituting the values of the rate constants of the deuterated compounds with the rate constants of the protio compounds multiplied by the magnitude of the isotope effect, eqn. (3) was obtained.

$$\log k_{obs} = -H_0 + \log \frac{1.97 k_1 k_2}{k_{-1} + 2.66\, k_2} \qquad (3)$$

The logarithm of k_{obs}-values plotted against the acidity function H_0 exhibits linearity (H_0 are taken at a given concentration of the sulfuric acid at 40 °C from a table presented by Johnson *et al.*[10]) The observed correlation is characterized by $r = 0.998$, whereas the values of the slope and intercept are calculated as -1.28 ± 0.05 and -4.23 ± 0.06, respectively (uncertainties are standard error). From the calculated slope, it may be concluded that in the limit of the experimental error, the rate determining process is first order with respect to the proton concentration. This is in accord with the reaction mechanism proposed in Scheme 1, in which one proton is required for the formation of activated complex in the rate determining process. We assume that the deviation of the slope from unity is due to the slight decrease of the acidity function caused by deuterated medium (larger effect at lower acid concentration).

Among the three rate constants, k_1, k_{-1} and k_2 respectively, only the value of k_2, which corresponds to the rate constant for the hydride shift step can be determined independently. The hydrogen migration rate was previously measured in the stable solution of 2,3-dimethylbutyl cation in superacid media (SbF_5 and SO_2Cl_2) at three different temperatures (temperature range from −119 to −138 °C).[4] Extrapolation of the reaction rate constant to the experimental temperature (40 °C) was carried out, and the value for the rate constant of 2.4×10^{10} s^{-1} was obtained. Admittedly, this is a long extrapolation and this makes the value at 40 °C somewhat uncertain. We also must note that the solvent is different. Because the solvent does not take part in the hydride shift step of the reaction, the extrapolated value for the hydride shift rate in water is not likely to be altered much from the rate in SO_2Cl_2, *i.e.* the value of 2.4×10^{10} s^{-1} can be taken as approximately the rate constant k_2 in acid-catalyzed rearrangement of carbinol **1**. Further support for the idea that the effect of changing the solvent on rate constant k_2 is likely to be modest comes from several studies of rearrangement processes of several stable carbocations done in different solvent media. Changing from BF_4^- salts in HF to SbF_6^- salts in SO_2 or in SO_2ClF caused only small changes in these rearrangement rates.[11]

At this point, we were able to determine the concentration of the intermediate carbocation **2** using the well known equation for the acidity function H_0 [eqn. (4)],

$$H_0 = pK_{R^+} + \log \frac{[ROH]}{[R^+]} \qquad (4)$$

in which K_{R^+} represents the equilibrium constant given in eqn. (5).

$$K_{R^+} = \frac{[ROH][H^+]}{[R^+]} = \frac{k_{-1}}{k_1} \qquad (5)$$

Therefore, the carbocation concentration can be calculated if the rate constants k_1 and k_{-1} are known. From the ratio $k_{-1}/k_2 = 9.5$, obtained in experiment with ^{13}C enriched substrate in $H_2{}^{18}O$, and from the extrapolated value of the hydrogen exchange rate constant ($k_2 = 2.4 \times 10^{10}$ s^{-1}) in superacid media, $k_{-1} = 2.3 \times 10^{11}$ s^{-1} was calculated. In that stage the single unknown rate constant k_1 was calculated from the intercept of the plot defined with eqn. (3) [$\log(1.97k_1k_2)/(k_{-1} + 2.66k_2) = -4.17$] and was estimated to be: $k_1 = 4.2 \times 10^{-4}$ M^{-1} s^{-1}.

From the ratio $k_{-1}/k_1 = 5.4 \times 10^{14}$, the value of $pK_{R^+} = -14.7$ was obtained. It should be mentioned that the pK_{R^+} obtained is close in magnitude to pK_{R^+} of related tertiary cations determined by various methods.[12] For example, the values of pK_{R^+} of *tert*-butyl cation range from −16.4 to −14.7, depending on whether it was obtained by measurement of the $H_2{}^{18}O$ incorporation,[12a] by measurement of the equilibrium concentrations of the cation using spectrometric determination,[12b] or by an electrochemical approach.[12c]

Using eqn. (4) for the acidity function, the carbocation concentration at a given concentration of sulfuric acid can be estimated according to eqn. (6).

$$[R^+] = [ROH] \times 10^{-(14.7 + H_0)} \qquad (6)$$

Throughout this study the total concentration of 2,3-dimethylbutan-2-ol **1** in sulfuric acid was ~0.06 M, thus at the highest concentration of the acid ($H_0 = -1.69$) the concentration of the 2,3-dimethylbutyl cation **2** is approximately $[R^+] = 6 \times 10^{-15}$ M.

In order to verify the applicability of the steady state approximation for the cation concentration in the studied rearrangement reaction, we carried out numerical simulation using a program for solving the homogenous differential equations related to the rate constants k_1, k_{-1} and k_2, respectively. The results revealed that the steady-state approximation is applied correctly, and that the steady concentration of carbocation intermediate **2** is achieved in less then 10 μs.

Experimental

Substrate preparation

Preparation of all required isotopomers of 2,3-dimethylbutan-2-ol was carried out as described earlier.[5a] As a source of deuterium, acetone-d_6 was used, and as a source of ^{13}C, acetic acid-1-[^{13}C], both by Cambridge Isotope Laboratories.

Kinetic measurements

^2H NMR spectra were recorded on a Bruker AM 500 instrument at 76.77 MHz in D_2O. The rearrangement was carried out in an NMR-tube using **1A** and the solution of sulfuric acid in D_2O. Typically, 0.5 mL of sulfuric acid solution (10, 15, and 20 vol%, resp.) was placed in the NMR tube and thermostatted for 5 min. Then, one drop (*ca.* 0.03 g) of **1A** sample was added quickly, and the NMR tube was placed into the probe. ^2H NMR spectra were recorded at equal time intervals, *e.g.* every 2 min when the kinetics were followed in 20 vol% H_2SO_4 at 40 °C, and every 7 min when 10 vol% sulfuric acid was used as a catalyst at 40 °C. The fractions of B and C (Fig. 1) in the overall mixture (A + B), were calculated after every Δt from the signal areas. For each kinetic run, at least eight points on the curve were determined. First order rate constants were calculated using a nonlinear least-squares program.

Establishing the rate determining step; experiment with 1D in $H_2{}^{18}O$

A solution of H_2SO_4 (250 μL, 20 vol%) in $H_2{}^{18}O$ was thermostatted at 40.0 °C for 10 min. 2,3-Dimethylbutan-2-ol-[^{13}C] (**1D**) (15 μL) was added and the reaction was stirred. After 4 min, the reaction mixture was placed in an ice bath, and quenched with 10% cold aqueous sodium hydroxide. The products were extracted with 10 mL of $CDCl_3$, dried and the volume was reduced to 0.5 mL. The ^{13}C NMR spectrum of that solution was recorded using a Varian Gemini 300 instrument and is presented in Fig. 2.

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References

1 For reviews see (*a*) *Molecular rearrangements*, P. De Mayo, ed., Wiley, New York, 1963; (*b*) *Molecular rearrangements*, P. De Mayo, ed., Wiley, New York, 1970.

2 (*a*) J. A. March, *Reactions, Mechanisms, and Structures*, 3rd edn., John Wiley and Sons, New York, 1985, pp. 958–963 and references cited therein; (*b*) T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd edn., Harper & Row Publishers, New York, 1987.

3 This observation led to the first proposal of carbocations as reaction intermediates (H. Meerwein and K. van Emster, *Ber.*, 1922, **55**, 2520).

4 M. Saunders and M. R. Kates, *J. Am. Chem. Soc.*, 1978, **100**, 7082.

5 (*a*) M. Saunders and G. W. Cline, *J. Am. Chem. Soc.*, 1990, **112**, 3955; (*b*) M. Saunders, H. A. Jimenez-Vazquez and O. Kronja, in *Stable Carbocation Chemistry*, G. K. Surya Prakash, ed., John Wiley and Sons, New York, 1997, pp. 297–321.

6 V. J. Nowlan and T. Tidwell, *Acc. Chem. Res.*, 1977, **10**, 252.

7 T. L. Mega and R. I. Ven Eten, *J. Am. Chem. Soc.*, 1988, **110**, 6371.

8 L. P. Hammet, *Physical Organic Chemistry*, 2nd edn., McGraw-Hill, New York, 1970, ch. 9.

9 (*a*) V. J. Shiner, B. L. Murr and G. Heinemann, *J. Am. Chem. Soc.*, 1963, **85**, 2413; (*b*) see also: *Isotope Effects in Chemical Reactions*, ACS Monograph, J. C. Collins and N. S. Bownamm, ed., Van Norstrand Reinhold, New York, 1970 and references cited therein.

10 C. D. Johnson, A. R. Katritzky and S. A. Shapiro, *J. Am. Chem. Soc.*, 1969, **91**, 6654.

11 Unpublished results, Yale University.

12 (*a*) R. H. Boyd, R. W. Taft, A. P. Wolf and D. R. Christman, *J. Am. Chem. Soc.*, 1960, **82**, 4729; (*b*) E. M. Arnett and T. C. Hofelich, *J. Am. Chem. Soc.*, 1983, **105**, 2889; (*c*) D. D. M. Wayner, D. J. McPhee and D. J. Griller, *J. Am. Chem. Soc.*, 1988, **110**, 132.

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