Acid-Catalyzed Hydrolysis of Bridged Bi- and Tricyclic Compounds. XXXII. 7-Oxa-2-oxobicyclo[2.2.1]heptane: Kinetics, Products and Mechanism

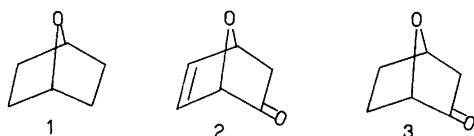Martti Lajunen,* Esa Kaitaranta and Martti Dahlqvist

Department of Chemistry, University of Turku, FIN-20500 Turku, Finland

Lajunen, M., Kaitaranta, E. and Dahlqvist, M., 1994. Acid-Catalyzed Hydrolysis of Bridged Bi- and Tricyclic Compounds. XXXII. 7-Oxa-2-oxobicyclo[2.2.1]-heptane: Kinetics, Products and Mechanism. – Acta Chem. Scand. 48: 399–403 © Acta Chemica Scandinavica 1994.

7-Oxa-2-oxobicyclo[2.2.1]heptane (7-oxa-2-norbornanone) produces in concentrated (7 mol dm^{-3}) aqueous perchloric acid ca. 31% phenol and several other products, which are mostly substituted phenols. The activation entropy, the solvent deuterium isotope effect and the slope parameters (m^+) of the linear excess acidity plots support the bimolecular mechanism (A-2) for the hydrolysis, but the products are evidently formed via the 3-oxo-4-hydroxy-1-cyclohexyl cation, which is typical of the unimolecular mechanism (A-1). Thus the reaction probably takes place by the A-2 (carbocation) mechanism. The data are compared with those recently measured for 7-oxabicyclo[2.2.1]heptane and 7-oxa-5-oxo-2-bicyclo[2.2.1]heptene.

7-Oxabicyclo[2.2.1]heptane or 7-oxanorbornane compounds have many kinds of biological effects, and in addition they are important intermediates in the syntheses of other biologically active compounds.[1,2] These syntheses often occur via cleavage of the oxygen bridge, which reaction can take place under reductive, basic or acidic conditions.[3]

The acid-catalyzed hydrolyses of two simple 7-oxanorbornanes, i.e. 7-oxabicyclo[2.2.1]heptane or 7-oxanorbornane (1) and 7-oxa-5-oxo-2-bicyclo[2.2.1]heptene or 7-oxanorbornenone (2), have recently been studied.[4,5] In both cases the oxygen bridge is opened, and major products are unsaturated monocyclic hydroxylic compounds with similar molecular formulae as those of the substrates. The gross reactions are thus mainly acid-catalyzed isomerizations. Differences have, however, been found in the kinetic parameters of the hydrolyses, and they suggest that the mechanisms of the reactions are evidently not the same. In order to get more information about the mechanisms, an additional 7-oxanorbornane, i.e. 7-oxa-2-oxobicyclo[2.2.1]heptane or 7-oxanorbornanone (3), is studied kinetically and product-analytically in the present paper.

1   2   3

Experimental

Materials. 7-Oxanorbornanone (3) was prepared by hydrogenation of 7-oxanorbornenone (2)[5] in acetone under catalysis of 10% Pd(C) in 960 kPa initial hydrogen pressure for 22 h. The yield was 65% after distillation in vacuum (b.p. ca. 90.5°C/4.4 kPa) and the purity ca. 99% by GC. The ^{1}H and ^{13}C NMR spectra were in agreement with the published chemical shifts.[6]

3-(4-Hydroxyphenyl)-2-cyclohexen-1-one (4, for iden-

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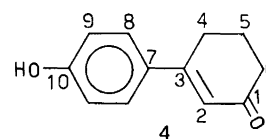
tification of hydrolysis products of 7-oxanorbornanone) was prepared according to a published method.[7] The product was rescued from aqueous 5% NaOH used for washing an ether solution by addition of sulfuric acid and extracting with ether.

^{13}C NMR [15.0 MHz, CDCl$_3$ + (CD$_3$)$_2$CO]: δ 201.2 (C1), 122.5 (C2), 116.5 (C3), 36.4 (C4), 25.3 (C5), 46.0 (C6), 131.3 (C7), 128.3 (C8), 115.7 (C9) and 155.4 (C10) (tentative assignments); GC/FTIR: 3651, 3040, 2947, 1695.5, 1611, 1514, 1263 and 1175 cm^{-1}; MS [IP 70 eV; m/e (% rel. int.)] 189 (12), 188 (94, M), 161 (11), 160 (100, $M-$CO), 132 (51), 131 (38), 121 (15), 77 (16), 51 (11), 44 (14) and 43 (23).

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* To whom correspondence should be addressed.

Kinetic measurements. The disappearance of 7-oxanor-bornanone (ca. 9×10^{-3} mol dm^{-3}) in concentrated aqueous perchloric acid solutions was followed by a GC method described earlier with cyclopentanone as internal standard.[5] First-order kinetics were always strictly obeyed, and parallel runs gave rate constants equal at least within 4% (av. 2%).

Product analysis. 7-Oxanorbornanone (0.1 or 0.5 cm^3) was stirred with 7 mol dm^{-3} HClO$_4$(aq) (50 cm^3) in a tightly stoppered bottle for 7 h (ca. 20 half-lives) at ca. 348 K, and several samples were taken after appropriate intervals. The colour of the solution became gradually reddish brown and a small amount of a solid material (insoluble in CH$_2$Cl$_2$ but soluble in acetone) was formed at the higher substrate concentration. Part of the samples was extracted with CH$_2$Cl$_2$, and part was neutralized with concentrated ammonia and centrifuged to remove the precipitated salt. The organic phases were then analyzed on a Perkin-Elmer Auto System gas chromatograph equipped with a SE-30 capillary column, and the aqueous samples were analyzed by GC by using a packed Carbowax 20 M column. Beside a main product peak, which was detected to be that of phenol, several other product peaks were observed. Response ratios between phenol and the substrate were measured by using both GC methods, and the integrals of the peaks were corrected according to them.

The organic phases of the samples taken after ten half-lives were combined and dried over Na$_2$SO$_4$, and CH$_2$Cl$_2$ was evaporated off under a low vacuum. The residue was analyzed by ^{1}H and ^{13}C NMR spectroscopy (Jeol JNM GX 400). The spectra showed that it mainly consisted of phenol, but also of some unsaturated components with carbonyl groups (200.8 and 215.2 ppm). In order to identify these components the residue (redissolved in CH$_2$Cl$_2$) was analyzed by GC/FTIR (Hewlett-Packard 5890 Series II gas chromatograph and Mattson 6030 Galaxy infrared spectrometer) and GC/MS (DANI 3800 gas chromatograph and VG 7070 E mass spectrometer) spectroscopies. According to the increasing retention times (RT) of a GC/MS study (an HP-1 capillary column, temperature-programmed from 323 to 553 K, 8 K min^{-1}; IP 70 eV) the hydrolysis products were as follows:

(i) 1,2-cyclohexadione (RT 151 s), identified with an authentic sample (Sigma, purity 85%);

(ii) phenol (RT 160 s), identified with an authentic sample (Merck, purity > 99%);

(iii) 1,2-dihydroxybenzene (RT 377 s), identified with an authentic sample (Aldrich, purity > 99%);

(iv) a hydroxyphenyl-substituted cyclohexenone (**5**, RT ≤ 600 s): IR: 3657, 2945, 1730, 1599, 1514, 1258 and 1175 cm^{-1};

(v) 5-(4-hydroxyphenyl)-2-cyclohexen-1-one (**6**, RT 603 s): IR: 3653, 3034, 2951, 1701, 1611, 1512, 1258 and 1175 cm^{-1}; MS [m/e (% rel. int.)]: 189 (11), 188 (79, M), 161 (12), 160 (100, M – CO), 159 (35), 146 (12), 145 (34),

143 (17), 131 (35), 118 (11), 115 (12), 91 (12), 77 (15), 63 (10), 51 (14) and 39 (17);

(vi) a benzofuranone (**7**, RT 634 s): IR: 3086, 2972, 1821, 1616, 1466, 1236, 1038, 965 and 876 cm^{-1}; MS [m/e (% rel. int.)]: 189 (10), 188 (67, M), 170 (37, M – H$_2$O), 169 (23), 160 (60, M – CO), 159 (14), 146 (21), 145 (48), 144 (76), 142 (19), 141 (18), 133 (10), 132 (88), 131 (100), 129 (10), 128 (34), 117 (10), 115 (25), 103 (35), 102 (11), 91 (16), 83 (12), 77 (40), 63 (10), 55 (38), 51 (18) and 39 (12);

(vii) a hydroxyphenyl-substituted cyclohexadienol (**8**, RT 883 s): IR: 3655, 3084, 2947, 1615, 1512, 1452, 1256 and 1173 cm^{-1}; MS [m/e (% rel. int.)]: 189 (12), 188 (100, M), 160 (23, M – CO), 159 (12), 146 (15), 145 (19), 133 (13), 132 (38), 131 (27), 119 (13), 118 (5), 115 (7), 103 (6), 91 (5), 79 (5), 77 (12), 63 (5), 51 (7) and 39 (7);

(viii) trimer 1 (RT 1157 s): molecular weight (MW) = 264;

(ix) trimer 2 (RT 1337 s): MW = 282.

Results and discussion

The disappearance rate constants (k_ψ) of 7-oxa-2-oxobicyclo[2.2.1]heptane (7-oxanorbornanone, **3**) in aqueous perchloric acid at different temperatures and acid concentrations, and in deuterioperchloric acid, are listed in Table 1. Table 2 contains the corresponding activation parameters, solvent deuterium isotope effect and slopes for log k_ψ vs. H_0 acidity function and two strictly linear excess acidity plots [eqns. (1) and (2); Fig. 1][8]

$$\log k_\psi - \log c_{H^+} = m_1 X_0 + \log(k_0/K_{SH^+}) \tag{1}$$

$$\log k_\psi - \log c_{H^+} - \log a_w = m_2 X_0 + \log(k_0/K_{SH^+}) \tag{2}$$

where X_0 stands for the excess acidity[9] and a_w for the activity of water[10] in HClO$_4$(aq) of concentration c_{H^+}, m_1

Table 1. Disappearance rate constants of 7-oxa-2-oxobicylo[2.2.1]heptane (**3**) in aqueous perchloric acid at different temperatures and acid concentrations.

T/K	c(HClO$_4$)/ mol dm^{-3} [a]	X_0 [a, b]	$k_\psi/10^{-4}$ s^{-1}
318.2	8.05		0.691(10)
328.2	8.01		2.37(3)
338.2	7.96		7.45(10)
348.2	7.92		21.4(6)
338.2	5.98	1.82	0.48(2)
338.2	6.39	2.05	0.86(2)
338.2	6.92	2.34	1.72(5)
338.2	7.36	2.61	3.36(4)
338.2	7.41		6.75(10)[c]
338.2	7.88	2.94	7.09(9)
338.2	7.96	3.00	7.45(10)
338.2	8.37	3.27	15.1(3)
338.2	8.80	3.55	28.6(4)

[a] Temperature corrected. [b] Excess acidity. [c] Measured in DClO$_4$(D$_2$O).

Table 2. Kinetic parameters of acid-catalyzed hydrolysis in HClO(aq) for 7-oxabicyclo[2.2.1]heptane (1),[4] 7-oxa-5-oxo-2-bicyclo[2.2.1]heptene (2)[5] and 7-oxa-2-oxobicyclo[2.2.1]heptane (3).

Parameter	1	2	3
$k_\psi/10^{-5}\ s^{-1}$ [a]	232	0.24	1.28
$\Delta H^{\ddagger}/kJ\ mol^{-1}$ [b]	101.6(6)	107.1(10)	103.5(6)
$\Delta S^{\ddagger}/J\ K^{-1}\ mol^{-1}$ [b]	7(2)	−32(3)	−17(2)
k_H/k_D	0.54(2)[b]	0.63(2)[c]	0.55(2)[d]
Slope for log k_ψ vs. H_o^e	−1.27(3)[b]	−0.77(2)[f]	−0.83(2)[d,g]
Slope for log k_a vs. X_o^h	2.02(2)[b,i]	0.85(2)[f]	0.92(1)[d,j]
Slope for log k_a − log a_w vs. $X_o^{h,\ k}$	2.29(3)[b,i]	1.01(2)[f]	1.26(1)[d,l]

[a] 6.85 M $HClO_4$ at 318.2 K. [b] 298.2 K. [c] A remeasured value at 348.2 K in 7.57 M $LClO_4(L_2O)$ (L=H or D). A recently published abnormal value, 0.34(2), is probably incorrect.[5] [d] 338.2 K. [e] H_o-Values at 298.2 K.[10] [f] 348.2 K. [g] Slightly curved ($r=-0.998$). [h] $k_a=k_\psi/c_{H^+}$. [i] A correction term (see text) was taken into account. [j] $r=0.9997$. [k] Activity of water (a_w) at 298.2 K.[10] [l] $r=0.9998$.

and m_2 are the slope parameters (see later) and $\log(k_0/K_{SH^+})$ is the intercept, which consists of the rate constant (k_0) of the rate-limiting stage (r.l.s.) under the ideal conditions and of the thermodynamic dissociation constant (K_{SH^+}) of the protonated substrate. The perfect equations (1) and (2) should also contain a correction term, $-\log[c_S/(c_S + c_{SH^+})]$ (c_S and c_{SH^+} are the concentrations of the unprotonated and protonated substrate, respectively), on the left side, but it has been eliminated, because the correction terms calculated by eqn. (3)

$$\log(c_{SH^+}/c_S) - \log c_{H^+} = m^*X_0 + pK_{SH^+} \qquad (3)$$

by using the slope parameter (m^*) value 1.0,[4,11,12] and the pK_{SH^+} value −2.80,[13] cause curvatures of the plots: $m_1 = 1.80 \pm 0.04$, $r_1 = 0.998$ and $m_2 = 2.14 \pm 0.04$, $r_2 = 0.998$ ($r =$ correlation coefficient). A similar linearity-decreasing effect of the correction term was also observed
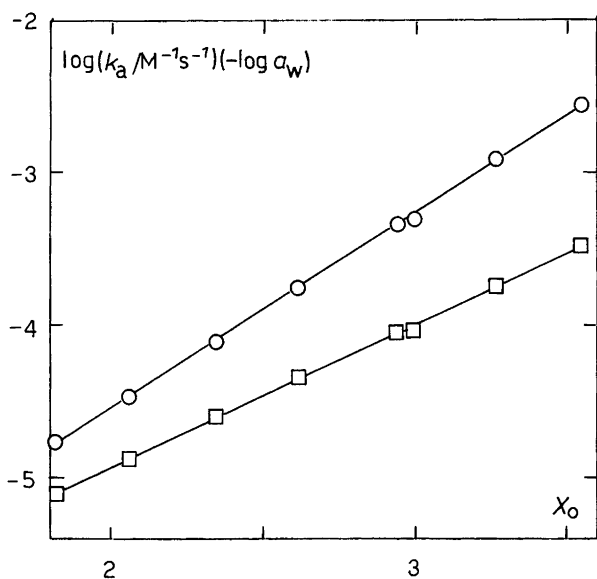

Fig. 1. Excess acidity plots for the hydrolysis of 7-oxa-2-oxobicyclo[2.2.1]heptane (3) in $HClO_4$(aq) at 338.2 K with exclusion [□; eqn. (1)] and inclusion [O; eqn. (2)] of the activity of water (at 298.2 K).

in the hydrolysis of 7-oxanorbornenone (2).[5] The pK_{SH^+}-values of these compounds are evidently much more negative than that of 7-oxanorbornane (− 2.80)[13] owing to the strong electron-withdrawing effect of the carbonyl group. An effort to measure the pK_{SH^+}-value for 7-oxanorbornanone spectrophotometrically failed (cf. Refs. 11 and 12).

For making comparisons between the hydrolyses of 7-oxanorbornane (1),[4] 7-oxanorbornenone (2)[5] and 7-oxanorbornanone (3), the kinetic parameters of the first two compounds are also collected in Table 2. In all cases the parameters for 7-oxanorbornanone are between the values for the two other substrates and mostly closer to those for 7-oxanorbornenone. The rate constants show that the rate-decreasing effect of the carbon double bond (5.3) is much smaller than that (180) of the carbonyl group.

The negative activation entropies (Table 2) of the carbonyl substituted substrates agree with the *A*-2 mechanism, where participation of a nucleophile in the rate-limiting stage is evident. The positive value of 7-oxanorbornane is in agreement with the unimolecular cleavage of the oxygen bridge (*A*-1 mechanism).

Similar mechanistic conclusions can also be drawn from the slopes (m_1 and m_2) of the excess acidity plots (Table 2). They are actually products of two parameters, m^+ and m^*, the former of which indicates the character of the transition state and the latter of which depends on the site of proton attack during the fast pre-equilibrium stage of the *A*-1 and *A*-2 mechanisms.[8] The value 1.0 can be applied to m^*, because the ether oxygen is protonated,[11,12] and thus $m_i = m^+_i$ ($i = 1$ or 2) to both mechanisms. Typically $m^+ \geq 2$ in the case of the *A*-1 mechanism,[8] as found here for 7-oxanorbornane, and $m^+ \approx 1$ in the case of the *A*-2 mechanism,[8] as found here for 7-oxanorbornanone and 7-oxanorbornenone. The linearity of eqn. (1) should also be typical of the *A*-1 mechanism and the linearity of eqn. (2) of the *A*-2 mechanism.[8] However, in the hydrolyses of all three 7-oxanorbornanes both plots are equally linear, probably owing to the rather narrow range of acid concentrations used, when a fair linearity also exists between X_0 and log a_w.[5]

The most problematic of the kinetic parameters in Table 2 is the solvent deuterium isotope effect. It has been stated that the k_H/k_D value ≤ 0.5 is typical of the A-1 mechanism and $k_H/k_D \geq 0.5$ of the A-2 mechanism in the acid-catalyzed epoxide hydrolysis.[14] This experimental limit also agrees well with that[4,5] estimated by the isotopic fractionation theory,[15] according to which the limit depends slightly on temperature. Probably the limit also depends somehow on acid concentration, at least in concentrated solutions. Thus it cannot be very strict, and is not a clear enough criterion of reaction mechanism in this case.

According to the product analysis, phenol is the main product (ca. 31% after 10 half-lives; Fig. 2) of hydrolysis of 7-oxanorbornanone (3) in 7 M perchloric acid. Thus one water molecule is eliminated from the substrate and the gross reaction is not mainly an isomerization as in the hydrolyses of 7-oxanorbornane (1) and 7-oxanorbornenone (2). Other products in the order of increasing retention times are according to their GC/FTIR and GC/MS spectra (see Experimental): 1,2-cyclohexanedione (5%); 1,2-dihydroxybenzene (trace; may be formed from an impurity of the substrate); a hydroxyphenyl-substituted cyclohexenone [e.g. 5, 1%, the molecular weight (MW) = 188, the carbonyl frequency (v_{CO}) = 1730.3 cm^{-1}, which is a typical value to a cyclic ketone without conjugation between the double bonds; cf. v_{CO} for cyclohexanone is 1736.5 cm^{-1}]; 5-(4-hydroxyphenyl)-2-cyclohexen-1-one [6, 17%, MW 188, v_{CO} = 1701.3 cm^{-1}; the band is shifted to a lower wavenumber owing to conjugation between the double bonds; cf. v_{CO} = 1713.0 cm^{-1} for 2-cyclohexenone and v_{CO} =

1695.5 cm^{-1} for 3-(4-hydroxyphenyl)-2-cyclohexen-1-one (4), which has an additional shift to a lower wavenumber owing to the increasing conjugation with the aromatic ring. It must be pointed out that the $v_{C=C}$ vibration can not be seen in the spectra of compounds 5 and 6 owing to overlapping with the broad phenolic $v_{C=C}$ vibration centered at 1610–1620 cm^{-1}. The same situation exists in the 3050–3100 cm^{-1} region, where the olefinic v_{C-H} vibrations overlap with the aromatic v_{C-H} bands.]; a benzofuranone [e.g. 7, 4%, MW 188, v_{CO} = 1820.9 cm^{-1}] and a hydroxyphenyl-substituted cyclohexadienol (e.g. 8, 3%, MW 188).

The products are evidently formed by the reaction of 3-oxo-4-hydroxy-1-cyclohexyl cation (9) with acidic water or phenol (e.g. according to Schemes 1 and 2).[11,16,17] However, it was not possible to confirm this, owing to the difficulty of obtaining the integrated rate equation, if the formation of phenol (Fig. 2) is in agreement with the schemes. The reaction of the cation (9) with 6-hydroxy-cyclohex-2- or -3-en-1-one is an alternative route to the dimeric products (5–8). The compounds with longer retention times (MW > 250) are possibly trimeric or larger phenolic products. According to the IR spectrum, the solid material formed in a small quantity in the hydrolysis is a (polymeric?) phenolic substance having an alkyl substituent without the carbonyl group. The portions of different products are approximate and depend on the acid concentration, and evidently also on the substrate concentration. The comparison of the hydrolysis products of 7-oxabicyclo[2.2.1]heptanes (1–3)[4,5] shows that the carbonyl group clearly promotes the aromatization of the substrate, as has earlier been found in the case of some bicyclo[2.2.1]heptan-2-ones.[18]

It is difficult to imagine the formation of the products without the cation (9), whose existence, however, supports the A-1 mechanism instead of the A-2 mechanism, which is in agreement with the kinetic parameters above. A possible compromise between these two mechanisms is

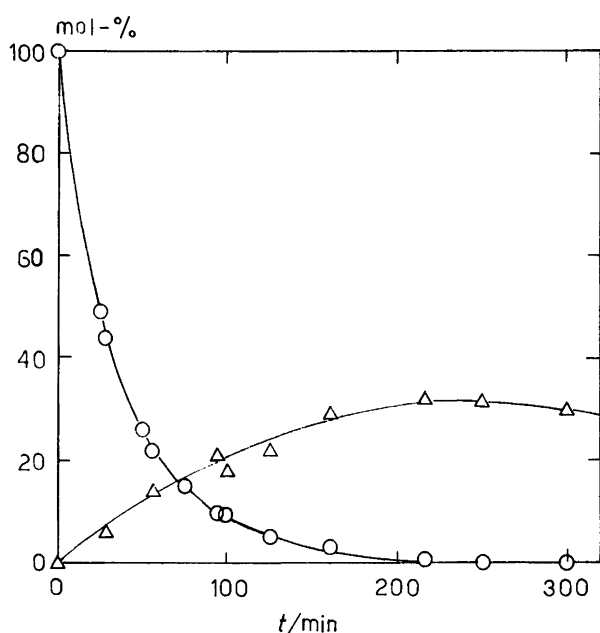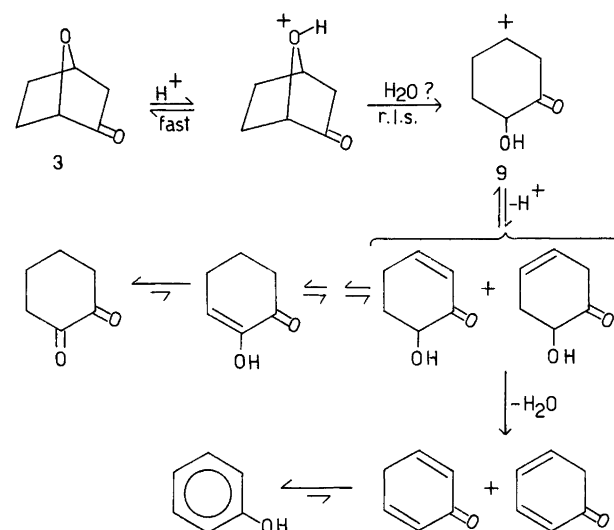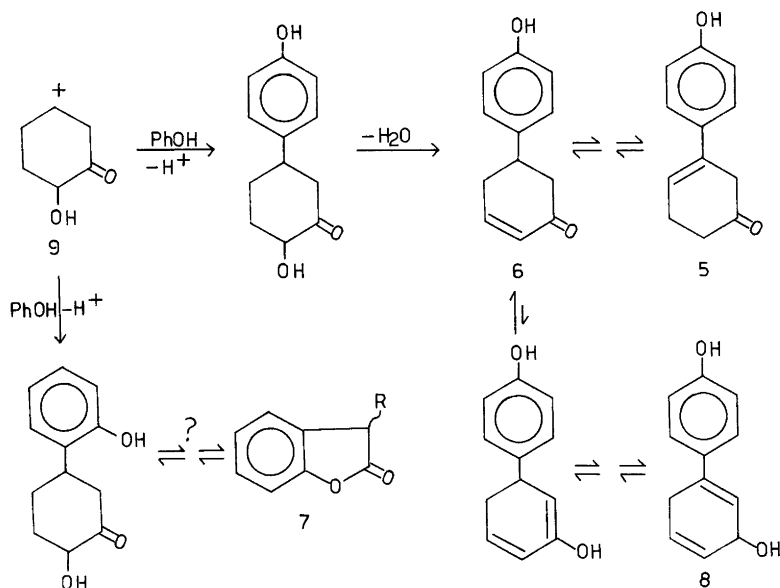*Fig. 2.* The disappearance of the substrate (○) and the formation of phenol (△) in the hydrolysis of 7-oxa-2-oxobicyclo[2.2.1]heptane (3) in 7 M HClO$_4$(aq) at ca. 348 K.

Scheme 1.

Scheme 2.

an *A*-2 (carbocation) mechanism [comparable to the S_N2 (intermediate) mechanism],[19] in which a nucleophile (water in this case) takes part in the rate-limiting stage (r.l.s.; Scheme 1), but the transition state, and especially the subsequent intermediate, have a carbocation character. The amount of the nucleophilic participation depends on the destability of the cation. Possible characteristics of the *A*-2 (carbocation) mechanism are the solvent deuterium isotope effect (k_H/k_D) being close to 0.5, and the linearity of both excess acidity plots [eqns. (1) and (2)]. This mechanism may also rationalize the hydrolyses of 7-oxanorbornenone (**2**) and several epoxides, which have features of both *A*-1 and *A*-2 mechanisms.[5,20]

References

1. Buchbauer, G. and Holbik, H. *Chem. Z. 115* (1991) 141.
2. e.g. (a) Warm, A. and Vogel, P. *J. Org. Chem. 51* (1986) 5348; (b) Suami, T. *Pure Appl. Chem. 59* (1987) 1509; (c) Vogel, P. *Bull. Soc. Chim. Belg. 99* (1990) 395.
3. Acena, J. L., Arjona, O., Fernandez de la Pradilla, R., Plumet, J. and Viso, A. *J. Org. Chem. 57* (1992) 1945 and references cited therein.
4. Lajunen, M. and Uotila, R. *Acta Chem. Scand. 46* (1992) 968.
5. Lajunen, M. and Mäki, E. *Acta Chem. Scand. 45* (1991) 578.
6. Moursoundis, J. and Wege, D. *Aust. J. Chem. 36* (1983) 2473.
7. Novello, F. C., Christy, M. E. and Sprague, J. M. *J. Am. Chem. Soc. 75* (1953) 1330.
8. Cox, R. A. *Acc. Chem. Res. 20* (1987) 27.
9. Cox, R. A. and Yates, K. *Can. J. Chem. 59* (1981) 2116.
10. Gordon, A. J. and Ford, R. A. *The Chemist's Companion*, Wiley-Interscience, New York 1972, pp. 64–66.
11. Lajunen, M. and Himottu, M. *Acta Chem. Scand. 43* (1989) 957.
12. Lajunen, M. and Kähkönen, M. *Acta Chem. Scand. 46* (1992) 726.
13. Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworths, London 1965, p. 433.
14. Pritchard, J. G. and Long, F. A. *J. Am. Chem. Soc. 78* (1956) 6008.
15. (a) Kresge, A. J., More O'Ferrall, R. A. and Powell, M. F. In: Buncel, E. and Lee, C. C., eds., *Isotopes in Organic Chemistry*, Vol. 7. *Secondary and Solvent Isotope Effects*, Elsevier, Amsterdam 1987; (b) Schowen, R. L. *Progr. Phys. Org. Chem. 9* (1972) 275.
16. Erman, W. F. *J. Am. Chem. Soc. 86* (1964) 2887.
17. Shiner, C. S., Vorndam, P. E. and Kass, S. R. *J. Am. Chem. Soc. 108* (1986) 5699.
18. Collins, C. J. and Eastham, J. F. In: Patai, S., ed., *The Chemistry of Functional Groups, The Chemistry of the Carbonyl Group*, Vol. 1, Interscience, London 1966, p. 774.
19. Bentley, T. W., Bowen, C. T., Morten, D. H. and Schleyer, P. v. R. *J. Am. Chem. Soc. 103* (1981) 5466.
20. Rochester, C. H. *Acidity Functions*, Academic Press, London 1970, pp. 138–140.