

# Acid-Catalyzed Hydrolysis of Bridged Bi- and Tricyclic Compounds. XXXVI. Kinetics of *exo*- and *endo*-2-Methoxynorbornanes

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The disappearance of *exo*- and *endo*-2-methoxynorbornanes in aqueous perchloric acid was followed by capillary GC at different temperatures and acid concentrations. The high *exo/endo* rate ratio (8850 at 308 K in 7.0 M HClO<sub>4</sub>), the positive entropies of activation, the parameters of the excess acidity equation and the products are in agreement with the hydrolysis by the A-1 mechanism. The ether oxygen of the *exo*-epimer is much more basic than that of the *endo*-epimer ( $\Delta pK_a \approx 2$ ) according to the excess acidity equations derived for both slightly and highly protonated substrates.

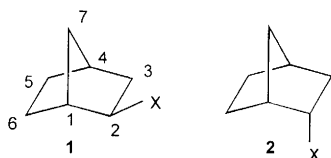
Acid-catalyzed hydrolysis of *exo*- and *endo*-phenoxynorbornanes (**1** and **2**, X=OPh) has recently been studied in our laboratory.<sup>1–3</sup> The kinetic parameters measured for the epimers in HClO<sub>4</sub>(aq), e.g. the entropies of activation (14–17 J mol<sup>-1</sup> K<sup>-1</sup>),<sup>1</sup> the solvent deuterium isotope effects ( $k_H/k_D \approx 0.47$ ),<sup>1</sup> and the slope parameters of the excess acidity plot ( $m^* = 0.99$  to 1.06 and  $m^\ddagger = 1.43$ –1.55)<sup>1–3</sup> are rather similar, although the rate ratio ( $k_{exo}/k_{endo} = 2570$  at 308 K)<sup>1</sup> is very high. The  $pK_{SH^+}$  values (=  $pK_a$ ), e.g. the negative logarithms of the thermodynamic dissociation constants of the protonated substrates, were, however, observed to be very different, –3.74 to –3.43 for the *exo*-epimer<sup>2,3</sup> and –5.73 for the *endo*-epimer<sup>1,2</sup> at 308 K, when  $\Delta pK_{SH^+} \approx 2$ . A similar, although smaller, difference has recently been measured for 2-norbornylamines (**1** and **2**, X=NR<sub>2</sub>):  $\Delta pK_{SH^+} = 0.30$ –0.65.<sup>4</sup> These experimental values do not accord with the estimation made by Schreiner *et al.*<sup>5</sup> that the energy difference between protonated *exo*- and *endo*-2-norbornanols (**1** and **2**, X=OH<sub>2</sub><sup>+</sup>; –5.0 kJ mol<sup>-1</sup> at 298 K) is equal to the energy difference between the unprotonated epimeric alcohols (**1** and **2**, X=OH),<sup>6,7</sup> when  $\Delta pK_{SH^+} \approx 0$ . In order to obtain more knowledge of

the  $pK_{SH^+}$  values of 2-norbornyl epimers structurally close to 2-norbornanols, *exo*- and *endo*-2-methoxynorbornanes (**1** and **2**, X=OMe) were, in this work, investigated kinetically in aqueous perchloric acid.

## Experimental

**Materials.** *exo*- and *endo*-2-Methoxynorbornanes (**1** and **2**, X=OMe) were synthesized from the corresponding 2-norbornanols<sup>8</sup> with the aid of sodium hydride and methyl iodide in dry tetrahydrofuran.<sup>9</sup> The purities by GC were 97% and 85%, respectively (the *endo*-epimer contained 11% of the *exo*-epimer observable by NMR). The substrates were identified from their <sup>1</sup>H and <sup>13</sup>C NMR spectra.<sup>9,10</sup>

**Kinetic measurements.** The disappearance of the substrates in HClO<sub>4</sub>(aq) was followed by GC (an FFAP capillary column) using norcamphor or nitrobenzene as the internal standard and dichloromethane as the extracting solvent.<sup>3</sup> The pseudo-first-order rate constants were calculated from the slopes of the linear ( $r = 0.998$ –0.99995) correlation  $\log(S_t - S_\infty)$  vs.  $t$ , in which  $S_t$  is the ratio of the GC integrals of the substrate and the internal standard at the time  $t$ . Parallel runs were made each time giving rate constants which were at least equal within 7% (av. 2.6%). The rate of hydrolysis of the *exo*-epimer was so much greater than that of the *endo*-epimer (see later) that its existence as an impurity in the latter substrate did not cause any harm, although retention times of the epimers were equal.



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**Product analyses.** The substrates produced, according to the GC analyses, *exo*-2-norbornanol (**1**, X=OH) and probably methanol (not observable by the method used) in the case of the *exo*-epimer (**1**, X=OMe) and a small amount of *endo*-2-norbornanol (**2**; X=OH) in addition to the first-mentioned in the case of the *endo*-epimer (**2**; X=OMe). The slight formation of the *endo*-alcohol is, however, probably due to the acid-catalyzed epimerization of the initially formed *exo*-2-norbornanol,<sup>1</sup> because the ratio [2]/[1] (X=OH) increased during the runs.

## Results and discussion

Rate constants of disappearance for *exo*- and *endo*-2-methoxynorbornanes (**1** and **2**; X=OMe) in aqueous perchloric acid at different temperatures and acid concentrations are listed in Table 1. These are slightly (*exo* epimer) or moderately (*endo* epimer) smaller than the rate constants measured earlier for *exo*- and *endo*-2-phenoxy norbornanes (**1** and **2**; X=OPh) under similar conditions.<sup>1,2</sup> Thus, the *exo/endo* rate ratio for the methoxy substrates (8850 in 7.0 M HClO<sub>4</sub>) is even greater than that for the phenoxy substrates (2570 in 7.0 M HClO<sub>4</sub>;<sup>1</sup> the ratio depends on the acid concentration).

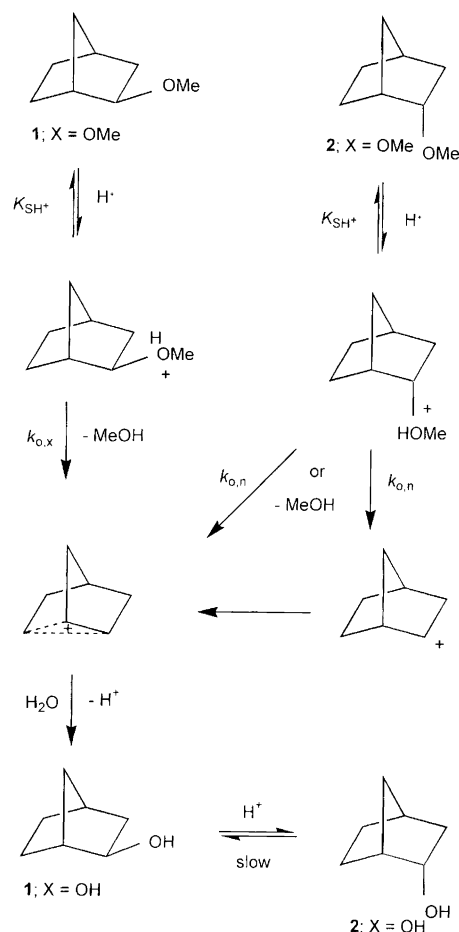
**Table 1.** Rate constants of disappearance for *exo*- and *endo*-2-methoxynorbornanes (**1** and **2**; X=OMe) in aqueous perchloric acid at different temperatures and acid concentrations.

Epimer	T/K	$c(\text{HClO}_4)/\text{mol dm}^{-3}$ <sup>a</sup>	$X_0$ <sup>b</sup>	$k_{\psi}/10^{-5} \text{ s}^{-1}$ <sup>c</sup>	
<i>exo</i>	308.2	4.90		5.18(3)	
	308.2	4.90		5.14(14) <sup>d</sup>	
	318.2	4.88		22.0(3)	
	328.2	4.84		92.6(12)	
	338.2	4.82		330(4)	
	308.2	4.91	1.43	5.18(3)	
	308.2	5.50	1.71	16.2(3)	
	308.2	6.12	2.04	51.8(5)	
	308.2	6.37	2.18	84.0(8)	
	308.2	6.87	2.48	224(4)	
	308.2	7.42	2.82	619(19)	
	308.2	7.79	3.07	1216(13)	
	<i>endo</i>	328.2	7.88		6.62(2)
		338.2	7.84		26.0(6)
348.2		7.78		93.4(6)	
358.2		7.73		299(5)	
308.2		7.99	3.21	0.347(7) <sup>d</sup>	
308.2		8.46	3.54	0.834(10)	
308.2		8.83	3.81	1.926(6)	
308.2		9.36	4.23	5.41(4)	
308.2		9.38	4.24	5.13(17)	
308.2		9.84	4.62	10.80(13)	
308.2		10.36	5.06	31.9(7)	
308.2		10.46	5.15	33.2(12)	
308.2		10.87	5.52	66.0(20)	
308.2		10.91	5.56	67.4(6)	
308.2	11.23	5.86	105.6(15)		
308.2	11.54	6.15	168(5)		

<sup>a</sup>Temperature corrected. <sup>b</sup>Excess acidity,<sup>12</sup> temperature corrected. <sup>c</sup>Error limits in parentheses are standard deviations. <sup>d</sup>Calculated from the activation parameters (Table 2).

The rate ratios are in agreement with a unimolecular mechanism of hydrolysis (A-1; Scheme 1), as are also the positive activation entropies (see above and Table 2) and the dominating formation of *exo*-2-norbornanol (**1**; X=OH; see Experimental).<sup>1-3</sup>

The excess acidity theory<sup>11</sup> was applied to the rate



**Scheme 1.**

**Table 2.** Parameters of activation and of the excess acidity equations [eqns. (1) and (2)] for the hydrolysis of *exo*- and *endo*-2-methoxynorbornanes (**1** and **2**; X=OMe) at 308.2 K in HClO<sub>4</sub>(aq). (Error limits in parentheses are standard deviations.)

Epimer	$c(\text{HClO}_4)/\text{mol dm}^{-3}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J mol}^{-1} \text{ K}^{-1}$
<i>exo</i>	4.90	118.4(11)	44(4)
<i>endo</i>	7.99	122.4(9)	30(3)

Epimer	Eqn.	$m^*$	$\text{p}K_{\text{SH}^+}$	$m^\ddagger$	$\log(k_0/\text{s}^{-1})$
<i>exo</i>	(1)	1.00(3)	-2.06(13)	2.29(4)	-5.82(15) <sup>a</sup>
<i>exo</i>	(2)	0.98(3)	-1.82(15)	2.14(7)	-5.32(20)
<i>endo</i>	(1)	1.01(3)	-4.46(18)	1.77(4)	-7.50(26) <sup>a</sup>
<i>endo</i>	(2)	1.00(2)	-3.63(12)	1.75(4)	-7.34(18)

<sup>a</sup> $\log(k_0/\text{s}^{-1}) = \log(k_0/K_{\text{SH}^+}) + \text{p}K_{\text{SH}^+}$  and its error limit  $\Delta[\log(k_0/\text{s}^{-1})] = \{\Delta^2[\log(k_0/K_{\text{SH}^+})] + \Delta^2(\text{p}K_{\text{SH}^+})\}^{1/2}$ .

constants measured at the same temperature, 308 K, at different acid concentrations (Table 1) using eqns. (1)<sup>2</sup> and (2).

$$\log k_{\psi} - \log c_{\text{H}^+} = m^{\neq} m^* X_0 - \log[1 + (c_{\text{H}^+}/K_{\text{SH}^+})10^{m^* X_0}] + \log(k_0/K_{\text{SH}^+}) \quad (1)$$

$$\log k_{\psi} = (m^{\neq} - 1)m^* X_0 - \log(1 + K_{\text{SH}^+}/10^{m^* X_0}) + \log k_0 \quad (2)$$

The former equation is applicable to the substrates slightly protonated and the latter to the substrates highly protonated in the solutions used for the kinetic measurements. In the equations,  $k_{\psi}$  is the pseudo-first-order rate constant in the aqueous acid with acid concentration  $c_{\text{H}^+}$  and excess acidity  $X_0$ ;<sup>12</sup>  $m^{\neq}$  and  $m^*$  are slope parameters being indicative of the transition state and of the site of proton attack, respectively.  $K_{\text{SH}^+}$  is the thermodynamic dissociation constant of the protonated substrate and  $k_0$  stands for the medium-independent rate constant of the rate-limiting stage of the reaction (Scheme 1).

The parameters of eqns. (1) and (2), i.e.  $m^*$ ,  $m^{\neq}$ ,  $K_{\text{SH}^+}$  and  $\log k_0$ , were iterated from the experimental values of  $k_{\psi}$ ,  $c_{\text{H}^+}$  [ $=c(\text{HClO}_4)$ ] and  $X_0$  with the method of nonlinear least-squares minimization. The parameters evaluated are shown in Table 2.

For Figs. 1 and 2, eqns. (1) and (2) were changed to the linear forms [eqns. (3) and (4)],<sup>2,11</sup>

$$\log k_{\psi} - \log c_{\text{H}^+} - \log[c_{\text{S}}/(c_{\text{S}} + c_{\text{SH}^+})] = m^{\neq} m^* X_0 + \log(k_0/K_{\text{SH}^+}) \quad (3)$$

$$\log k_{\psi} - \log[c_{\text{SH}^+}/(c_{\text{S}} + c_{\text{SH}^+})] = (m^{\neq} - 1)m^* X_0 + \log k_0 \quad (4)$$

in which the correction terms,  $-\log[c_{\text{S}}/(c_{\text{S}} + c_{\text{SH}^+})]$  and  $-\log[c_{\text{SH}^+}/(c_{\text{S}} + c_{\text{SH}^+})]$ , can be calculated from the  $m^*$  and  $\text{p}K_{\text{SH}^+}$  values in Table 2 with eqn. (5).<sup>11</sup>

$$\log(c_{\text{SH}^+}/c_{\text{S}}) - \log c_{\text{H}^+} = m^* X_0 + \text{p}K_{\text{SH}^+} \quad (5)$$

In eqns. (3)–(5),  $c_{\text{S}}$  and  $c_{\text{SH}^+}$  are the concentrations of the unprotonated and protonated substrate. Figure 1 shows that the lines for both epimers are strictly linear ( $r=0.9997$ – $0.9994$ ) when using eqn. (3), but according to Fig. 2 the line for the *exo* epimer is also strictly linear ( $r=0.9995$ ) whereas that for the *endo* epimer is only slightly linear ( $r=0.996$ ) when applying eqn. (4). [The line may consist of two linear parts, the upper comprising the six highest acid concentrations where the substrate is almost totally ( $\geq 99.6\%$ ) protonated. Elimination of the four highest spots in iterations does not significantly change the values of the parameters.] Owing to this poor linearity both eqns. (1) and (2) were used to iterate the best values of the parameters, although the ratio  $c_{\text{SH}^+}/c_{\text{S}} > 1$  [calculated by eqn. (5) from the  $m^*$  and  $\text{p}K_{\text{SH}^+}$  values in Table 2] at almost all acid concentrations used for the kinetic runs, and thus eqn. (2) should be more suitable.

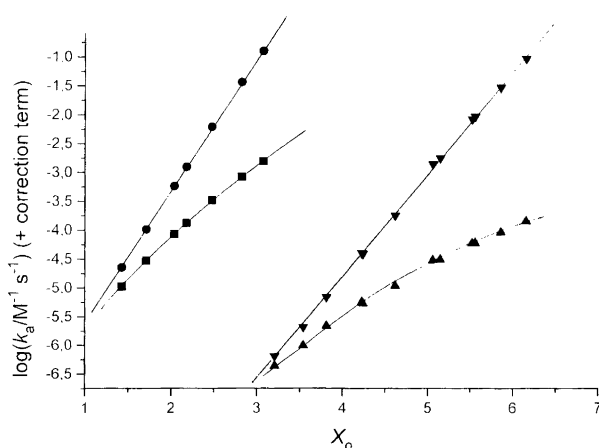


Fig. 1. Excess acidity plots [slightly protonated substrates, eqn. (3)] for the hydrolysis of *exo*- and *endo*-2-methoxynorbornanes (**1** and **2**; X=OMe) at 308.2 K in  $\text{HClO}_4(\text{aq})$  ( $k_a = k_{\psi}/c_{\text{H}^+}$ ): ■, without the correction term for **1**; ●, with the correction term for **1**; ▲, without the correction term for **2**; and ▼, with the correction term for **2**. The correction term,  $-\log[c_{\text{S}}/(c_{\text{S}} + c_{\text{SH}^+})]$ , has been calculated with eqn. (5) from the  $m^*$  and  $\text{p}K_{\text{SH}^+}$  values in Table 2.

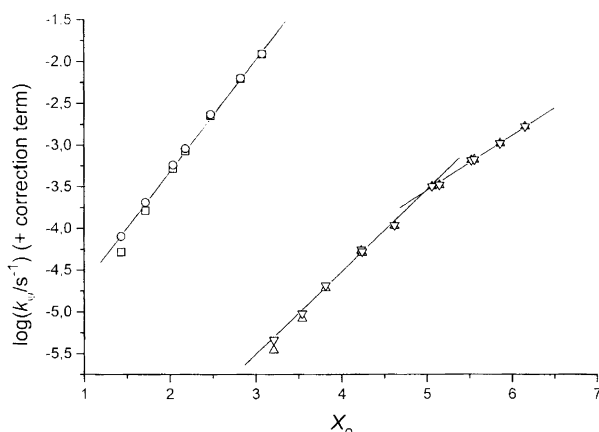


Fig. 2. Excess acidity plots [highly protonated substrates, eqn. (4)] for the hydrolysis of *exo*- and *endo*-2-methoxynorbornanes (**1** and **2**; X=OMe) at 308.2 K in  $\text{HClO}_4(\text{aq})$ . The open symbols correspond formally to the closed ones in Fig. 1. Only the straight lines have been marked for clarity. The correction term,  $-\log[c_{\text{SH}^+}/(c_{\text{S}} + c_{\text{SH}^+})]$ , has been calculated with eqn. (5) from the  $m^*$  and  $\text{p}K_{\text{SH}^+}$  values in Table 2.

The evaluated values of  $m^*$  (0.98–1.01) are typical of the protonation of an ether oxygen in  $\text{HClO}_4(\text{aq})$ .<sup>1–3,13,14</sup> Similarly, the values of  $m^{\neq}$  (2.14–2.29 for *exo* and 1.75–1.77 for *endo*) accord with those measured for the *A*-1 hydrolysis of ethers.<sup>1–3,15</sup> In the case of the 2-methoxynorbornanes, however, there seems to be a considerable difference between the  $m^{\neq}$  values of the *exo*- and *endo*-epimers in contrast to the small difference measured in the case of *exo*- and *endo*-2-phoxynorbornanes ( $m^{\neq} = 1.43$ – $1.55$ ).<sup>1–3</sup>

A remarkable difference can be seen between the  $\text{p}K_{\text{SH}^+}$  values of the *exo* (–1.82 to –2.06; av.  $-1.9 \pm 0.2$ ) and *endo* (–3.63 to –4.46; av.  $-4.0 \pm 0.5$ ) epimers

(Table 2). The former values are typical of dialkyl ethers ( $pK_{SH^+} \approx -2$ ),<sup>16-18</sup> the latter being exceptionally negative. The *exo*-form is much more basic (ca. 100 times) than the *endo*-form, the difference being similar to that observed in the case of *exo*- and *endo*-2-phenoxy-norbornanes (**1** and **2**; X=OPh).<sup>2,3</sup> Thus the estimation that the energy difference between the *exo*- and *endo*-epimers in the case of protonated 2-norbornanols (**1** and **2**, X=OH<sub>2</sub><sup>+</sup>) is equal to that in the case of unprotonated norbornanols (**1** and **2**; X=OH), when  $\Delta pK_{SH^+} \approx 0$  (see above),<sup>5</sup> does not seem appropriate in the light of the present results.

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