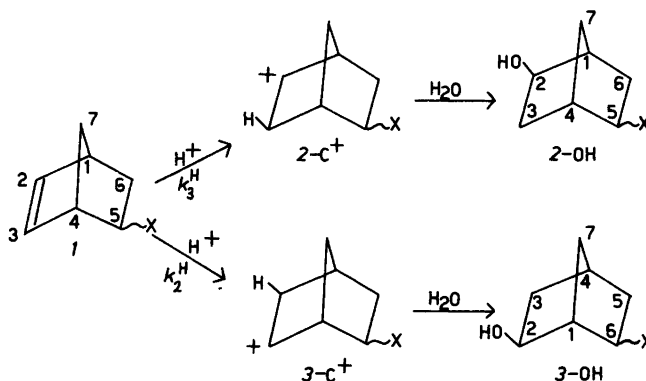# Acid-catalyzed Hydrolysis of Bridged Bi- and Tricyclic Compounds. XXIV. A Kinetic Method for Determination of Protonation Site in Hydration of 5-Substituted 2-Norbornenes

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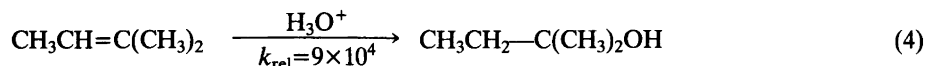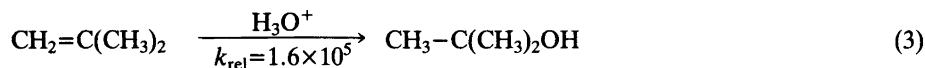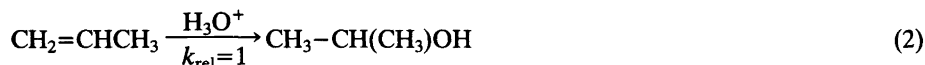Department of Chemistry and Biochemistry, University of Turku, SF-20500 Turku 50, Finland

A methyl-substitution at C-2 or C-3 of 5-cyano-2-norbornenes forces protonation of the double bond to take place at C-3 or C-2, respectively. The ratio of the hydration rate constants of 2-methyl-5-cyano-2-norbornene and 3-methyl-5-cyano-2-norbornene (exo or endo epimers, respectively) is the same as the product ratio of the hydration of 5-cyano-2-norbornenes ([5-cyano-exo-2-norborneol]:[6-cyano-exo-2-norborneol]=98:2). Thus, hydration rate measurements of 2- and 3-methyl-5-X-2-norbornenes can be used to determine the portions of protonation at C-3 and C-2 in the hydration of 5-X-substituted norbornenes in the cases where hydration products are complicated due to deprotonations, rearrangements or fragmentations of intermediate carbocations. The mechanism of hydration must, however, be the same, i.e. $A-S_E2$, in all cases.

There are two possibilities for a 5-X-substituted 2-norbornene (1) to be protonated in acidic solutions, namely, at carbon 2 (C-2) or at carbon 3 (C-3), provided that the substituent X is not protonated [eqn. (1)]. The rate-determining protonation takes place most probably from the exo side.[1-3] The subsequent reaction stage in aqueous solutions is a hydration of the carbocations (2-C$^+$ and 3-C$^+$). However, deprotonations, fragmentations and rearrange-

ments can occur before hydration in the carbocations.[2,4,5] Thus, the product analyses do not always give the proper portions of protonation sites. Therefore a new method is needed to determine the amounts of protonation at different sites in these complicated cases. This is the aim of the present work.

A methylation of an olefinic carbon usually results in the increase of hydration rate of olefins by a factor of 10^4–10^6 [eqns. (2) and (3)].[6]

$$CH_2=CHCH_3 \xrightarrow[k_{rel}=1]{H_3O^+} CH_3-CH(CH_3)OH \tag{2}$$

$$CH_2=C(CH_3)_2 \xrightarrow[k_{rel}=1.6\times10^5]{H_3O^+} CH_3-C(CH_3)_2OH \tag{3}$$

$$CH_3CH=C(CH_3)_2 \xrightarrow[k_{rel}=9\times10^4]{H_3O^+} CH_3CH_2-C(CH_3)_2OH \tag{4}$$

The protonation occurs at the less substituted end of the ethylenic bond (Markovnikov rule). However, if a hydrogen at the carbon that is protonated is displaced by a methyl group, the hydration rate is slightly decreased [eqns. (3) and (4)].[6]

If C-2 of 5-X-substituted 2-norbornene is methylated, protonation most probably takes place at C-3 [eqn. (5)] and if C-3 is methylated, protonation most probably occurs at C-2 [eqn. (6)] and the reaction rate is increased by a factor of 10^4—10^6. Sterically the substrates, 2-methyl-5-X-2-norbornenes (4) and 3-methyl-5-X-2-norbornenes (5), are very similar, when the protonation occurs from the exo direction. If we assume that the effect of the methyl substitution on the protonation rate is the same in both cases [eqns. (5) and (6)] and, for testing the method, that no deprotonations, fragmentations or rearrangements occur, then the ratio of the hydration rate constants is equal to the ratio of the hydration products of 5-X-2-norbornenes [eqn. (1)]: $k_3^{Me}:k_2^{Me}=k_3^H:k_2^H=[2\text{-OH}]:[3\text{-OH}]$.

This kinetic method is tested in the present work in the case of X=CN. The cyano group is a strong electronegative substituent.[7,8] Thus, the protonation of C-3 and the formation of the carbocation 2-C$^+$ should dominate and, if no deprotonations, fragmentations or rearrangements occur (cf. Ref. 9), the alcohol 2-OH should be the main product. In this case the hydration rate of 2-methyl-5-cyano-2-norbornenes (4, X=CN) should also be much greater than that of 3-methyl-5-cyano-2-norbornenes (5, X=CN). For the test, the following cyanonorbornenes were synthesized and their hydration rates and/or products were
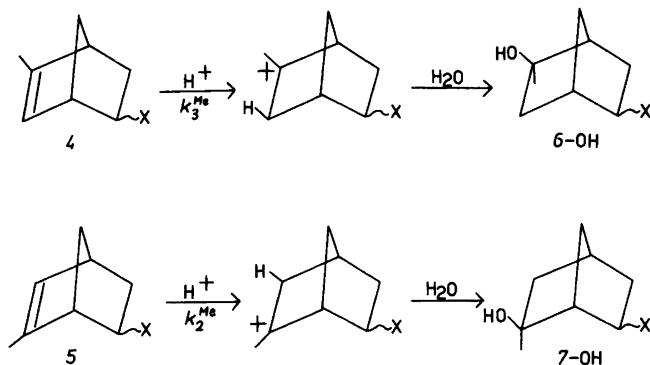
investigated: *exo*- and *endo*-5-cyano-2-norbornenes (*1-exo* and *1-endo*, X=CN), 2-methyl-*exo*- and *endo*-5-cyano-2-norbornenes (*4-exo* and *4-endo*, X=CN), and 3-methyl-*exo*- and --*endo*-5-cyano-2-norbornenes (*5-exo* and *5-endo*, X=CN).

EXPERIMENTAL

Syntheses. A mixture of *exo*- and *endo*-5-cyano-2-norbornenes (*1-exo* and *1-endo*) was prepared from cyclopentadiene and acrylonitrile.[10] A mixture of eight methylcyanonorbornenes was prepared from methylcyclopentadiene and acrylonitrile.[11] The isomers were separated partly on a Perkin Elmer 251 Auto Annular Still and partly on a Perkin Elmer F 21 Preparative Gas Chromatograph (FFAP column). Only *1-exo*, *1-endo* and 2-methyl-*endo*-5-cyano-2-norbornene (*4-endo*) were obtained as pure (>99 %) by these means. Other isomers were still mixtures. 2-Methyl-*exo*-5-cyano-2-norbornene (*4-exo*) was prepared by isomerization of pure *4-endo* in a KOBu^t−HOBu^t solution to a 1:1 mixture of *4-exo* and *4-endo*,[12] which could be separated by GLC. 3-Methyl-*exo*-5-cyano-2-norbornene (*5-exo*) was used as a 16 % mixture, since it gave a separate peak in the GLC analyses (XE 60 capillar column). 3-Methyl-*endo*-5-cyano-2-norbornene (*5-endo*) was used as a 50 % mixture with 2-methyl-*exo*-5-cyano-2-norbornene (*4-exo*) and 1-methyl-*endo*-5-cyano-2-norbornene, whose retention times were nearly equal with that of *5-endo* in the GLC analyses.

The substrates were identified from their IR, ^{1}H and ^{13}C NMR spectra.[11,13–16] The ^{13}C chemical shifts were calculated from those of 2-norbornene, 2-methyl-2-norbornene, and *exo*- and *endo*-5-cyano-2-norbornenes.[14–16]

Kinetics. The disappearance of a substrate (initial concentration *ca.* 4×10^{-3} mol dm^{-3}) in aqueous 1.00 mol dm^{-3} HClO$_4$ was followed by taking samples after appropriate intervals, by neutralizing them with concentrated ammonia (final pH *ca.* 7), and by analyzing them by GLC (mostly using a packed Carbowax 20 M column). Norcamphor was used as inert internal standard. In the case of methylcyanonorbornenes the product, a tertiary alcohol, was easily dehydrated in the gas chromatograph. The dehydration was eliminated almost totally by adding Sörensen phosphate buffer (pH 6.8) into the samples.

In the case of 3-methyl-*endo*-5-cyano-2-norbornene (*5-endo*), which formed a mixture with the other two isomers, the hydration of the most rapid isomer (*4-exo*) was first allowed to proceed to the end (*ca.* 12 half-lives), then the hydration of *5-endo* was followed for *ca.* 3 half-lives and the peak of 1-methyl-*endo*-5-cyano-2-norbornene [$k \ll k(5\text{-}endo)$] was noticed to remain nearly unchanged (*cf.* Ref. 17).

The neutralized and buffered samples of 3-methyl-*exo*-5-cyano-2-norbornene (*5-exo*) were extracted with CCl$_4$ and the organic phases were analyzed on a Perkin Elmer Sigma 2 B Gas Chromatograph (XE 60 capillar column).

The disappearance of the substrates always obeyed fairly the first-order kinetics.

Product analyses. About 0.5−1 g of a substrate was hydrated for over ten half-lives by stirring efficiently in 70 cm^3 of 1−5 mol dm^{-3} HClO$_4$. The mixture was cooled and extracted with CH$_2$Cl$_2$ several times. The combined organic phases were washed with water, dried on sodium sulfate and the solvent was distilled off *in vacuo*. The residue was analyzed by GLC and by IR, ^{1}H and ^{13}C NMR spectroscopy. The signal of the cyano group (IR 2240 cm^{-1}) remained practically unchanged in all the cases. The products were identified from the observed and calculated [15,16] ^{13}C NMR chemical shifts (Table 1).

RESULTS AND DISCUSSION

The hydration rates of 5-cyano-2-norbornenes (*1*, X=CN) have been measured earlier.[17] The kinetic parameters are typical of the $A-S_E2$ hydration of the carbon−carbon double bond and differ clearly from those measured for the hydration of the cyano group.[18] The main hydration products are, according to the GLC and ^{13}C NMR analyses (Table 1), *exo*- and *endo*-5-cyano-*exo*-2-norborneols (2-OH) in a ratio of 44:56, respectively, from both the

Table 1. Comparison of the ^{13}C NMR chemical shifts in CDCl$_3$ of the hydration products of cyanonorbornenes with those calculated for certain structures.

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C≡N	CH$_3$	Ref.
Norbornane	36.8	30.1	30.1	36.8	30.1	30.1	38.7			
Δδ(exo-2-OH)	+7.7	+44.3	+12.3	-1.0	-1.3	-5.2	-4.1			15
Δδ(exo-2-OH, endo-2-CH$_3$)	+12.7	+48.0	+18.8	+0.3	-2.2	-6.1	-1.2		+25.7	a, 16
Δδ(endo-5-CN)	+0.2	-0.7	-4.9	+3.4	+0.1	+5.5	0	+122.6		15
Δδ(exo-5-CN)	-0.3	-1.5	-1.6	+5.5	+1.0	+6.3	-1.3	+123.4		15
1st GLC peak of 1 (56 %)	44.2	73.5	37.6	39.1	29.0	30.5	34.9	122.3		
endo-5-cyano-exo-2-norborneol	44.7	73.7	37.5	39.2	28.9	30.4	34.6	122.6		
2nd GLC peak of 1 (44 %)	43.8	73.1	40.9	40.9	30.0	31.1	33.3	123.2		
exo-5-cyano-exo-2-norborneol	44.2	72.9	40.8	41.3	29.8	31.2	33.3	123.4		
Product of 4-exo	48.9	76.6	47.1	42.6	30.0	30.7	36.1	123.5	25.4	
endo-2-methyl-exo-5-cyano-exo-2-norborneol	49.2	76.6	47.3	42.6	28.9	30.3	36.2	123.4	25.7	
Product of 4-endo	49.2	77.0	43.4	40.5	28.8	29.7	37.6	122.4	25.2	
endo-2-methyl-endo-5-cyano-exo-2-norborneol	49.7	77.4	44.0	40.5	28.0	29.5	37.5	122.6	25.7	

^{a} This work.

Table 2. Disappearance rate constants of methylcyanonorbornenes in 1.00 mol dm^{-3} HClO$_4$ at different temperatures, and activation parameters (at 298.2 K) and solvent deuterium isotope effects.

Sub-strate	Temp./ K	k_1/ 10^{-4} s^{-1}	Activation parameters and solvent isotope effects
4-exo	288.2	2.33(2)	
	298.2	7.48(5)	$\Delta H^{\neq}$=81(1) kJ mol^{-1}
	298.2	7.39(16)^a	$\Delta S^{\neq}$=−34(4) J mol^{-1} K^{-1}
	298.2	4.85(33)^b	k_H/k_D=1.55(22)
	308.2	21.0(6)	
	318.2	62.3(4)	
4-endo	288.2	1.42(1)	
	298.2	4.73(24)	$\Delta H^{\neq}$=86(1) kJ mol^{-1}
	298.2	4.85(6)^a	$\Delta S^{\neq}$=−20(3) J mol^{-1} K^{-1}
	298.2	3.00(6)^b	k_H/k_D=1.58(11)
	308.2	15.7(3)	
	318.2	45.2(8)	
5-exo	298.2	0.236(14)^a	
	308.2	0.82(3)	$\Delta H^{\neq}$=91(2) kJ mol^{-1}
	318.2	2.36(4)	$\Delta S^{\neq}$=−28(6) J mol^{-1} K^{-1}
	318.2	1.87(6)^b	k_H/k_D=1.29(6)
	328.2	7.2(6)	
	338.2	20.3(4)	
5-endo	298.2	0.105(8)^a	
	308.2	0.46(1)	$\Delta H^{\neq}$=107(2) kJ mol^{-1}
	318.2	1.58(2)	$\Delta S^{\neq}$=18(7) J mol^{-1} K^{-1}
	318.2	1.34(13)^b	k_H/k_D=1.19(13)
	328.2	5.69(8)	
	328.2	19.6(3)	

^{a} Calculated from the activation parameters; rate constants in dm^3 mol^{-1} s^{-1}. ^{b} Measured in 1.00 mol dm^{-3} DClO$_4$.

pure epimers (*1-exo* and *1-endo*). Careful analyses on the capillar gas chromatograph, however, showed two minor peaks, which were concluded, according to their retention times, to be signals of *exo-* and *endo*-6-cyano-*exo*-2-norborneols (*3-OH*). The GLC analyses gave for the product ratio: [2-OH]:[3-OH]=98:2 (±0.4). The epimerization of the cyano group in the products shows that Wagner-Meerwein rearrangement occurs during the hydration (epimerization of the substrates, *1-exo* and *1-endo*, does not occur),[17] but it does not alter the [2-OH]:[3-OH] ratio.

2-Methyl-*exo*- and -*endo*-5-cyano-2-norbornenes (*4-exo* and *4-endo*) yield only one hydration product, *endo*-2-methyl-*exo*-5-cyano-*exo*-2-norborneol and *endo*-2-methyl-*endo*-5-cyano-*exo*-2-norborneol (*6-OH*), respectively [eqn. (5)]. No epimerization of the cyano group occurs. Thus, the positive charge of the carbocations is localized at C-2, *i.e.*, at the tertiary carbon, and the proton attack must take place at C-3.

The disappearance rate constants of methylcyanonorbornenes were measured in 1.00 mol dm^{-3} HClO$_4$ (or DClO$_4$) and they are presented in Table 2 with the activation parameters and solvent deuterium isotope effects. The activation entropies are negative (−20 to −34 J mol^{-1} K^{-1}) and thus typical of the $A-S_E2$ mechanism except in the case of 3-methyl-*endo*-5-cyano-2-norbornene (*5-endo*), whose approximate positive value (18±7 J

mol^{-1} K^{-1}) may be erroneous due to the inaccurate rate measurements (see Experimental). The solvent deuterium isotope effects are all typical of the slow proton transfer from a hydronium ion to a carbon atom (k_H/k_D 1.2 to 1.6).[1,6,17]

A methyl substitution at C-2 of 5-cyano-2-norbornenes results in the increase of the reaction rate by a factor of 2×10^4 to 3×10^4 (Table 2 and Ref. 17), which is a typical value for the olefin hydration (see above).[6] In the case of the 3-methyl substitution the increase is only by a factor of 520 to 890, which seems strange. However, the rate constant measured for the hydration of 5-cyano-2-norbornenes is the sum of two rate constants: k_2^H and k_3^H [eqn. (1)].

The ratios of the rate constants measured for 2- and 3-methyl-substituted cyanonorbornenes in 1 mol dm^{-3} $HClO_4$ at 298.2 K are the following: $k_3^{Me}:k_2^{Me}=97:3$ (± 0.4) for the *exo* epimers and 98:2 (± 0.4) for the *endo* epimers (Table 2). They are very similar to the product ratio ([2-OH]:[3-OH]=98:2) measured for the hydration of 5-cyano-2-norbornenes in 5 mol dm^{-3} $HClO_4$ at 348 K. Thus, the kinetic method gives the same protonation site ratio (98 % at C-3 and 2 % at C-2) as the product analysis in the case where no dehydrations, fragmentations or rearrangements occur.

By taking into account that $k_2^H \approx 0.02(k_2^H + k_3^H)$ in the hydration of 5-cyano-2-norbornenes, the methylation of C-3 increases the hydration rate by a factor of 2×10^4 to 4×10^4, which is normal. Since $k_3^H \approx k_2^H + k_3^H$, the increase of rate caused by the 2-methylation does not practically change from that (see above) calculated from the total disappearance rates.

The similarity of the results obtained in this work by kinetic and product-analytic measurements agrees with the results obtained earlier for the hydration of 5-hydroxy-2-norbornenes (kinetically: 58 % of protonation at C-3)[19] and 5-acetoxy-2-norbornenes (product analysis: 60 % of protonation at C-3)[1]. The portions for the two differently substituted norbornenes are nearly equal, because the inductive substituent constants of the hydroxyl and acetoxyl groups are similar.[7,8] The ratio (60:40) is, however, very different from that measured for the cyanonorbornenes (98:2). This is expected, since the electronegativity of the cyano group is much higher.[7,8] The similarity of the results obtained by kinetic and product-analytic methods shows that in the cases where deprotonations, fragmentations or rearrangements cause complicated hydration products, the kinetic measurents can be used to determine the amount of protonation at different sites in the hydration of norbornenes.

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