185. Proximity Effects in Acid and Base-Catalysed Ether Formation

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Summary

When heated with sodium ethoxide in ethanol 7-methylidenebicyclo[3.3.1]nonan-3-*endo*-ol (*endo*-**1**) is converted into 1-methyl-2-oxa-adamantane (**3**). This reaction involves nucleophilic addition of a hydroxy group to an unactivated olefinic bond. Formation of the cyclic ether **3** also takes place when *endo*-**1** is heated in aqueous ethanol. This electrophilic addition is strongly catalysed by weak acids and suppressed by weak bases. These unusual reactions proceed more slowly with 7-methylbicyclo[3.3.1]non-6-en-3-*endo*-ol (*endo*-**2**) and can be ascribed to a proximity effect. This follows from the IR. and NMR. spectra of *endo*-**1** and *endo*-**2** which show strong intramolecular hydrogen (OH-π) bonding. The unsaturated *endo*- and *exo*-alcohols **1** and **2**, respectively, undergo only *exo*-complexation with silver ion.

According to molecular models[1]) the hydroxy groups in the *endo*-isomers of 7-methylidenebicyclo[3.3.1]nonan-3-ol (*endo*-**1**) and 7-methylbicyclo[3.3.1]non-6-en-3-ol (*endo*-**2**) are within *van der Waals* distance of the olefinic double bonds when the six-membered rings adopt the twin-chair **1** and chair-half chair conformation **2**[2]). Unusual interactions between these functional groups are therefore to be expected. In fact *endo*-**1** undergoes facile cyclization to the cyclic ether 1-methyl-2-oxa-adamantane (**3**) when treated with 25% sulfuric acid [3][3])[4]).

In view of the anticipated strong intramolecular hydrogen bonds in *endo*-**1** and *endo*-**2** it was of interest to determine whether addition of a nucleophile would take place in the absence of an external acid. The π-bonded hydroxy group might serve as a sufficiently strong electrophilic catalyst for attack of external nucleophiles, such as water or an alcohol, leading to an addition product of type **4** and **5** (S = H or alkyl).

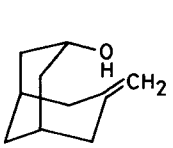
Furthermore, the presence of π-electrons in unactivated olefinic bonds renders them accessible to electrophilic attack, whereas strongly electron-withdrawing sub-

[1]) *e.g.* CPK Precision Molecular Models, *Ealing Beck Ltd.*, Watford, England.

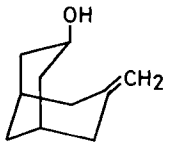
[2]) Unsubstituted bicyclo[3.3.1]nonane appears to prefer a distorted twin-chair conformation, 3- and 7-substituted derivatives a chair-boat conformation [1] [2].

[3]) Also when *endo*-**1** is treated with CH_2I_2 and the zinc-copper couple [4].

[4]) Numerous other intramolecular reactions of 3,7-substituted bicyclo[3.3.1]nonanes have been reported, *e.g.* [1–3] [5–9].



endo-**1**



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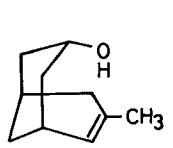
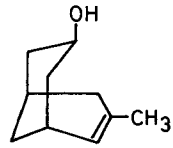
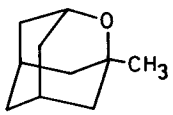


endo-**2**



exo-**2**



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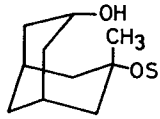

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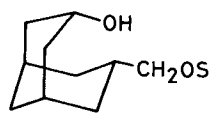

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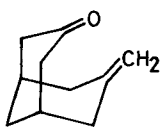
stituents, such as C=O and C≡N, are required to promote nucleophilic attack[5]). Conceivably, the resistance towards attack by nucleophiles could be overcome in the conjugate bases of the unsaturated alcohols *endo*-**1** and *endo*-**2** because of the proximity of the negatively charged oxygen atom and the double bond, base-catalysed cyclization to the cyclic ether **3** becoming a mechanistic alternative.

Finally, a comparison of silver-olefin complexation of *endo*-**1** and **2** with that of *exo*-**1** and **2**, respectively, should show whether the neighbouring hydroxy group in the former compounds favours the formation of 'sandwiched' *endo*-complexes, in spite of a severe deformation of the twin-chair and chair-half chair conformations.



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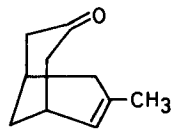

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Results. According to the literature [12] [3], reduction of 7-methylidenebicyclo[3.3.1]nonan-3-one (**6**) [13] [9] with lithium aluminium hydride in ether produces *endo*- and *exo*-**1** (5:1). Surprisingly, a mixture of 50% cyclic ether **3**, 30% *endo*-**1** and 20% *exo*-**1** was obtained by this procedure, as determined by GC. of the crude reaction mixture after neutral or basic work-up. Apparently, the first-formed aluminium alkoxide derivative of *endo*-**1** undergoes facile cyclization, a fact which has been overlooked by previous workers. However, by reduction of ketone **6** with sodium borohydride in boiling 2-propanol for 20 h, only 3% ether **3** was produced beside 82% *endo*-**1** and 15% *exo*-**1**.

7-Methylbicyclo[3.3.1]non-6-ene-3-one (**7**) was obtained by isomerization of the ketone **6** with H_2/Pd according to *Kimoto et al.* [2]. Addition of pyrrolidine to the reaction mixture reduced side reactions, such as the formation of 1-hydroxyadamantane. Reduction of the oily ketone **7** by $LiAlH_4$ afforded *endo*- and *exo*-**2** (4:5), no cyclic ether **3** being formed.

[5]) Exceptions to this rule are the addition of very reactive carbanions [10] and some metal salts of amines [11].

All four olefinic alcohols *endo*- and *exo*-**1** and **2**, yielded isolable crystalline 1:1 silver complexes. Treatment of these complexes with aqueous ammonia liberated the olefinic alcohols, thus conveniently purified.

The ν(OH) region of the IR. spectra of the *endo*-alcohols **1** and **2** in CCl_4 showed only strong sharp absorption bands for H-bonded hydroxy groups at 3510 and 3560 cm^{-1} respectively, unaffected by dilution. On the other hand, both *exo*-isomers **1** and **2** showed weaker bands at 3620 cm^{-1} due to free OH-groups, and broad, concentration dependent absorption between 3200 and 3500 cm^{-1} for associated OH-groups. The frequency shifts due to intramolecular H-bonding are therefore 110 cm^{-1} for *endo*-**1** and 60 cm^{-1} for *endo*-**2**.

The IR. spectra (KBr) of the silver complexes of *endo*-**1** and *endo*-**2** showed the absorption bands of the hydroxy groups at 3310 and 3450 cm^{-1} respectively, indicating that the latter are not involved in the complexation. The shifts of the absorption band for the double bond to lower frequency by *ca.* 50 cm^{-1} in *exo*-**1** and *exo*-**2** agree with literature values [14] and indicate complexation on the *exo*-side for both alcohols **1** and **2**.

The NMR.-spectrum of *endo*-**1** showed the deshielding effect of the internal H-bond on the exocyclic 7-methylidene protons since the corresponding singlet (broadened by long-range coupling) was shifted downfield by 0.23 ppm as compared to the corresponding signal for *exo*-**1**. In the spectrum of *endo*-**2** the doublet for the olefinic proton at C(6) and the singlet for the methyl group at C(7) were also shifted downfield by 0.33 and 0.1 ppm respectively, again indicating strong internal H-bonding. A comparison of the chemical shifts in the spectra of the silver complexes of the four olefinic alcohols with those of the free compounds also indicated *exo*-complexation since the splitting patterns of the C(7) protons were the same. Furthermore, conformational changes in the complexes are unlikely, since the slight paramagnetic shifts (0.07–0.08 ppm in CD_3OD) of the olefinic protons in the complexes correspond to those reported in other cases [15].

The *endo*-isomers **1** and **2** were subjected to the neutral, acidic and basic reaction conditions summarized in the Table. Cyclization to the ether **3** was the only observable reaction. In pure ethanol no reaction occurred after 15 h at 150°. In 80% aqueous ethanol, however, 94% ether **3** was obtained under these conditions, whereas 0.1N silver nitrate caused quantitative cyclization after 15 h at 100°.

As little as 0.01N HCl sufficed to cause quantitative cyclization of *endo*-**1** after 48 h at 22° or 4 h at 50°. With 0.1N HCl a quantitative yield of **3** was obtained after 3 h at 22° from *endo*-**1**, but only 10% from *endo*-**2**. Somewhat more severe conditions were required for catalysis by 0.1N acetic acid, namely 15 h at 100°.

Little or no cyclization occurred in the presence of 0.1N sodium hydroxide or triethylamine in 80% ethanol. However, with sodium ethoxide in ethanol at concentrations higher than 0.1M practically quantitative formation of the ether **3** occurred. Again *endo*-**2** proved to be considerably less reactive. Under comparable conditions lithium and potassium ethoxide gave somewhat lower yields of **3**, whereas sodium *t*-butoxide in *t*-butanol was at least equivalent to sodium ethoxide.

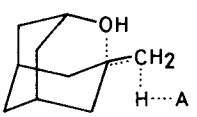
Discussion. The IR. and NMR. spectra of *endo*-**1** and **2** confirm the presence of a strong intramolecular H-bond between the hydroxy group and the olefinic bond

Table. *Yield of 1-methyl-2-oxa-adamantane* (**3**) *from* endo-**1** *and* **2**.

No.	Solvent	Catalyst	Temp. °C	Reaction time (h)	% yield from *endo*-**1**	*endo*-**2**
1	100% EtOH	–	150	15	–	–
2	80% EtOH	–	150	15	94	–
3	„ „	0.1M $AgNO_3$	100	15	100	
4	„ „	0.01N HCl	22	48	100	
5	„ „	„ „	50	4	100	
6	„ „	0.1N „	22	3	100	10
7	„ „	„ „	50	4	100	100
8	„ „	0.1N AcOH	100	15	100	
9	„ „	„ „	150	15	100	36
10	„ „	1N „	100	15	100	61
11	„ „	„ „	150	15	100	100
12	„ „	0.1M NEt_3	150	15	–	–
13	„ „	0.1N NaOH	150	15	3	–
14	100% EtOH	0.01M NaOEt	150	15	trace	
15	„ „	0.1M „	150	15	94	
16	„ „	1M „	150	15	100	3
17	„ „	0.1M LiOEt	150	15	51	
18	„ „	„ KOEt	150	15	92	
19	100% MeOH	„ $NaOCH_3$	150	15	80	
20	100% *t*-BuOH	„ NaO-*t*-Bu	150	15	100	

in both compounds (see introduction). The interaction between the OH-group and the π-bond is stronger in *endo*-**1**. In this case the double bond is inclined towards the OH-group, in *endo*-**2** it is tilted away.

In accord with these conclusions *endo*-**1** was more reactive than *endo*-**2** wherever a comparison is available. Thus, *endo*-**1** already cyclized upon heating in 80% aqueous ethanol, not however in pure ethanol (Table, No. 1 and 2). Surprisingly, cyclization was drastically reduced in weakly basic solution (No. 12 and 13). This is an indication that in 80% ethanol, water itself is acting as an acid catalyst (H–A) by transfering a proton to the methylidene group, presumably with participation of the OH-group, as in **8**. In keeping with this view, cyclization is readily brought about by such weak acids as 0.01N HCl at 22° and 0.1N acetic acid at 100° (No. 4 and 8). Stronger acid or higher temperature are required for cyclization of *endo*-**2** (No. 7 and 11) presumably reacting by way of the transition state **9**. It is noteworthy that addition of external nucleophiles to form products such as **4** or **5** does not compete successfully with addition of the neighbouring OH-group.



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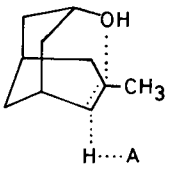

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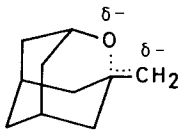

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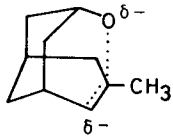

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The most striking result, however, is the observed *base catalysis of ether formation*[6]): 0.1N NaOEt, LiOEt and KOEt in ethanol are markedly effective at 150° (No. 15, 17, 18) in contrast to pure ethanol (No. 1). Plausibly, the negative charge on the oxygen atom in the conjugate base of *endo*-**1** is transferred to the methylidene group of the double bond **(10)** proton transfer from the solvent then leading to the ether **3**. The analogous route **11** for *endo*-**2** is evidently less favourable (No. 16), presumably because of the greater distance between the oxygen atom and the double bond and because of the need to spread negative charge onto the secondary carbon atom C(6).

Finally, it is noteworthy that silver ion complexes the double bond in *endo*-**1** and *endo*-**2** only on the *exo*-side, *i.e.* away from the OH-group, although neighbouring OH-groups are reported to stabilize olefinic silver complexes [15] [17]. The reason, as suggested by molecular models, is that the insertion of silver ion into the concave *endo*-position of **1** and **2** would entail serious conformational deformations.

The technical assistance of *Mr. Rolf Bielmann* is gratefully acknowledged.
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Experimental Part

Melting points (m.p.) were determined with a *Kofler*-Block and are corrected to ±1°C. IR. spectra are given in cm^{-1} and NMR. spectra in δ-values (ppm.).

1. **Reduction of 7-methylidenebicyclo[3.3.1]nonan-3-one (6).** – *a) With sodium borohydride.* To a suspension of $NaBH_4$ (2.5 g, 65.5 mmol) in 100 ml boiling 2-propanol, a solution of ketone **6** [9] (2.5 g, 16.5 mmol) in 2-propanol (50 ml) was added dropwise over 30 min. After refluxing for 20 h., the solvent was distilled through a *Vigreux*-column. The residue was taken up in ether and water, the ether solution washed with water, dried over Na_2SO_4 and distilled through a *Vigreux*-column. GC. of the oily residue, 10% *Carbowax* 20 M, 185°, revealed the presence of 82% *endo*-**1**, 15% *exo*-**1** and 3% 1-methyl-2-oxa-adamantane (**3**). The mixture was dissolved in 30 ml petrol ether and chromatographed on basic Al_2O_3, activity I (*Woelm*). With the same solvent a mixture of *endo*-**1** and ether **3**[7]) was eluted. Fractional sublimation of the latter mixture at 65–70°/12 Torr removed the oily ether **3** leaving 1.42 g (57%) *endo*-**1**, m.p. 84–85° (cold petrol ether) ([3] m.p. 88° in closed capillary).

Petrolether/benzene 4:1 and benzene eluted mixtures of *endo*- and *exo*-**1** and pure *exo*-**1**, respectively. Crystallization from cold petrol ether yielded 300 mg (12%) pure *exo*-**1**, m.p. 89–90°.

7-Methylidenebicyclo[3.3.1]nonan-3-endo-*ol* **(1).** – IR. (CCl_4): 3510 (bonded OH); 3065 ($C=CH_2$); 1109, 1083 (C–O); 895 ($R_2C=CH_2$). – IR. (KBr): 3230 (OH); 3058, 1636 ($C=CH_2$). – NMR. (CCl_4): 4.86 (br. *s*, 2H, $CH_2=C$); 3.67 (br. *m*, 1H, CHOH); 2.51 (*s*, 1H, OH).

$C_{10}H_{16}O$ (152.2) Calc. C 78.89 H 10.59% Found C 78.78 H 10.78%

7-Methylidenebicyclo[3.3.1]nonan-3-exo-*ol* **(1).** – IR. (CCl_4): 3620 (free OH); 3300–3500 (assoc. OH); 3065 and 1636 ($C=CH_2$); 1040 (C–O); 880 ($R_2C=CH_2$). – IR. (KBr): 3290, 3225 (OH); 3070, 1638 ($C=CH_2$). – NMR. (CCl_4): 4.63 (br. *s*, 2H, $CH_2=C$); 4.36 (*m*, 1H, C*H*OH); 2.5 (*s*, 1H, OH).

$C_{10}H_{16}O$ (152.2) Calc. C 78.89 H 10.59% Found C 78.86 H 10.74%.

[6]) Facile base-catalysed addition of this type has also been observed by Priv. Doz. Dr. *C. Ganter*, Federal Institute of Technology, Zürich (private communication).

[7]) This compound was identical with authentic 1-methyl-2-oxa-adamantane (**3**) kindly provided by Prof. *H. Stetter* [3].

b) With lithium aluminium hydride. Ketone **6** (2.55 g, 17.0 mmol) in 50 ml dry ether was slowly added to a refluxing solution of $LiAlH_4$ (0.628 g, 17.95 mmol) in 100 ml of dry ether. After refluxing for a further 5 h., 1N NaOH (2.7 ml) was slowly added with cooling. The precipitate was filtered off and washed with ether. Evaporation of the filtrate left a semicrystalline mixture consisting of 50% cyclic ether **3**, 30% *endo*-**1** and 20% *exo*-**1** (GC.). Column chromatography of the mixture on basic alumina as described under a) yielded the pure components.

2. **7-Methylbicyclo[3.3.1]non-6-en-3-one (7).** A solution of **6** (2.0 g, 13,3 mmol) in 100 ml ethanol containing 2 ml of pyrrolidine was shaken with 10% Pd/C (200 mg) in H_2 atmosphere for 18 h. After filtration the ethanol was distilled at normal pressure yielding a liquid residue. This was taken up in ether, the solution washed with 2N HCl and water, dried over Na_2SO_4 and evaporated to yield the isomerized ketone **7** [2], 1.90 g (95%). – NMR. (CCl_4): 1.61 (*s*, 3H, CH_3); 5.38 (*d*, $J = 4.5$ Hz, 1H, C=CH). Addition of less pyrrolidine leads to the formation of adamantan-1-ol.

3. ***endo-* and *exo*-7-Methylbicyclo[3.3.1]non-6-en-3-ol (2).** – Ketone **7** (1.90 g, 12,6 mmol) was reduced with $LiAlH_4$ in ether as described for the ketone **6** to yield a mixture of *endo-* and *exo*-**2** (1.91 g). This was chromatographed on basic Al_2O_3 *(Woelm)* with pentane and increasing amounts of CH_2Cl_2 to yield crude *endo*-**2** (0.77 g) and crude *exo*-**2** (0.95 g)[8]) beside fractions containing mixtures of both isomers.

endo-**2**. After sublimation at 120° long needles m.p. 33.5–34.5°. – IR. (CCl_4): 3560 conc. independent (bonded OH); 3000 and 1660 (C=CH); 1110 (C–O). – IR. (KBr): 3560, 3460 (OH). – NMR. (CCl_4): 5.78 (*d*, 1H, H–C(6)); 3.30 (br. *s*, 1H, C*H*OH); 1.70 (*s*, 3H, CH_3–C(7)).

$C_{10}H_{16}O$ (152.2) Calc. C 78.89 H 10.59% Found C 78.89 H 10.56%

exo-**2.** After sublimation and recrystallization from pentane at dry ice temperature, needles m.p. 49–50.5°. – IR. (CCl_4): 3620 (free OH); 3300–3500 (assoc. OH, disappears upon dilution); 3000 (=CH); 1042 (C–O). – IR. (KBr): 3280 (OH); 1670 (C=CH_2). – NMR.: 5.45 (*d*, 1H, H–C(6)); 3.75 (*m*, 1H, C*H*OH); 3.2 (*s*, 1H, OH), disappears with D_2O; 1.60 (*s*, 3H, CH_3–C(7)).

Found C 78.59 H 10.36%

4. **Silver nitrate complexes of *endo-* and *exo*-1 and 2.** – To the unsaturated alcohols (1.0 mmol) in acetone (*ca.* 1 ml), 5M $AgNO_3$ solution (1 equiv.) was added. After standing for several h at –15° the resulting crystals were filtered off and washed with cold acetone. Concentration of the mother liquors afforded further amounts of silver complex.

Calc. for $C_{10}H_{16}O \cdot AgNO_3$ C 37.29 H 5.00%

endo-**1**: m.p. 125° (dec.). – IR. (KBr): 3310 (bonded OH); 3059, 1637, 1583 (C=CH_2). – NMR. (CD_3OD): 4.84 (*s*, 2H, C=CH_2); 3.77 (*m*, 1H, C*H*OH).

Found C 37.00 H 4.90%

exo-**1**: m.p. 116.5–118° (dec.). – IR. (KBr): 3400, 3300 (OH); 3070, 1638, 1588 (C=CH_2). – NMR. (CD_3OD): 4.72 (*m*, 2H, C=CH_2); 4.52 ($t \times t$, $J = 5.5$ and 11.0 Hz, C*H*OH).

Found C 37.47 H 5.22%

endo-**2**: m.p. 214–215° (dec.). – IR. (KBr): 3450 (OH); 1610 (C–CH). – NMR. (CD_3OD): 5.87 (*m*, 1H, H–C(6)); 4.01 (br. *s*, C*H*OH); 1.74 (*s*, 3H, CH_3–C(7)).

Found C 37.20 H 4.75%

exo-**2**: m.p. 114–117° (dec.). – IR. (KBr): 3435 (free OH); 1616 (C=CH). – NMR. (CD_3OD): 5.56 (*m*, 1H, H–C(6)); 3.83 ($t \times t$, $J = 5.5$ and 11.0 Hz, C*H*OH); 1.66 (*s*, 3H, CH_3–C(7)).

Found C 37.14 H 5.20%

[8]) This fraction was contaminated with 1-hydroxyadamantane as determined by GC.

To liberate the unsaturated alcohols, the complexes were treated with conc. aq. NH_3 and extracted with pentane. Recovery was practically quantitative.

5. **Cyclization reactions of *endo*-1 and 2.** – The unsaturated alcohol (*ca.* 20 mg) was dissolved in *ca.* 2 ml of solvent containing a known quantity of acid or base and heated in a sealed tube *(Table)*. The indicated reaction times include the warming and cooling period of *ca.* 1 h. The product was analysed by GC. (10% *Carbowax* 20 M, 165°), the solution being injected directly. Peak heights were calibrated with authentic samples of **1, 2** and **3.**

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