Diagnostic OH ^{1}H-NMR Shift Differences in *syn* and *anti* β-Hydroxy Ethers

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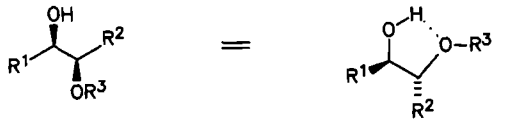
Received September 29, 1986

In a pair of diastereomeric β-hydroxy ethers the relative ^{1}H-NMR chemical shift of the OH proton is diagnostic for the *syn* or *anti* stereostructure. This is probably based on the presence of internally hydrogen-bonded structures. The rule is therefore restricted to those compounds for which only this type of internal hydrogen bonding is accessible.

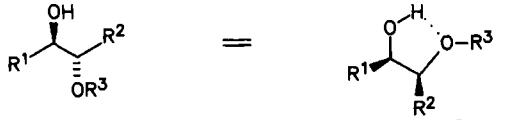
Diagnostische Unterschiede der OH-^{1}H-NMR-Verschiebungen bei *syn*- und *anti*-β-Hydroxyethern

Die relative chemische Verschiebung des OH-Protonen-Signals in den ^{1}H-NMR-Spektren eines Paares diastereomerer β-Hydroxyether erlaubt eine *syn/anti*-Zuordnung der relativen Konfiguration. Dies basiert vermutlich auf der Bildung von Strukturen mit intramolekularer Wasserstoff-Brücke. Insofern ist diese Regel auf solche β-Hydroxyether beschränkt, bei denen nur dieser Typ von intramolekularer H-Brücke ausgebildet werden kann.

While structural assignment to *cis* and *trans* isomers of variously substituted cyclic compounds can traditionally be effected by NMR spectroscopy assignment of *syn/anti* diastereomers[1] of open-chain compounds is more difficult. Frequently such compounds have to be converted into cyclic derivatives first, in order to ascertain their stereostructure[2]. It is only recently that empirical rules emerge focussing on certain diagnostic features in the NMR spectra, which give hints as to the stereostructure of the diastereomer at hand. This holds particularly for those classes of compounds in which intramolecular hydrogen bonds favor one particular cyclic conformation, e.g. β-hydroxycarbonyl compounds[3], β-hydroxyalkyl fluorides[4], γ-hydroxy amines[5], γ-hydroxy ethers[6], or less pronounced 4-hydroxyalkynes[7]. In this paper we describe some structure-specific features in the ^{1}H-NMR spectra of *syn* (**1**) and *anti* β-hydroxy ethers (**2**).



syn **1**



anti **2**

Heathcock[3] recently studied the related tertiary β-hydroxy ethers **3** and surmised the predominance of hydrogen-bonded conformations, which was reflected in the ^{13}C-NMR chemical shifts of the methyl group, an effect substantiated in other examples[8]. No significant effect of this nature was, however, found in the ^{13}C-NMR spectra of various compounds of the structures **1** or **2**, representing secondary β-hydroxy ethers.

The predominance of hydrogen-bonded conformations should also be reflected in different vicinal coupling constants $H-C^1-C^2-H$ for the *syn* and *anti* isomers **1** and **2** ($J_{syn} > J_{anti}$). This has been noted in some β-amino alcohols, glycols, and β-hydroxy ethers[9]. However, depending on additional coupling from the residues R^1 and R^2 the relevant coupling constants are not always easily obtained.

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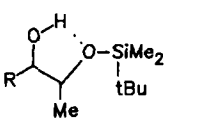
We focussed on the chemical shift of the OH proton, which depends on the extent of hydrogen bonding[10]. The extent to which hydrogen-bonded conformations are populated should be larger for the *syn* (**1**) than for the *anti* isomers (**2**)[11]. Accordingly we noted structure-specific differences in the ^{1}H-NMR chemical shifts of the OH signal. The data from our own studies as well as those kindly provided by other research groups are collected in Table 1. These data can be summarized by the statement $\delta_{OH}(syn) > \delta_{OH}(anti)$, with the difference amounting to 0.48 ± 0.3 ppm.

This generalization holds also for a number of compounds of general structure **4** (cf. Table 2). However, the limits of the above generalization are more important: With simple structures **1** or **2** we encountered only two cases, which fell out of line:



R	δOH *syn*	*anti*
CH_3	1.86	2.17
CH_2=CH–CH_2	2.30	2.30

In view of other well-behaved examples with the *tert*-butyldimethylsilyl protecting group in Table 1, the above-mentioned breakdown of the rule might therefore be confined to cases, in which the steric bulk of R^3 is much larger than that of R^2. Since the above generalisation is based on the predominance of hydrogen-bonded structures **1** and **2**, it is no surprise that any structural feature that gives rise to

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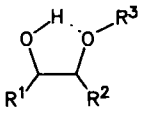
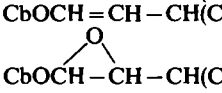
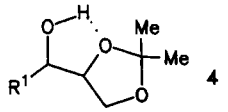
Table 1. OH chemical shifts (δ values, $CDCl_3$) of *syn* and *anti* β-hydroxy ethers



No.	R^1	R^2	R^3	δ(OH) *syn*	δ(OH) *anti*	Ref.
1	CH_3	$CH_2=CH$	CH_3	2.8	2.15	[12]
2	CH_3CH_2	$CH_2=CH$	CH_3	2.8	2.07	
3	$(CH_3)_2CH$	$CH_2=CH$	CH_3	2.7	2.13	
4	Ph	$CH_2=CH$	CH_3	3.4	2.6	
5	CH_3	$CH_2=CH$	$CH_2CH_2Si(CH_3)_3$	2.84	2.17	[12]
6	CH_3CH_2	$CH_2=CH$	$CH_2CH_2Si(CH_3)_3$	2.74	2.13	
7	$(CH_3)_2CH$	$CH_2=CH$	$CH_2CH_2Si(CH_3)_3$	2.54	2.21	
8	Ph	$CH_2=CH$	$CH_2CH_2Si(CH_3)_3$	3.32	2.64	
9	CbOCH=CH−CH(CH$_3$)[a] (*Z*)	CH_3	CH_2Ph	2.65	2.3	[13]
10	CbOCH=CH−CH(CH$_3$)[a] (*Z*)	CH_3	$Si(CH_3)_2Ph$	2.5	2.35	
11	CbOCH=CH−CH(CH$_3$)[a] (*Z*)	CH_3	$C(CH_3)_3$	2.7	2.4	
12	CbOCH=CH−CH(CH$_3$)[a] (*Z*)	CH_3	$CH_2OCH_2CH_2OCH_3$	2.9	2.25	
13	CbOCH=CH−CH(SiMe$_3$)[a] (*Z*)	CH_3	CH_2Ph	2.85	1.7	
14	CbOCH=CH−CH(CH$_3$)[a] (*E*)	CH_3	CH_2Ph	2.35	2.30	
15	 (*cis*)	CH_3	CH_2Ph	2.9	2.5	
16	CH_3	$Ph_3COCH_2CH(CH_3)$	$Si(CH_3)_2C(CH_3)_3$	2.33	2.10	[14]
17	CH_3	$PhCH_2OCH_2CH(CH_3)$	$Si(CH_3)_2C(CH_3)_3$	2.61	2.33	
18	CH_3	$PhCH_2OCH_2CH(CH_3)$	$Si(Ph)_2C(CH_3)_3$	2.38	2.32	
19	CH_3	CH_3	CH_2Ph	2.76	2.16	[15]
20	CH_3	CH_3	CH_2SCH_3	2.37	2.29	
21	CH_3	CH_3	$CH_2-CH=CH_2$	2.87	2.19	
22	CH_3	CH_3	CH_2OCH_2Ph	2.87	2.44	
23	$CH_2=CH-CH_2$	CH_3	CH_2Ph	2.57	2.21	[15]
24	$CH_2=CH-CH_2$	CH_3	CH_2OCH_2Ph	2.62	2.56	
25	$CH_2=C(CH_3)-CH_2$	CH_3	CH_2Ph	2.24	2.10	
26	$CH_2=CH-CH_2$	CH_3CH_2	CH_2Ph	>2.16	2.12	[16]
27	CH_3CH_2	$CH_2=CH-CH_2$	CH_2Ph	3.10	2.10	
28	CH_3CH_2	$CH_2=C(SiMe_3)$	CH_2Ph	2.32	1.78	[17]
29	CH_3CH_2	$CH_2=C(SiMe_3)$	CH_3	2.94	2.02	

[a] CbO = Diisopropylcarbamoyl.

Table 2. OH chemical shifts ($CDCl_3$) of *syn*- and *anti*-4-(1-Hydroxyalkyl)-2,2-dimethyl-1,3-dioxolanes (**4**)



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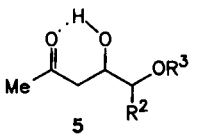
R^1	δ(OH) *syn*	δ(OH) *anti*	Ref.
$CH_3CH_2CH_2$	2.16	1.98	[18]
$CH_2=CH-CH_2$	2.24	2.01	
$Cl-CH=CH-CH_2$	2.32	2.03	
$(CH_3)_2C=CH-CH(CH_3)$	2.21	2.09	[19]
$CH_2=CH-CH(CH_3)$[a]	2.20	1.82	
$(CH_3)_2C=CH-CH(CH_3)$[a]	2.19	1.99	
$CH_2=C(SiMe_3)$	2.50	2.31	[17]
$CH_2=CH$	2.99	2.49	
$CH_2=CH-CH(CH_3)$ (*erythro*)	2.27	2.04	[20]
(*threo*)	2.55	1.95	

[a] Cyclohexylidene instead of isopropylidene derivative.

other hydrogen-bonded conformations will render the above rules inapplicable. Structures of the sort **5** or **6** provide obvious cases. This holds also for **7**, in which the ester oxygen is no longer a good enough hydrogen bond acceptor.



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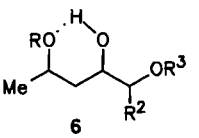

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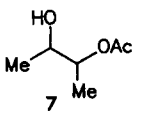

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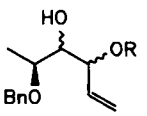

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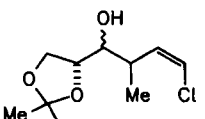

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Finally, in situations such as **8**, in which the direction of the hydrogen bond is not defined, the differences in δ_{OH} between the stereoisomers became too small to be of diagnostic value.

Nevertheless, we feel that with proper judgement the rules set forth above could be quite helpful in indicating the *syn* or *anti* configuration of a β-hydroxy ether, when spectra for both diastereomers are available. It is comforting that the effect is not sensitive to adventitious moisture: Even saturating the $CDCl_3$ solution of *syn*- and *anti*-**9** with water led to line broadening but not to an interchange in the relative chemical shifts of the OH signals[21].

Another aspect which is affected by the extent and geometry of hydrogen bonding was noted, but turned out not to be general for all the compounds examined: the vicinal coupling constant $H-C^1-O-H$ was found to be larger for the *syn* isomer ($\geqq 5$ Hz) than for the *anti* isomer ($\leqq 3$ Hz) for the series of compounds 14–18 of Table 1 and, when reported, for the first six entries of Table 2.

We would like to thank the *Deutsche Forschungsgemeinschaft* for support of this study. We are grateful to Prof.'s *D. Hoppe, J. Mulzer, W. R. Roush, M. T. Reetz, F. Sato,* and *T. Oishi* for providing us with spectral data of numerous β-hydroxy ethers.

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[21] Experiment kindly carried out by S. Dresely.

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