PH DEPENDENCE OF HYDROLYTIC REMOVAL OF SILYL GROUP FROM TRIALKYLSILYL ETHERS

Nachiro Shirai, Kiyoshi Moriya, and Yutaka Kawazoe

Faculty of Pharmaceutical Sciences, Nagoya City University Tanabedori, Mizuho-ku, Nagoya 467, Japan

(Received in Japan 16 January 1986)

Abstract — Rate constants for the acid and base-catalyzed hydrolysis of the trialkylsilyl ethers of alcohols were quantitatively correlated with Taft's σ^* and Es values of the substituents on Si and O atoms of the ether linkage. The regression equations for $k_{\rm H}$ and $k_{\rm OH}$ were satisfactorily computed.

Trialkylsilyl groups are widely used to derive various hydroxy compounds for analytical and synthetic purposes. Silylation may also be effective in the masking of hydroxy-containing bioactive molecules¹⁻³ and, in such cases, its spontaneous (hydrolytic) demasking is a matter of both chemical and biological interest. It has been suggested⁴⁻⁷ that silyl ethers are hydrolyzed between Si and O atoms, following first order kinetics for both [H₂O⁺] and [OH⁻],

$$k_{obs} = k_H [H_3 O^T] + k_{OH} [OH^T] + k_{sp}$$

where k_{gp} is the rate constant in the spontaneous hydrolysis due to an attack of H_2O . Acid-catalyzed hydrolyses conform to the following general scheme:

$$R_3SI-OR' \xrightarrow{H} R_3SI-O^+H(R') \xrightarrow{H} 2^{O} R_3SI-OH + R'-OH$$

The more electron-donating the nature of either R or R', the greater increase in the rate of hydrolysis, whereas an increase in the bulkiness of the substituents decreases this rate. In contrast, base-catalyzed hydrolysis which follows the S $_{\rm N}^{\rm i}$ or S $_{\rm N}^{\rm 2}$ mechanism proceeds faster when the substitutents are more electron-withdrawing. However, few quantitative treatments of the rate have yet been achieved. The present study presents a regression analysis of the hydrolytic rates of several silylated alcohols as a function of the electronic effect (Taft's d*)⁸ and steric effect (Taft's Es)^{8,9} of the substitutents on the Si and the O atoms of the ether linkage.

EXPERIMENTAL

Rate Measurements for Hydrolysis of Silyl Ethers The silyl ethers listed in Table I were prepared and purified by distillation.¹⁰ An ether to be examined (50 µl) was dissolved in 100 ml of 45% acetone-containing aqueous buffer at an This had previously been maintained at 37°C. appropriate pH. At appropriate time intervals, 4 ml of the reaction mixture was withdrawn and extracted with 4 ml of hexane. The extract was analyzed by gas-chromatography, referred to an appropriate internal standard, in a 2m x 3mm column packed with either 5% SE-30 on 60/80 Chromosorb W for most compounds or 20% DC-550 on the same adsorbent for The internal standards used are (Comp. Nos. are given in Table t-butyl TMS ether. I): Naphthalene for Nos.6, 8, and 11; 2-methylnaphthalene for Nos.1 and 7; 2-methoxynaphthalene for Nos.2-5, and 12; toluene for No.10; mesitylene for No.9. The buffers used are: M/10 NaOH-M/10 borax (pH 11-12.5); M/30 KH₂PO₄-M/30 Na₂HPO₄ (pH 5.5-8.0); M/20 KH_PO_-M/40 borax (pH 8.0-9.25); M/20 AcOH-AcONa (pH 4.5-5.0); M/10 AcOH-M/10 AcONa (pH 3.0-5.5); M/10 Na₂HPO₄-M/20 citric acid (pH 2.5-5.0); M/80 HCl (pH 2.19); M/20 HCl (pH 1.67). Each k_{obs} value is the mean from 3 separate experiments.

<u>Correction of pH</u> The pH* (pH value in the thermodynamic sense) in the reaction medium was evaluated by the following equation; ¹¹ $pH^* = pH_{obs} - \delta$, where pH* is the -log value of $[H_30^+]$ in an acetone-containing reaction mixture, the pH_{obs} is read on an ordinary pH meter, and δ is a correction factor previously evaluated as -0.09 for 45% acetone-containing buffer solutions.¹¹ The ionic product, [pH* + pOH*], is evaluated as 16.54, assuming that pOH* equals pH* (8.27 = 8.18 + 0.09) in neutral aqueous buffer (pH 7.00) diluted with acetone to 45%. Thus, pOH* can be written as [16.54 - pH*].

RESULTS

Tabl	<u>e I Rate Consta</u>	nts for Acid- an	d Base-Catalyzed	Hydrolyses of Si	ilyl Ethers				
in 45% Acetone-Containing Aqueous Buffers at 37°C									
No.	Compound	k _H x10 ⁻³ M≁min	k _{OH} ×10 ⁻³ M·min	k _{sp} ×10 ³ M∙min	₽ ^{H*} min				
1	benzyl TMS	325.5	118.8	0.693	8.49				
2	benzyl nPDMS	90.08	7.108	0.2268	8.82				
3	benzyl tBDMS	0.05153	0.004188	0.0000	8.82				
4	benzyl CMDMS	33.73	1362.	0.9440	7.47				
5	p-NO ₂ -benzyl TMS	129.0	546.0	1.379	7.96				
6	p-MeO-benzyl TMS	412.7	123.1	0.4125	8.53				
7	phenethyl TMS	388.2	115.3	0.8912	8.53				
8	cyclohexyl TMS	376.5	1.872	0.4486	9.42				
9	isopentyl TMS	610.4	23.79	0.8920	8.97				
10	t-butyl TMS	44.33	0.01236	0.04574	10.05				
11	phenyl TMS	2.641	21650.	89.80	6.31				
12	phenyl tBDMS	0.0005322	0.4546	0.000	6.80				

TMS: trimethylsilyl ether; nPDMS: n-propyldimethylsilyl ether; tBDMS: t-butyldimethylsilyl ether; CMDMS: chloromethyldimethylsilyl ether. pH* min: pH* expected for the slowest hydrolysis.

The $k_{\rm H}$, $k_{\rm OH}$, and $k_{\rm sp}$ were computed from the $k_{\rm obs}$ values measured at various pH*'s at 37°C using the SALS (Statistical Analysis of Least Square Fitting) program.¹² The results are summarized in Table I, which also lists the pH* min at which the observed rate, $k_{\rm obs}$, is computed to minimum. The latter is the pH* at the intersection of two lines described by the equations: (1) log $k_{\rm obs} = \log k_{\rm H} - pH*$ and (2) log $k_{\rm obs} = \log k_{\rm OH} - pOH*$. Hence, pH* min is written as (log $k_{\rm H} - \log k_{\rm OH} + 16.54)/2$

Correlation of Rate Constants, k_H and k_{OH}, with o* and Es

The values of σ^* and Es used in the present study are described below. Most of the σ^* values are from the parameter file of Pomona University¹³. Those values of the benzyl derivatives were estimated by the correlation with pKa values of the corresponding carboxylic acids.^{14,15} The Es values are taken from the parameter file mentioned above¹³ and those of p-substituted benzyl derivatives were estimated to be the same as that of the non-substituted benzyl derivative.

	<u>0*</u>	<u>Es</u>		0*	<u>E8</u>
Сн	0.00	0.00	CICH2-	1.05	-0.24
сн,сн,сн,-	-0.12	-0.36	C ₆ H ₅ CH ₂ -	0.22	-0.38
Me_CHCH_CH	-0.16	-0.35	02NC6H4CH2-	0.37 ^{a)}	-0.38
c-C ₆ H ₁₁ -	-0.15	-0.79	MeOC 6H4CH2-	0.17 ^{a)}	-0.38
Me ₃ C-	-0.30	-1.54	C6H5CH2CH2-	0.08	-0.38

a) See reference 16.

The rate constants, $k_{\rm H}$ and $k_{\rm OH}$, shown in Table I were subjected to a multiple regression analysis as a linear function of the σ^* 's and the Es's of the substituents on the Si and the O atoms of the ether linkage, respectively. The terms of $\sigma^*(Ox)$ and Es(Ox) are used for those of R_1 and $\Sigma\sigma^*(Si)$ and Σ Es(Si) are for the sums of those of R_2 , R_3 , and R_4 , respectively, in the following formula.

$$R_1 - 0 - \frac{\sum_{i=1}^{R_2}}{\sum_{i=1}^{R_3}}$$

 $log k_{H}(/M \cdot min) = -1.079(\pm 0.481)\sigma^{*}(Ox) + 1.160(\pm 0.267)Bs(Ox)$ $-0.365(\pm 0.199) \Sigma\sigma^{*}(Si) + 2.482(\pm 0.155) \Sigma Bs(Si) + 6.174(\pm 0.188)$

r = 0.992 (n=10)

 $log k_{OH}(/M^{*}min) = + 2.435(\pm 0.374) \sigma^{*}(Ox) + 2.479(\pm 0.207) Es(Ox) + 1.499(\pm 0.155) \Sigma \sigma^{*}(Si) + 2.728(\pm 0.120) \Sigma Es(Si) + 5.626(\pm 0.146)$

r = 0.998 (n=10)

Standard errors of the coefficients are given in the parentheses. All the coefficients are 0.01 levels of significance except for those of the σ^* values of log k_{μ} .



N. SHIRAI et al.

DISCUSSION

For the acid hydrolysis, an increase in the electron-withdrawing nature of the substituents on both the Si and the O atoms decreases the rate (more contribution from the substituent on the O atom than those on the Si). An increase in their steric size also effectively reduces the rate (more contribution from the substituents on the Si than that on the O). For the base-catalyzed hydrolysis, in contrary to the acid-catalysis, an increase in the electron-donating nature of the substituents on both the Si and the O atoms decreases the rate (more contribution from the substituent on the O atom than those on Si). An increase in their steric size reduces the rate remarkably (the same degree of decrease from the substituents on both the Si and the O atoms). Some pH-profiles of the observed rates are It is worth noting that the most stabilizing pH may be estimated shown in Fig. 1. for any silylated alcohols using the correlation equation presented here. For demonstration, some plots of the observed rate constants versus those calculated are shown in Figs. 2a and 2b.

References and Note

- 1 E. Chang and V. K. Jain, J. Med. Chem., 9, 433 (1966).
- 2 R. Tacke and U. Wannagat, "Bioactive Org. Silicon Compds" (in Topics in Current Chemistry, vol. 84), pp.13-14 (1979).
- 3 T. W. Greene, "Protective Groups in Organic Syntheses", pp. 39-50, John Wiley & Sons, New York (1981).
- 4 R. J. P. Corriu and C. Guerin, Adv. Organometal. Chem., 20, 265 (1982).
- 5 B. Boe, J. Organometal. Chem., 107, 139 (1976).
- 6 E. Akerman, Acta Chem. Scand., 10, 298 (1956)
- 7 E. Akerman, Acta Chem. Scand., 11, 373 (1957).
- 8 R. W. Taft, "Steric Effects in Organic Chemistry" ed. M. S. Newman, pp. 556-675, Wiley, New York (1956).
- 9 E. Kutter and C. Hansch, J. Med. Chem., 12, 647 (1969).
- 10 S. H. Langer, S.Connell, and I. Wender, J. Org. Chem., 23, 50 (1958); K. K. Ogilvie and D. J. Iwacha, Tetrahedron Lett., 317 (1973); H. Miyazaki, M. Ishibashi, M. Itoh, and T. Nanbara, Biomedical Mass Spectroscopy, 4, 23 (1977); B. E. Cooper, Chem. & Ind., 21, 794 (1978); T. Morita, Y. Okamoto, and H. Sakurai, Tetrahedron Lett., 835 (1980).
- 11 R. G. Bates, M. Paabo, and R. A. Robinson, J. Phys. Chem., 67, 1833 (1963); G. Douheret, Bull. Soc. chim. France, 1412 (1967).
- 12 T. Nakagawa and Y. Oyanagi, Program System SALS for Non-linear Least-Squares Fitting in Experimental Sciences "Recent Developments in Statistical Inference and Data Analysis", ed. K.Matusita, pp. 221-225, North Holland Publishing Co. (1980).
- 13 Y. C. Martin, "Quantitative Drug Design. A Critical Introduction", Appendix II, Marcel Dekker, Inc., New York (1978)
- 14 A. J. Hoefnagel, M. A. Hoefnagel, and B. M. Wepster, J. Org. Chem., 43, 4720 (1978).
- 15 J. J. Christensen, M. D. Slade, D. E. Smith, M. R. Izatt, and J. Tsang, J. Am. Chem. Soc., 92, 4164 (1970).
- 16 These values were evaluated from the correlation of pKa's with σ^* and Es by use of 13 carboxylic acids: pKa = -1.648 σ^* + 4.644 ; r=0.988, n=13 (No contribution of Es was proved). The observed pKa values used for the estimation of σ^* : 4.04 for p-nitrophenylacetic acid; 4.37 for p-methoxyphenylacetic acid.