Migration of t-Butyldimethylsilyl Protecting Groups

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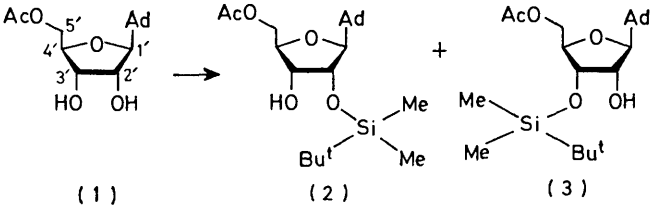
Isomeric 2'- and 3'-*O*-t-butyldimethylsilylribonucleoside derivatives (2) and (3) undergo interconversion by a first-order equilibration reaction. This intramolecular reaction takes place particularly readily in methanol solution and in the presence of base.

THE t-butyldimethylsilyl group may conveniently be used for the protection of isolated hydroxy functions;[1] it is usually easy to introduce and may readily be removed by treatment with fluoride ion. The use of this group has also been suggested[2] for the selective protection of the 2',3'-*cis*-diol system in ribonucleosides. Indeed, Ogilvie and his co-workers[3,4] and Sadana and Loewen[5] have recommended the use of 2'-*O*-t-butyldimethylsilyl protected ribonucleosides as building blocks in oligoribonucleotide synthesis.

Dodd *et al.* have reported[6] that the 2-*O*-t-butyldimethylsilyl derivative of glycerol is slowly converted (*ca.* 10% in 30 h) into its 1-isomer when it is heated at 118 °C either alone or in pyridine solution. However, we are unaware of the publication of any other report relating to the migration of the t-butyldimethylsilyl group prior to the completion of our own studies. Very recently, Ogilvie and his co-workers[4] have reported that 2',5'- and 3',5'-bis-t-butyldimethylsilyl derivatives of ribonucleosides are interconverted under certain conditions. These workers have found[4] that silica gel promotes the isomerization of the latter derivatives and that isomerization also occurs in dimethyl sulphoxide, dimethylformamide, 95% ethanol, pyridine–water, and triethylamine–water solutions. Ogilvie *et al.* observed[4] no isomerization in acidic media (acetic acid and methanolic hydrogen chloride) or in anhydrous pyridine and triethylamine solutions. Sadana and Loewen[5] have also very recently commented on the interconvertibility of 2'- and 3'-*O*-t-butyldimethylsilylribonucleoside derivatives. We now report that 2'- and 3'-*O*-t-butyldimethylsilyl derivatives of ribonucleosides [*i.e.* (2) and (3), respectively] readily undergo interconversion, especially in methanol solution, and that the process, which is base-catalysed, displays the kinetics of a first-order equilibration reaction.



Treatment of 5'-*O*-acetyladenosine[7] (1) with an excess of t-butyl dimethylsilyl chloride and imidazole in acetonitrile solution at 20 °C gives a mixture of the 2'- and 3'-*O*-t-butyldimethylsilyl derivatives (2) and (3), respectively, in 76% combined yield. Each of the latter compounds may be isolated as an analytically pure crystalline solid following short-column chromatography[8] of the mixture; these compounds may be characterized[9] on the basis of their ^{1}H n.m.r. spectra in [$^2H_6$]DMSO solution. In the case of the higher R_F isomer (see Experimental section) the anomeric proton resonates at δ 5.93 with $J_{1',2'}$ 5.0 Hz whereas in the case of the lower R_F isomer the anomeric proton resonates at δ 5.90 with $J_{1',2'}$ 6.2 Hz. A number of years ago, we noted[9] that the anomeric proton of a 2'-ribonucleoside derivative generally resonates downfield from that of the corresponding 3'-isomer. We further noted[9] that $J_{1',2'}$ is usually greater for the 3'- than for the 2'-isomer. On the basis of these generalizations, it seemed reasonable to assign structures (2) and (3) to the higher and lower R_F t-butyldimethylsilyl derivatives, respectively. However, a difference between the chemical shifts of the anomeric protons of a pair of 2'- and 3'-isomers of only 0.03 p.p.m. seemed to us to be too small to allow structural assignments to be made on a firm basis. Fortunately, it was possible to confirm the above assignments on the basis of spin-decoupling experiments. Irradiation at the frequency of the triplet resonance signal at δ 4.81 (assigned to H-2') in the n.m.r. spectrum of the higher R_F isomer caused the doublet at δ 5.93 (assigned to H-1') to collapse to a singlet while irradiation at the frequency of the latter signal caused the triplet at δ 4.81 to collapse to a doublet. In the same way irradiation at the frequency of the centre of the multiplet at δ 4.83 in the n.m.r. spectrum of the lower R_F isomer caused both the doublets at δ 5.47 and 5.90 (assigned to 2'-OH and H-1', respectively) to collapse to singlets.

$$(2) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (3) \qquad (1)$$

When a solution of (2) in anhydrous pyridine is maintained at 36° (Table, experiment no. 1), a 1 : 1 mixture of (2) and (3) is eventually obtained. No other products can be detected. This isomerization process displays the kinetics of a first-order equilibration reaction:[10] a good straight line is obtained by plotting $\ln[(A_o - A_e)/(A_t - A_e)]$ against reaction time t where A_o, A_e, and A_t represent the respective concentrations of (2) initially, at equilibrium and after time t. The sum of the forward and backward rate constants [$k_1 + k_{-1}$; see equation (1)] at 36 °C was found from the slope of the

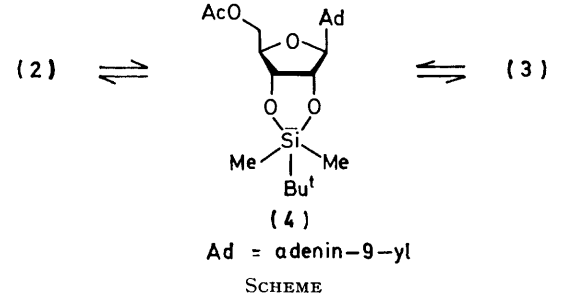
straight line to be 0.61×10^{-3} min^{-1} (Table) and the half-time ($t_{\frac{1}{2}}$) for equilibration was found to be 19 h. The relative proportions of (2) and (3) in the reaction mixture were estimated by ^{1}H n.m.r. spectroscopy (integration of the t-butyl resonance signals at δ 0.77 and 0.93, respectively) after suitable intervals of time.

Equilibration is much faster ($t_{\frac{1}{2}} < 1$ h at 36 °C) in [$^2H_4$]methanol solution (experiments 5 and 6) and, as expected, the rate of equilibration is the same, within experimental error, when equilibrium is approached from either side [equation (1)]. Addition of benzylamine (0.1 mol. equiv. with respect to substrate) to pyridine (experiment no. 2) increases the equilibration rate by a factor of three while addition of benzylamine or triethylamine (0.1 mol. equiv. with respect to substrate) to [$^2H_4$]methanol leads to complete equilibration at 20 °C within 10 and 5 min, respectively (experiments 7 and 8). It is therefore apparent that the reaction is subject to base catalysis. In support of this, the addition of pyridinium toluene-*p*-sulphonate (0.5 mol. equiv. with respect to substrate) leads to an immeasurably slow reaction in pyridine solution. The reaction also proceeds immeasurably slowly in [$^2H_6$]DMSO solution unless base is added (experiment 4); however, it proceeds quite rapidly in [$^2H_6$]DMSO–[$^2H_4$]methanol solution (experiment 3) in the absence of additional base. It can be seen from the Table that the equilibrium constant [k_1/k_{-1}, equation (1)] is dependent upon the reaction conditions. In none of the above experiments could any product other than (2) and (3) be detected. When a solution of (3) in methanol is heated, under reflux, for 75 min, a mixture of (2) (40%) and (3) (60%) may be recovered in 96% yield.

Equilibration of 2′- and 3′-*O*-t-butyldimethylsilyl-5′-*O*-acetyladenosines (2) and (3) at 36 °C

Experiment	Substrate	Molar concentration	Solvent	Added base [a]	(k_1/k_{-1}) [b]	$10^3(k_1 + k_{-1})$/min^{-1}	$t_{\frac{1}{2}}$/min
1	(2)	0.12	C_5H_5N [c]		1.0	0.61	1 140
2	(3)	0.12	C_5H_5N	(5)	1.07	1.8	380
3	(3)	0.24	$(CD_3)_2SO$–CD_3OD (4 : 1 v/v)		1.12	5.2	133
4	(3)	0.11	$(CD_3)_2SO$	(5)	0.96	45	15.5
5	(2)	0.06	CD_3OD		0.85	11.7	59
6	(3)	0.06	CD_3OD		0.84	12.1	57
7	(3)	0.08	CD_3OD	(5)			~1 (~10) [d]
8	(3)	0.08	CD_3OD	(6)			~0.5 (~5) [d]

[a] In the experiments with added base, the reaction solutions were made 0.01M with respect to either benzylamine (5), pK_a 9.34, or triethylamine (6), pK_a 10.8. [b] See Scheme; $k_1/k_{-1} = [(3)]/[(2)]$. [c] This result and our observation (see text) that isomerization occurs at an immeasurably slow rate in $(CD_3)_2SO$ solution are not in accordance with the results reported by Ogilvie *et al.*[4] [d] These results, which relate to experiments which were carried out at 20 °C, were obtained by t.l.c. rather than by n.m.r. spectroscopic analysis of the products. The numbers in parentheses represent the approximate times for complete equilibration, also at 20 °C.



SCHEME

We believe that the above results establish conclusively that the migration of the *O*-t-butyldimethylsilyl group is intramolecular and that it most probably involves an intermediate, such as (4), which contains a pentacovalent silicon atom. The most important practical consequence of this study is that it clearly demonstrates that great care must be exercised in the use of the t-butyldimethylsilyl group (and presumably of related silicon-containing groups) in the partial protection of vicinal diols (*e.g.* ribonucleosides) and polyols. The presence of base and the use of methanol and possibly of related solvents should be avoided in reactions involving such intermediates.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured at 90 MHz with a Bruker HFX 90 spectrometer and at 60 MHz with a Perkin-Elmer R12B spectrometer. T.l.c. was carried out on Merck high performance silica gel 60 F_{254} plates which were developed in the solvent system chloroform–methanol (9 : 1 v/v). Reeve Angel SO.TLC silica gel was used for short column chromatography.

Preparation of 5′-O-Acetyl-2′(3′)-O-t-butyldimethylsilyladenosines (2) and (3).—t-Butyldimethylsilyl chloride (2.65 g, 17.5 mmol) and imidazole (2.39 g, 35.1 mmol) were added to a suspension of 5′-*O*-acetyladenosine * (4.17 g, 13.5 mmol) in acetonitrile (25 ml) at 20°. After 1 h, more t-butyldimethylsilyl chloride (0.61 g, 4.0 mmol) and imidazole (0.55 g, 8.1 mmol) were added and, after a further 1 h, the products were concentrated under reduced pressure and the residue dissolved in chloroform. The resulting solution was washed with saturated aqueous sodium hydrogencarbonate (50 ml) and 0.1M-hydrochloric acid (50 ml) and then dried ($MgSO_4$). The crude products obtained following evaporation of the chloroform were fractionated by short column chromatography [the column (8 cm × 8 cm) was eluted with chloroform–methanol (97 : 3 v/v)].

5′-O-Acetyl-2′-O-t-butyldimethylsilyladenosine (2.52 g, 44%) was eluted from the column first; it crystallized from ethyl acetate–light petroleum (b.p. 60—80 °C) as platelets (Found: C, 50.9; H, 6.8; N, 16.5. $C_{18}H_{29}N_5O_5Si$ requires C, 51.0; H, 6.9; N, 16.5%), m.p. 165.5—166 °C; R_F 0.48 δ[$(CD_3)_2SO$] −0.08 (3 H, s), 0.02 (3 H, s), 0.77 (9 H, s), 2.03 (3 H, s), 4.1—4.5 (4 H, m), 4.81 (1 H, t, *J* 4.8 Hz), 5.27 (1 H, d, *J* 5.3 Hz), 5.93 (1 H, d, *J* 5.0 Hz), 7.32br (2 H,

* This material was contaminated with adenosine (*ca.* 5%).

s), 8.13 (1 H, s), and 8.31 (1 H, s). After the next fractions which contained a mixture (1.55 g, 27%) of the 2'- and 3'-isomers (2) and (3), pure 5'-O-*acetyl*-3'-O-*t-butyldimethylsilyladenosine* (0.27 g, 5%) was eluted from the column; it crystallized from ethyl acetate–light petroleum (b.p. 60—80 °C) as fine needles (Found: C, 51.0; H, 6.8; N, 16.7%), m.p. 169.5—170 °C; R_F 0.44; δ[$(CD_3)_2SO$]: 0.13 (6 H, s), 0.92 (9 H, s), 2.01 (3 H, s), 4.0—4.4 (4 H, m), 4.83 (1 H, m), 5.47 (1 H, d, *J* 6.2 Hz), 5.90 (1 H, d, *J* 6.2 Hz), 7.32br (2 H, s), 8.13 (1 H, s), and 8.34 (1 H, s). The combined yields of (2) and (3) were 4.34 g (76%).

Interconversion of 5'-O-*Acetyl*-2'-(*and* 3')-O-*t-butyldimethylsilyladenosines* (2) *and* (3).—(a) The interconversion of (2) and (3) in various solvents in the absence and the presence of additional base or acid was monitored by ^1H n.m.r. spectroscopy at 36 °C. The relative proportions of (2) and (3) after suitable intervals of time were most conveniently estimated by integration of their t-butyl proton resonance signals at δ 0.77 and 0.92, respectively (see above). Good straight lines resulted when the kinetic data obtained in experiments 1—6 (Table 1) were plotted in the usual way for a first-order equilibration reaction.[10]

(b) A solution of 5'-*O*-acetyl-3'-*O*-t-butyldimethylsilyladenosine (0.300 g) in methanol (50 ml) was heated, under reflux, for 75 min. The products were evaporated under reduced pressure and dried to constant weight. Examination of the products (0.288 g, 96%) by n.m.r. spectroscopy and t.l.c. revealed that they consisted *solely* of (2) (*ca.* 40%) and (3) (*ca.* 60%).

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