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Silatranyl-nucleosides: transition state analogues for phosphoryl transfer reactions

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Abstract—A novel class of compounds that contain a silatrane moiety attached to or incorporated within a nucleoside is described. These compounds are transition state analogues for phosphoryl transfer reactions and as such have potential antiviral and anticancer properties. The two-step synthesis of 3′-*O*-(trimethyl)silatranylthymidine (**1**) in 17% yield is reported. The aqueous half-life of **1** was determined to be 62 h by ^{1}H NMR. The syntheses of three 2′,3′-protected-5′-*O*-silatranyladenosines in 25–55% yields are also described.

In the four decades since the concept of a transition state analogue (TSA) was first put forth[1] a plethora of applications for TSAs have been proposed and realized. For example, the TSA method allows for the rational design of enzyme-inhibiting drugs,[2] the analysis of enzyme conformational changes and mechanism by X-ray crystallography,[3] and the generation of new catalysts.[4,5] However, there are few examples of TSAs for phosphoryl transfer reactions. This is despite the fact that inhibition of phosphoryl transfer enzymes such as HIV reverse transcriptase[6] and telomerase[7] has profound implications for the treatment of AIDS and cancer, respectively. The ideal TSA for phosphoryl transfer should contain a trigonal bipyramidal atom that mimics the oxyphosphorane transition state (or intermediate).[8] Additionally, the TSA must be soluble and stable in aqueous solutions if its biological properties are to be tested. Furthermore, many enzymes that catalyze phosphoryl transfer have nucleotide substrates or cofactors; therefore the TSA should also be a nucleoside derivative. We now report that silatranyl-nucleosides (Fig. 1) are a novel class of TSAs for phosphoryl transfer reactions.† Specifically, a silatranyl-thymidine meets all of the aforementioned criteria. Prior to this work, the only TSAs that met most of the criteria were ribonucleoside derivatives that contained a vanadium[9] or rhenium[10] atom attached at the 2′ and 3′ positions of the ribose; i.e. comparable to the silatranyl-

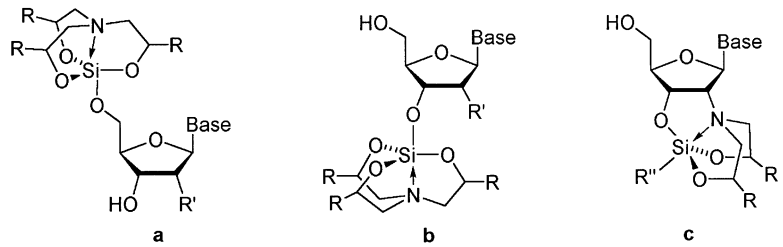

Figure 1. Three classes of silatranyl-nucleosides: R = H or CH_3, R′ = H or OH, R″ = alkoxy or 5′-*O*-nucleosidyl, base = thymidin-1-yl, adenin-9-yl, uracil-1-yl, cytosin-1-yl, guanin-9-yl.

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† It has been argued that in a strict sense the term 'transition state analogue' should be reserved for compounds whose actual mode of binding has been rigorously confirmed.[4] However, here we are invoking the term as it is more commonly used; i.e. for compounds that have been designed to be TSAs.[3]

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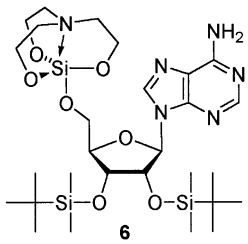
nucleoside shown in Fig. 1c. There is no literature precedent for TSAs comparable to those shown in Fig. 1a and Fig. 1b, in which the trigonal bipyramidal atom is tethered to the nucleoside at only one position, 5′ and 3′, respectively. Silatranes[11] are the most studied of the atranes,[12] and both NMR[13] and X-ray crystallographic[14] means have confirmed their trigonal bipyramidal geometry. The aqueous stability[15] and biological activity[16] of silatranes has also been investigated. However, silatranyl-nucleosides are unprecedented.‡ Reported herein is the synthesis of three protected 5′-*O*-silatranyladenosines and 3′-*O*-(trimethyl)-silatranylthymidine (**1**).

Silatranes adorned with methyl groups (Fig. 1, R = CH_3) have the advantage of being more stable towards hydrolysis,[15] whereas those without (Fig. 1, R = H) may have an advantage in terms of inhibiting an enzyme because the active site should better accommodate the less bulky ligands. Therefore, the synthesis of both types is desired. Our approach to 5′-*O*-silatranyl-adenosines **4a**/**4b** started with silatranylation of commercially available 2′,3′-*O*-isopropylideneadenosine (**2**) using a modification of Voronokov's procedure.[17] Thus, **2** was heated in DMF with potassium hydroxide, tetraethyl orthosilicate and triethanolamine or triisopropanolamine, to provide **3a** (47%) or **3b** (55%), respectively (Scheme 1).[18] Commercially available triisopropanolamine is sold as a mixture of four stereoisomers, therefore **3b** was formed as a mixture of four diastereomers. This is clearly indicated in the NMR spectra, for example the ^{29}Si NMR of **3b** shows four peaks in the characteristic silatrane region around −96 ppm.[13] With **3a** in hand, numerous deprotection methods, including both acidic and neutral conditions, were tested.[19] Unfortunately, in each case either no reaction occurred, or both the isopropylidene and the silatrane moieties were removed yielding adenosine. The deprotection of **3b** also failed to generate useful quantities of **4b**.

Since the selective removal of the isopropylidene group was unfruitful, another protecting group was sought for the 2′- and 3′-hydroxyl groups. The *tert*-butyldimethylsilyl (TBDMS) group was chosen since 2′,3′-bis(-*O*-TBDMS)-adenosine (**5**, not shown) was readily available from adenosine following Ogilvie's two-step procedure.[20] Thus, when **5** was subjected to the usual silatranylation conditions (5.0 equiv. $Si(OCH_2CH_3)_4$, 5.0 equiv. $N(CH_2CH_2OH)_3$, 0.1 equiv. KOH, DMF, 120°C, 44 h) silatrane **6** was furnished in 25% yield. The ^{29}Si NMR of **6** is particularly revealing, showing peaks at 21.2 and 19.7 ppm for the TBDMS silicon atoms and a characteristic peak at −95.7 ppm for the silatrane silicon atom.[13] The large chemical shift difference clearly shows the vastly different electronic environments of these silicon atoms, suggesting that the selective removal of the TBDMS groups might be possible due to the lower electrophilicity of the silatrane silicon atom. Unfortunately, deprotection attempts with various fluoride sources and under other conditions proved otherwise; again either no reaction occurred or adenosine was formed. This result suggests that the bulkier steric environment of the silicon atoms in the adjacent TBDMS groups is playing an important role. This is not surprising given that many silyl protecting groups have been developed with varying steric demands to allow selective removal of the less bulky derivatives.[19] Attempts to prepare **4a** from unprotected adenosine resulted in inseparable product mixtures. Future work towards **4** will begin with 2′,3′-bis(-*O*-DMT)-adenosine (vide infra).



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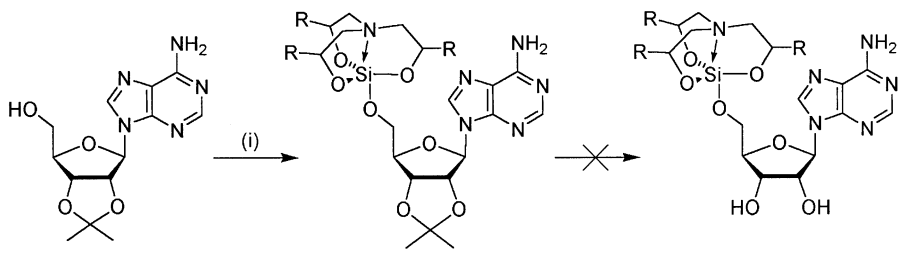
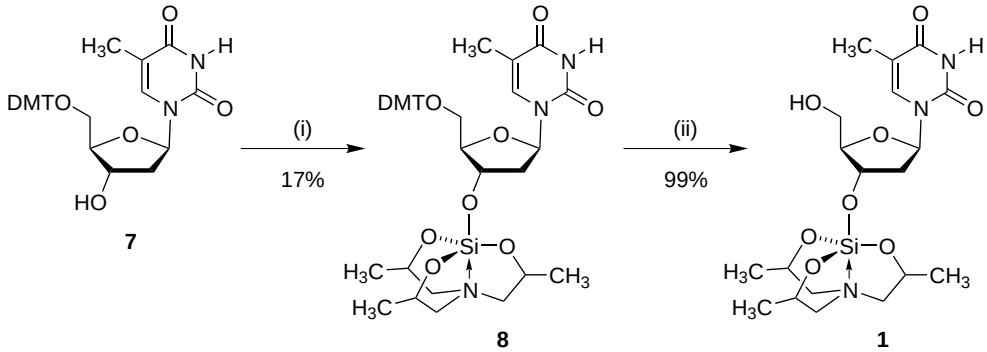
The synthesis of **1** began with the silatranylation of commercially available 5′-*O*-(4,4′-dimethoxytrityl)-thymidine (DMT-T, **7**). Thus, heating **7** with tetraethyl



2 **3a** R = H 47% **3b** R = CH_3 55% **4a** R = H **4b** R = CH_3

Scheme 1. (i) 5.0 equiv. $Si(OCH_2CH_3)_4$, 5.0 equiv. $N[CH_2CH(R)OH]_3$, 1.0 equiv. KOH, DMF, 100°C, 18–24 h.

‡ There are also no known ribose or deoxyribose siltrane derivatives. However, there is one report in the Russian literature of the syntheses of a protected glucose and mannose with a silatrane moiety attached: Stepanenko, B. N.; Kopkov, V. I.; Luzin, A. P. *Dokl. Akad. Nauk SSSR* **1977**, *235*, 969–971; *Chem. Abstr*. **1977**, *87*, 201926b. There is also a report in the Chinese literature of a silatrane tethered through an alkylurea linker to the nucleobase 5-fluorouracil (no sugar moiety is present in this compound): Ye, F.; Luo, X.; Zhuo, R. *Zhongguo Yaowu Huaxue Zazhi* **1995**, *5*, 245–249, 265; *Chem. Abstr*. **1996**, *125*, 10923s.



Scheme 2. (i) 3.0 equiv. $Si(OCH_2CH_3)_4$, 3.0 equiv. $N[CH_2CH(CH_3)OH]_3$, 0.5 equiv. KOH, DMF, 115°C, 18.5 h; (ii) 2.5% $CHCl_2CO_2H/CH_2Cl_2$, rt, 3.5 min.

orthosilicate, triisopropanolamine, and potassium hydroxide in DMF provided DMT-protected silatranyl-thymidine **8** in 17% yield (Scheme 2). The lower yield observed for this reaction compared to Scheme 1 is attributed to the fact that the silatrane group is now being attached to a secondary 3′-alcohol versus a primary 5′-alcohol. Deprotection of **8** was accomplished by treatment with 2.5% dichloroacetic acid[21] in methylene chloride affording **1** in nearly quantitative yield.[22] The overall yield from **7** to **1** was improved to 24% when crude **8** was not purified, but simply subjected to the deprotection conditions. In any case, the low yield of **1** is tolerable because the synthesis is only two steps and only relatively small quantities are required for medicinal testing.

We investigated the aqueous stability of **1** by monitoring its decomposition to thymidine by NMR and thin-layer chromatography (TLC). Thus, ^1H NMR spectra of a 30 mM solution of **1** in D_2O were taken periodically over a 12-day period and peak integrations of the 1′-deoxyribose proton for **1** and thymidine were compared. From this data the first half-life of **1** was found to be approximately 62 h. TLC confirmed that **1** and thymidine were the only nucleoside compounds present in solution.

In conclusion, silatranyl-nucleosides are introduced as a new class of TSAs for phosphoryl transfer reactions. These TSAs offer the flexibility of having the trigonal bipyramidal atom attached at either the 3′- or 5′-positions of a DNA or RNA nucleoside, or the 2′- and 3′-positions of an RNA nucleoside (Fig. 1). Silatranyl-nucleosides should prove to be useful tools for the study of phosphoryl transfer enzymes and ribozymes. They also possess potential antiviral or anticancer applications, for example **1** represents the first nucleoside TSA of reverse transcriptase and telomerase. The stereoselective syntheses of each of the four diastereomers of **1** using the appropriate enantiopure triisopropanolamine,[23] and of TSA atranes of the type shown in Fig. 1c are currently in progress. These results, as well as the results of medicinal testing of silatranyl-nucleosides at the NIH, will be reported in due course.

Acknowledgements

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22. Characterization data for compound **1** (mixture of four diastereomers): mp 159–160°C; ^{1}H NMR (300 MHz, D_2O) δ 7.48 (s, 1H, H6), 6.11 (t, $J_{1',2'}=6.6$ Hz, 1H, H1′), 4.36 (m, 1H, H3′), 4.07 (m, 1H, H1″), 3.95–3.88 (m, 3H, H1″, H4′), 3.71 (dd, $J_{5'a,5'b}=12.4$ Hz, $J_{4',5'a}=3.3$ Hz, 1H, H5′a), 3.62 (dd, $J_{5'a,5'b}=12.4$ Hz, $J_{4',5'b}=5.2$ Hz, 1H, H5′b), 3.18–2.77 (m, 4H, H2″), 2.42–2.31 (m, 2H, H2″), 2.22–2.10 (m, 2H, H2′), 1.73 (s, 3H, H7), 1.13–1.03 (m, 9H, H3″); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.13, 150.31, 136.89, 136.84, 110.33, 110.26, 86.00, 85.91, 65.62, 70.72, 70.38. 66.34, 66.26, 64.95, 64.92, 64.84, 64.78, 63.53, 62.37, 62.19, 61.67, 61.56, 60.89, 58.88, 58.83, 40.31, 23.50, 23.40, 20.46, 20.26, 20.23, 14.19, 14.12, 12.61; ^{29}Si NMR (59.6 MHz, $CDCl_3$) δ –96.12, –96.14, –96.21, –96.24; mass spec. (FAB) 458.2 (M^{+}+1, 14), 234.1 (100), 216.1 (silatrane, 66); HRMS calcd for $C_{19}H_{32}N_3O_8Si$: 458.1959. Found: 458.1958 (0.2 ppm difference).
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