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Nucleoside Syntheses, XXIII [1]

On the Mechanism of Nucleoside Synthesis

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During the silyl-Hilbert-Johnson nucleoside synthesis with Friedel-Crafts catalysts three processes occur simultanously:

A) The formation of the electrophilic sugar cation.
B) The σ-complex formation between the silylated base and the Friedel-Crafts catalyst and finally
C) the reaction of the electrophilic sugar cation with the silylated base to the nucleoside.

Mode and rate of σ-complex formation between the silylated base and the Friedel-Crafts catalysts were monitored by ^{13}C-NMR. The probable mechanism of nucleoside synthesis and the factors which influence course and yield of nucleoside synthesis are discussed.

Nucleosid-Synthesen, XXIII [1]
Über den Mechanismus der Nucleosid-Synthese

In der Silyl-Hilbert-Johnson-Reaktion geschehen drei Prozesse gleichzeitig:

A) Die Bildung des elektrophilen Zucker-Kations.
B) Die σ-Komplex-Bildung zwischen der silylierten Base und dem Friedel-Crafts-Katalysator.
C) Die Reaktion des elektrophilen Zucker-Kations mit der silylierten Base zum Nucleosid.

Art und Geschwindigkeit der σ-Komplex-Bildung zwischen der silylierten Base und den Friedel-Crafts-Katalysatoren wurden mit Hilfe der ^{13}C-NMR verfolgt. Der wahrscheinliche Mechanismus der Nucleosid-Synthese und die Faktoren, die Verlauf und Ausbeute der Nucleosid-Synthese beeinflussen, werden diskutiert.

1) Introduction

The synthesis of naturally occuring nucleosides from tRNA, of nucleoside antibiotics as well as of nucleoside analogues for antiviral and cancer therapy has been intensively investigated during the last 25 years [2,3]. The different mechanisms of all these synthetic methods were carefully reviewed and discussed in 1974 by *Fox* et al. [4].

Among the various synthetic methods [2,3] the reaction of silylated heterocyclic bases with peracylated sugars in the presence of Friedel-Crafts catalysts [5-10] has become a standard procedure which affords nucleosides routinely in high yields. It is only this reaction and its mechanism which is discussed in this paper, although the results of this investigation might also have some significance for some of the other methods.

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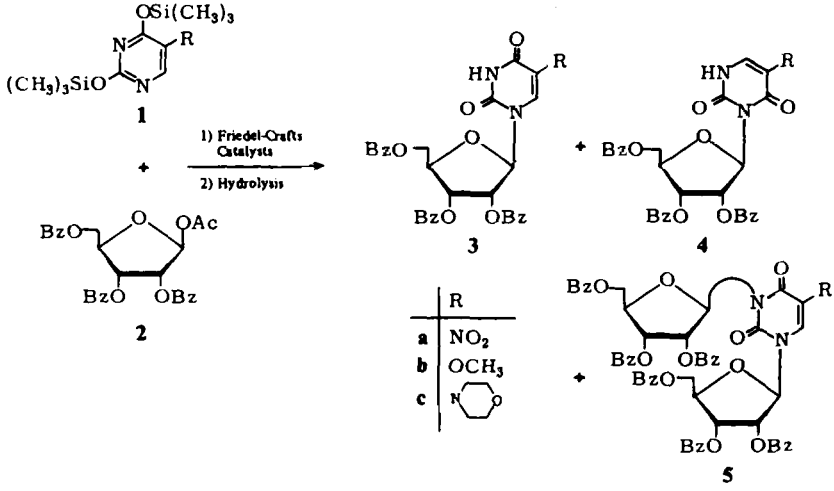
While investigating the scope of the Friedel-Crafts-catalyzed, silyl-Hilbert-Johnson reaction, we observed to our surprise that silylated 5-nitrouracil **1a** reacts with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and small amounts of $SnCl_4$ in 1,2-dichloroethane very rapidly to form the benzoylated 5-nitrouridine **3a** in practically quantitative yield[1,5a,5f]. In contrast to the silylated 5-nitrouracil **1a**, the more basic silylated 5-methoxyuracil **1b** and 5-morpholinouracil **1c** did not react at all with **2** in the presence of less than one equivalent of catalyst. Apparently one equivalent of $SnCl_4$ was inactivated or neutralized by complex formation with the silylated base and only an excess of $SnCl_4$ led to the formation of the electrophilic sugar cation and thus to nucleoside synthesis, however at a much slower rate than **1a**.

Besides the desired natural *N*-1-nucleosides **3b** and **3c** we obtained large amounts of the undesired *N*-3-nucleosides **4b** and **4c** as well as of the *N*-1,*N*-3-bis-nucleosides **5b** and **5c**[5f].



Replacing $SnCl_4$ by the weaker Friedel-Crafts catalysts $(CH_3)_3SiOSO_2CF_3$ or $(CH_3)_3SiOSO_2C_4F_9$[6,8] and switching from 1,2-dichloroethane to acetonitrile increased the yield of the natural *N*-1-nucleosides **3b** and **3c** to ca. 90% as the complex formation between the Friedel-Crafts catalysts and the silylated base is diminished in the more nucleophilic solvent acetonitrile.

How can these results, which are just opposite to the behavior of the "classical" Hilbert-Johnson reaction[11], be explained and any explanation be proven?

We believe that these seemingly contradictory results can be reconciled if we assume that during nucleoside synthesis three reversible processes occur:

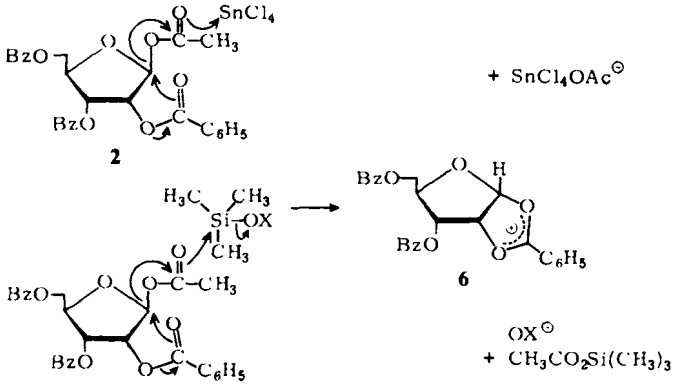
A) The reaction of the peracylated sugar with the Friedel-Crafts catalyst to give the electrophilic sugar cation.

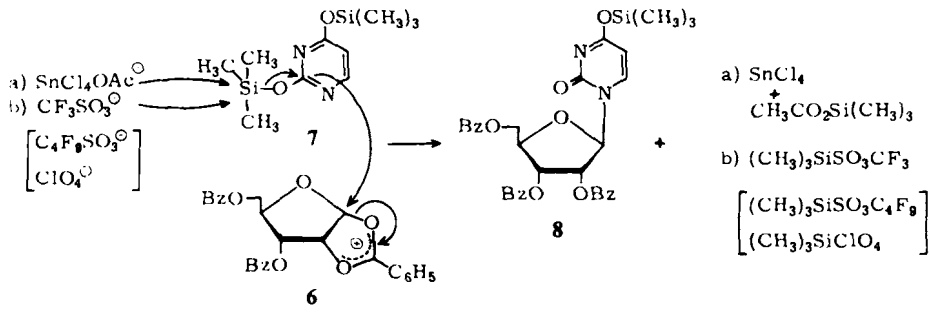
B) The competing formation of σ-complexes between the silylated bases and the Friedel-Crafts catalysts.

C) The reaction of the electrophilic sugar cation with the uncomplexed silylated base to form the nucleoside bond.

2) The Formation of the Sugar Cation

In the first process (A) the Friedel-Crafts catalysts $SnCl_4$ or $(CH_3)_3SiSO_3CF_3$, $(CH_3)_3SiSO_3C_4F_9$, $(CH_3)_3SiClO_4$ convert the peracylated sugar in the presence of a 2-α-acyloxy group as in 1-*O*-acetyl-2,3,5-*O*-benzoyl-β-D-ribofuranose (**2**) into the rather stable 1,2-acyloxonium salts like **6**[4,12] as the *only* electrophilic sugar moiety with concomitant formation of either $SnCl_4OAc^-$, $CF_3SO_3^-$, $C_4F_9SO_3^-$ or ClO_4^- and, in the case of the silyl catalysts, silylated acetic acid $(CH_3)_3SiOCOCH_3$.





only formation of β-nucleosides!

Under these reversible and thus thermodynamically controlled conditions, the nucleophilic silylated base **7** can *only* attack the stable sugar cation from the top (the β-side) to afford exlusively the β-nucleoside **8**.

Simultaneously the activated α-trimethylsilyl group on the heterocycle (in bases like 4-(trimethylsilyloxy)pyridine the γ-trimethylsilyl group!) reacts with the $SnCl_4OAc^-$ anion to regenerate $SnCl_4$ with formation of $(CH_3)_3SiOCOCH_3$ and with the triflate-, nonaflate- or perchlorate ions to regenerate the corresponding electrophilic silyl esters.

The only exceptions to the exclusive β-attack of the silylated base on the sugar cation can apparently occur when

1) the base contains strongly polarized or negatively charged groups which can associate with the positively charged α-side of the cation **6** as in silylated 2-nitroimidazole[13]

2) the sugar cation is not formed quantitatively as in the case of the 5-thio sugars[14] or when

3) the sugar cation contains polar groups like substituted amides or nitro groups on the α-side[15,16].

However, peracylated *N*-trifluoroacetyl or 2,4-dinitrophenylglucosamine in which the amino function is "neutralized" by a strongly electron attracting group gave more than 80% β-nucleoside with silylated uracil[17].

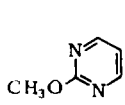
4) a stabilized cation can form *above* the plane of the sugar as a chloronium cation in 1-*O*-acetyl-3,4-*O*-benzoyl-2-chloro-2-deoxy-α-D-arabinose thus resulting exclusively in α-attack of the silylated base leading therefore *only* to α-nucleoside formation[18].

The reversibility of nucleoside formation and therefore its thermodynamic control is exemplified by some of our own work e. g. the rearrangement of persilylated *N*-3→*N*-1 nucleosides[8] as well as work by *Isono*[19] and *Eckstein*[20], and *Suhadolnik*[21] on the transglycosilylation of nucleosides in the presence of trimethylsilyl triflate or $SnCl_4$.

3) The σ-Complexes between Silylated Pyrimidines and Friedel-Crafts Catalysts

The second process (B), the formation of σ-complexes[22] between the silylated base and the Friedel-Crafts catalysts or Lewis acids which became evident by the reactions of different silylated 5-substituted uracils have hitherto been virtually ignored, although some π-complexes of pyrimidine and purine bases as well as nucleosides with mercury(II)-halides have been discussed[4].

Since σ-complexes become more stable with increasing basicity of heterocyclic bases, we have compiled pK_a values from the literature[23] for a series of methoxysubstituted pyridines and pyrimidines as well as the pK_a value of adenine. We believe that these pK_a values are pertinent to our work because *O*-methyl groups are chemically very similar to *O*-trimethylsilyl groups[24] and basicity data on *O*-silylated heterocycles are not as yet available.



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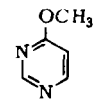

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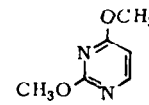

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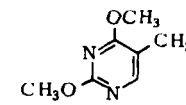

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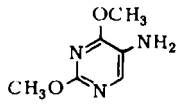

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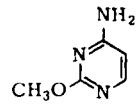

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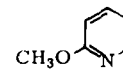

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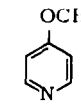


6,5

The increase in basicity turning from 2-methoxypyridine (pK_a = 3.2) to 4-methoxypyridine (pK_a = 6.5) is striking and explains why 4-(trimethylsilyloxy)pyridine forms nucleosides only under more stringent conditions[5d,8].

The basicity of 2,4-dimethoxypyrimidine (pK_a = 3.1) is increased to pK_a = 3.63 on introduction of an electron donating methyl group. Unfortunately, the pK_a values of 2,4,5-trimethoxypyrimidine and 5-amino-2,4-dimethoxypyrimidine as models for silylated 5-methoxy- and 5-morpholinouracil have not as yet been described. 4-Amino-2-methoxypyrimidine (pK_a = 5.3) is a good model for silylated cytosine. Adenosine (pK_a = 4.12) will be referred to later.

To elucidate the nature of these σ-complexes[25] between the silylated bases and $SnCl_4$ or $(CH_3)_3SiSO_3CF_3$, we have measured the ^{13}C-NMR spectra of different mixtures of these bases with $SnCl_4$ and $(CH_3)_3SiSO_3CF_3$ in $CDCl_3$ using $(CH_3)_4Si$ as internal standard[26]. As described in the literature[27], protonization of pyridine as the most simple case of a σ-complex results in a pronounced upfield of the α-C atoms adjacent to the nitrogen atom.

We have found analogously that the σ-complexes of silylated 2-pyridone (Fig. 1) with 2 equivalents of $(CH_3)_3SiSO_3CF_3$ and $SnCl_4$ exhibit likewise an upfield shift of the 2- and 6-carbon atoms adjacent to the nitrogen. As can be readily seen, $SnCl_4$ as the stronger Friedel-Crafts catalyst, leads to higher concentrations of the σ-complex in the equilibrium and thus to more pronounced upfield shifts of the 2- and 6-carbon atoms as with $(CH_3)_3SiSO_3CF_3$[28].

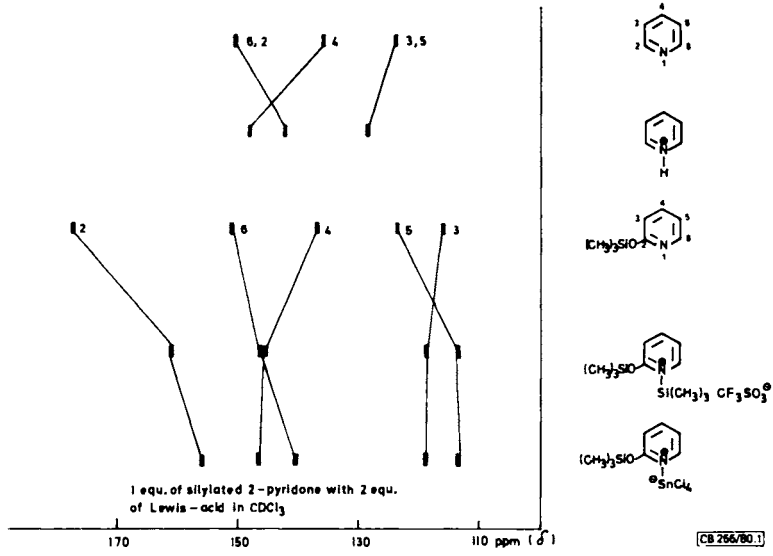


Fig. 1. ^{13}C-NMR upfield shifts of pyridine and silylated 2-pyridone on σ-complex formation applying 2 equivalents of $(CH_3)_3SiSO_3CF_3$ or $SnCl_4$

Turning now to silylated uracils, we measured the ^{13}C-NMR spectra of silylated 5-methoxyuracil with 0.25 equivalents of $SnCl_4$ and $(CH_3)_3SiSO_3CF_3$ (Fig. 2).

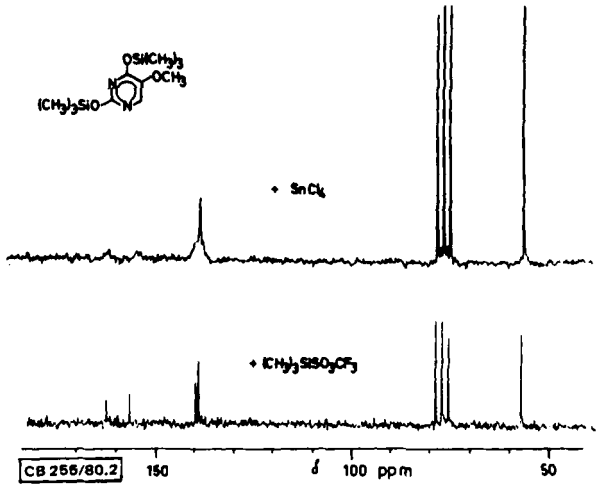


Fig. 2. ^{13}C-NMR *spectra of silylated 5-methoxyuracil employing 0.25 equivalents of* $SnCl_4$ *and* $(CH_3)_3SiSO_3CF_3$

Whereas the sharp C-6 signal at δ = 139 for the $(CH_3)_3SO_3CF_3$ σ-complex indicates the rapid exchange between the σ-complex and the free silylated 5-methoxyuracil and $(CH_3)_3SiSO_3CF_3$, the rather broad C-6 signal in the case of the $SnCl_4$ complex points to a much tighter binding and consequently a much slower exchange on the NMR-timescale between the N-1 of silylated base, the center of the highest electron density and the stronger Friedel-Crafts catalyst $SnCl_4$.

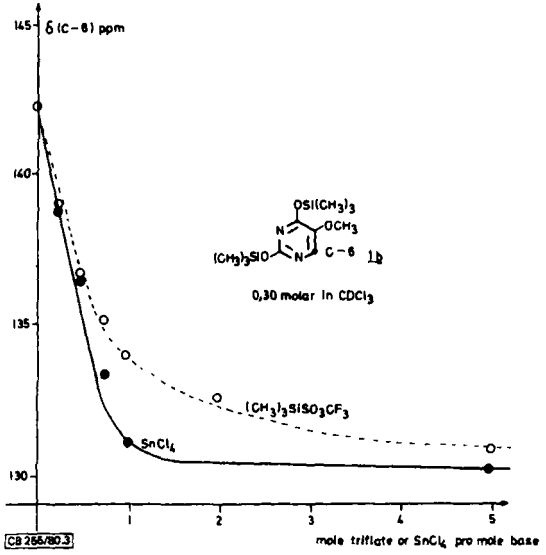


Fig. 3. Influence of the concentration of $(CH_3)_3SiSO_3CF_3$ or $SnCl_4$ on the ^{13}C-NMR upfield shift of C-6 in silylated 5-methoxyuracil

This tighter binding of $SnCl_4$ is demonstrated (Fig. 3) if different concentrations of both Friedel-Crafts catalysts are plotted against the ^{13}C-NMR upfield shifts of C-6 in silylated 5-methoxyuracil. Whereas one equivalent of $SnCl_4$ leads already to a practically complete upfield shift of the C-6 atom, with the weaker Friedel-Crafts catalyst $(CH_3)_3SiSO_3CF_3$ nearly 5 equivalents are needed in the equilibrium to achieve a maximal upfield shift of the C-6 signal.

Among the different C-atoms of silylated 5-methoxyuracil, only the C-6 signal is shifted markedly upfield on addition of increasing amounts of $(CH_3)_3SiSO_3CF_3$ as depicted on Fig. 4.

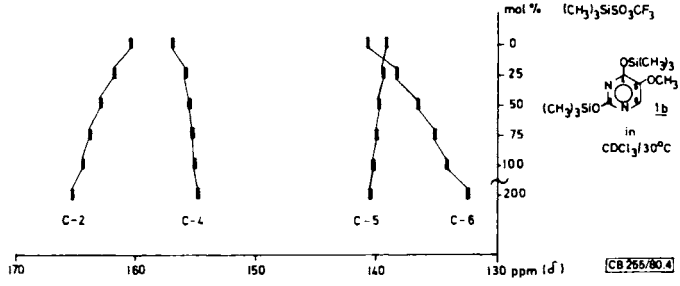


Fig. 4. ^{13}C-NMR shifts of the ring C-atoms in silylated 5-methoxyuracil as a function of increasing amounts of $(CH_3)_3SiSO_3CF_3$

In contrast to the upfield shift of C-2 in silylated 2-pyridone, the signal of C-2 in **1b**, which is located between two nitrogen atoms, is shifted downfield. This effect cannot as yet be explained because σ-complex formation at N-3 should also cause an upfield shift of the C-2 atoms.

Compared to silylated 5-methoxyuracil, very similar results were obtained with other silylated 5- and 6-mono or 5,6-disubstituted uracils with either $SnCl_4$ or $(CH_3)_3$-$SiSO_3CF_3$ permitting the same conclusions as with **1b**.

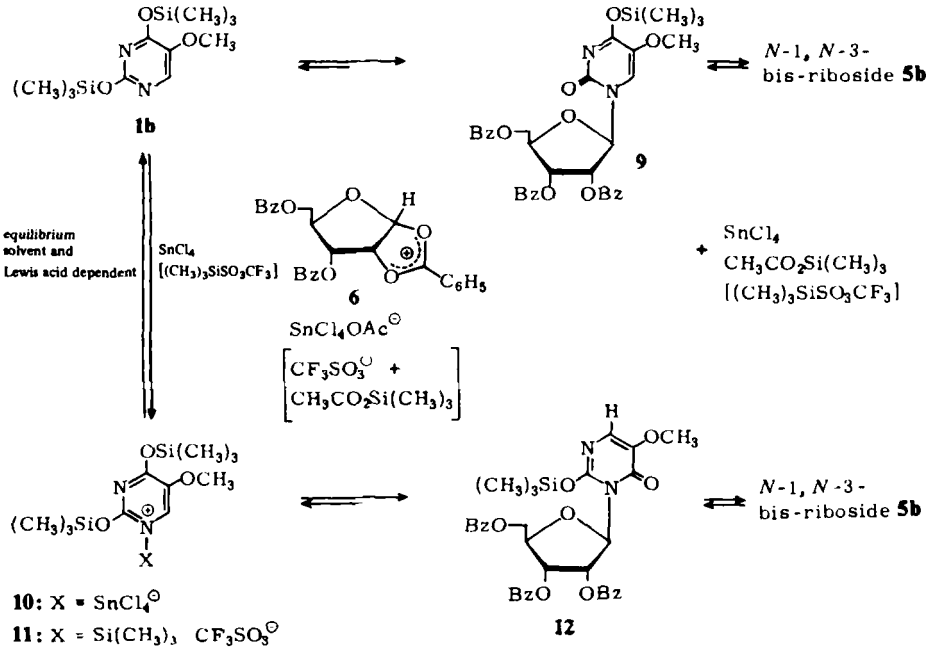
Recently, *Kaufmann*[29] observed similar σ-complexes of nitrogen heterocycles during the Friedel-Crafts acylation of 2-thienylpyridine with acetyl chloride/$SnCl_4$. Due to formation of the rather stable σ-complex at the pyridine nitrogen as a deactivated intermediate, the Friedel-Crafts acylation compared to thiophene or 2,2'-bithiophene is slowed down considerably and proceeds only if an additional equivalent of acetyl chloride is employed.

There is also a close analogy to "normal" Friedel-Crafts[30] reactions as was pointed out by us earlier[5]. Due to strong σ-complex formation, basic aromatic amines like *N,N*-dimethylaniline undergo Friedel-Crafts acylations only under very special conditions in the presence of $AlCl_3$[31] but apparently not with BF_3-etherate[32]. However, *N,N*-dimethylaniline is readily transformed into the *p*-trifluoroacetyl derivative by trifluoroacetic anhydride in boiling ether[33], since trifluoroacetic acid is a much weaker acid compared to $AlCl_3$ or BF_3-etherate.

In a very interesting recent study, *Buckley* and *Rapoport* have investigated the influence of the amount of Friedel-Crafts catalyst on the acylation of alkyl aryl ethers and provided proof for strong σ-complex formation between the ether oxygen and $AlBr_3$[34].

4) Mechanism of Pyrimidine Nucleoside Synthesis

Taking all these results into account, the mechanism of the Friedel-Crafts catalyzed silyl-Hilbert-Johnson synthesis of pyrimidine nucleosides seems to be quite simple as exemplified for the reactions of silylated 5-methoxyuracil **1b** in the presence of $SnCl_4$ or $(CH_3)_3SiSO_3CF_3$.



The reaction of **1b**, **6** and $SnCl_4$ gives an equilibrium in which the σ-complex **10** between N-1 of **1b** (the center of highest electron density) predominates in unpolar solvents like $CDCl_3$ or 1,2-dichloroethane. What apparently happens is:

a) Only the free silylated base **1b** seems to react with the 1,2-acyloxonium ion **6** to form the 4-*O*-trimethylsilylated *O*-benzoylated 5-methoxyuridine **9**. Since there is only a rather small concentration of the free silylated base **1b** in the equilibrium, this reaction is rather slow.

b) The predominating σ-complex **10** between $SnCl_4$ and N-1 is in equilibrium with the dissociated form in which the $SnCl_4$ stays close to N-1. And it is this slightly dissociated form, in which the N-1 is still blocked, the N-3 however is available, that reacts with **6** to form the silylated *O*-benzoylated *N*-3-nucleoside **12**.

c) Both the silylated *O*-benzoylated *N*-1- (**9**) and *N*-3- (**12**) nucleosides can react further with the sugar cation **6** to give the *O*-benzoylated *N*-1,*N*-3-bis-riboside **5b**[5f,8].

As already emphasized, the ratio of the free and complexed form is dependent on the polarity of the solvent. The more polar nucleophilic solvent acetonitrile[35,36] directly competes with the silylated base for the electrophile. Consequently in acetonitrile more

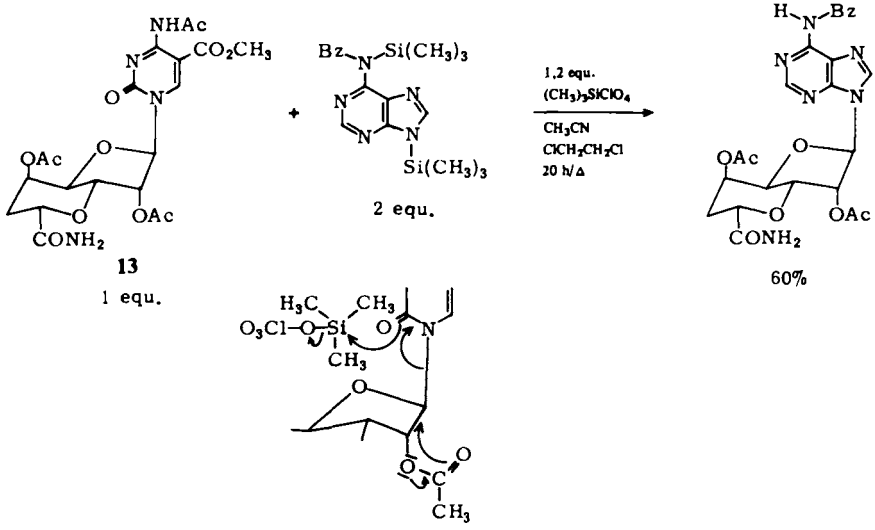
silylated free base **1b** is present and thus more of the desired natural *N*-1-nucleoside is formed.

The corresponding reaction with $(CH_3)_3SiSO_3CF_3$ is analogous.

However, since $(CH_3)_3SiSO_3CF_3$ is a much weaker Lewis acid than $SnCl_4$ (cf. Fig. 3), less σ-complex **11** is formed in the equilibrium and therefore much more free base **1b** is present and more silylated *N*-1-nucleoside **9** is obtained. Again, both the silylated *N*-1- as well as the *N*-3-nucleoside can react with **6** to afford the *N*-1,*N*-3-bis-riboside **5b**. As can be readily seen from our rearrangement experiments with silylated *N*-3-nucleosides as well as with *N*-1,*N*-3-bis-ribosides[8], there is much experimental evidence for the depicted equilibria between the different reaction products.

Even more striking are the already mentioned experiments of several groups with transglycosidylations in the presence of $(CH_3)_3SiClO_4$[19] $(CH_3)_3SiSO_3CF_3$[20] as well as with $SnCl_4$[21]. The probable mechanism of such a transformation of a pyrimidine nucleoside antibiotic (**13**) into a purine nucleoside[19] is shown in the following scheme.

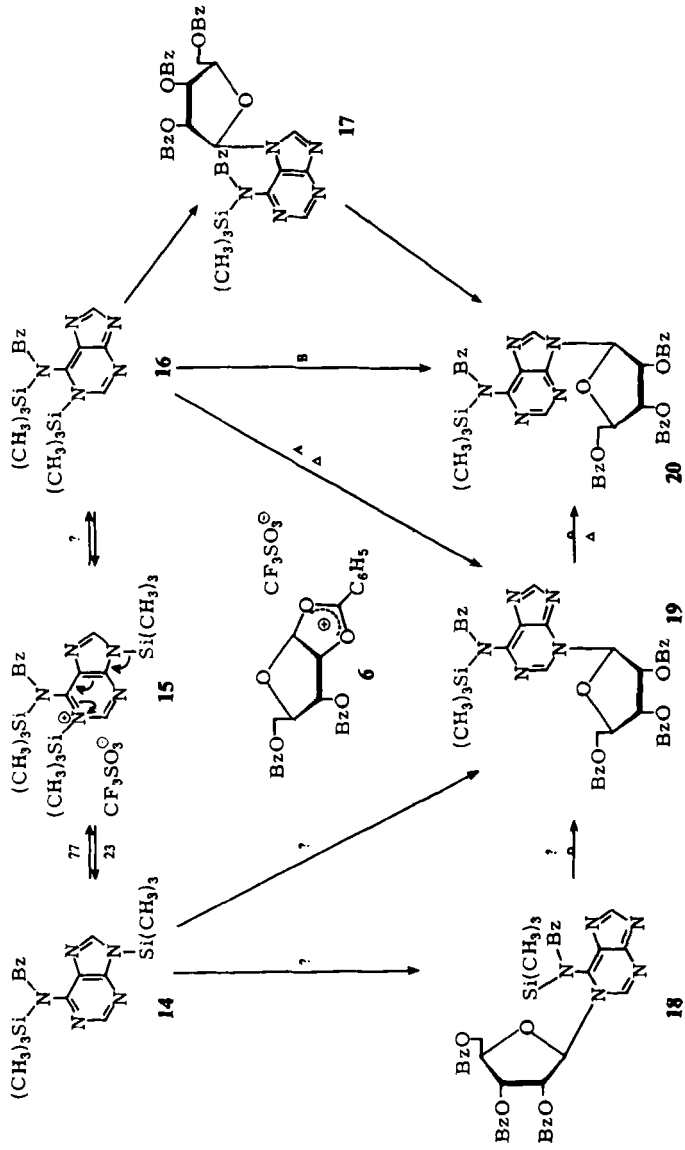
$(CH_3)_3SiClO_4$–Catalyzed Base–Transfer[19]



Applying our methods and approach[1] to the synthesis of the antiviral antibiotic 5,6-dihydro-5-azathymidine, *Wierenga* and *Skulnick*[37] recently investigated similar σ-complexes between the rather basic silylated 5,6-dihydro-5-azathymine and two equivalents of $SnCl_4$ by ^{13}C-NMR.

5) The Mechanism of Purine Nucleosides Synthesis

Turning to the reaction of silylated purine with peracylated sugars in the presence of $SnCl_4$[9,10] or $(CH_3)_3SiSO_3CF_3$[6–8] to afford purine nucleosides, we have investigated the σ-complex formation between silylated N^6-benzoyladenine **14** (cf. Fig. 5) and $(CH_3)_3SiSO_3CF_3$.



On measuring the ^{13}C-NMR spectra of **14** in the presence of increasing amounts of $(CH_3)_3SiSO_3CF_3$, the signal of the C-2 atom is practically not affected. Only the C-8 atom shows a pronounced downfield shift, as was described for N-1-protonated purines[38]. This points to σ-complex formation of the trimethylsilyl group at N-1 in **15**, the center of highest electron density.

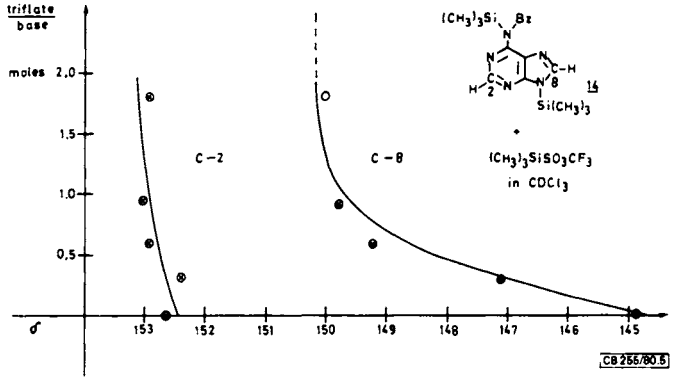


Fig. 5. ^{13}C-NMR shifts of the 2- and 8-C atoms of silylated N^6-benzoyladenine as function of increasing amounts of $(CH_3)_3SiSO_3CF_3$

We assume that the σ-complex **15** is in equilibrium with the *N*-1-silyl compound **16**. **16** should then react readily with the sugar cation **6** (path A) to give the silylated *N*-3-nucleoside **19** as a kinetically-controlled intermediate which can be isolated[10] after a short reaction time or rearranged subsequently to the thermodynamically most stable silylated natural *N*-9-nucleoside[8] **20**. Alternatively, **16** could also react directly with **6** to form the desired silylated *N*-9-nucleoside **20** (path B).

A further possible kinetic intermediate could be the *N*-1-nucleoside **18** which probably rearranges readily via **19** to **20** as well as the *N*-7-riboside **17**. However, on prolonged reaction time practically all the intermediates in the reaction between **14** and **6** are eventually rearranged to **20** to give, after saponification of the benzoate groups, an 81% yield of free adenosine[8], the thermodynamically-controlled end product.

Itoh[39] investigated the reaction between persilylated adenine and 1,2,3,4-tetra-*O*-acetyl-β-D-ribofuranose in the presence of $SnCl_4$ in acetonitrile for 20 h at room temperature and isolated, in addition to the 2′,3′,5′-tri-*O*-acetyladenosine, the corresponding β- and α-*N*-7-ribosides.

6) Conclusions

Although a number of questions are still open, we can now give plausible explanations, why and under what conditions the unnatural *N*-3- and *N*-1,*N*-3-nucleosides are formed in the uracil series as well as *N*-3- or *N*-7-nucleosides in the purine series. We can thus recommend optimal combinations of Friedel-Crafts catalysts and solvents for the different silylated bases and sugars to afford the desired *N*-1- (or *N*-9-)nucleosides in high yields and at an optimal reaction rate[8].

Experimental

A) *Solutions:* The $CDCl_3$ was distilled over P_2O_5 and reagents $(CH_3)_3SiSO_3CF_3$ (bp. 142 – 143 °C)[28] and the silylated 2-pyridone as well as silylated 5-methoxyuracil were redistilled prior to their use. The different solutions were prepared in a dry box with careful exclusion of humidity.

B) *NMR-Measurements:* The ^{13}C-NMR spectra of freshly prepared solutions were recorded on a Varian CFT-20 instrument at 30 °C with $CDCl_3$ as internal reference ($CDCl_3$ = 77.2 ppm).

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