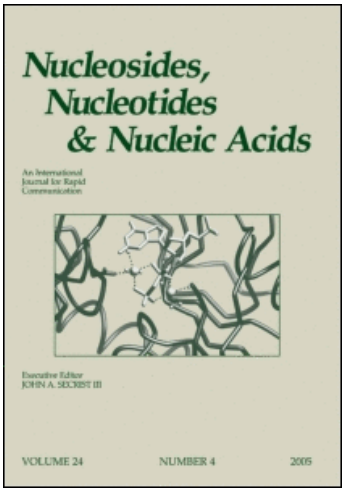

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Transglycosylation Reactions of Purine Nucleosides. A Review

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REVIEW

TRANSGLYCOSYLATION REACTIONS OF PURINE NUCLEOSIDES. A REVIEW +

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ABSTRACT: Mechanism, regio- and stereoselectivity, reversibility as well as some practical applications of transglycosylation reactions in the chemistry of purine nucleosides are reviewed. There are two main reaction pathways of glycosylation and transglycosylation in the purine series: i) the better known and generally accepted 3→9 sequence of adenine and its derivatives ii) the equally conceivable 7⇄9 mechanism for guanine and other 6-oxopurines, which is hereby supported by the author's study.

1. Introduction: Glycosyl Migration Reactions in Nucleoside Chemistry

Glycosyl migration reactions play an important role in nucleoside chemistry. All reactions of this type are generally called "transglycosylation". The reaction was observed during chemical synthesis of pyrimidine and purine nucleosides.[1-3] Migration of the glycosyl moiety in the pyrimidine series was originally suggested by Ulbricht in 1962,[4] whereas the first example of transglycosylation in the purine series was given by Shimizu and Miyaki in 1966.[5]

It has been well established that in most cases glycosylation of heterocyclic bases proceeds in two steps.[1] In the first step, direct reaction of a protected heterocyclic base and an appropriate sugar component results in the formation of a kinetic glycosylation product, which, in the second step of synthesis, undergoes transglycosylation to the most stable thermodynamic product. Time and temperature of glycosylation as well as the choice of catalysts, solvents and protecting groups may affect the ratio of the obtained regioisomers of the product.

It has been shown that transglycosylation of purine nucleosides represents an intermolecular reaction and is catalyzed by Lewis acids such as $Hg(CN)_2$, $HgBr_2$, $HgCl_2$.[5] On the

+ This paper is dedicated to Prof. Yoshihisa Mizuno on the occasion of his 75th birthday.

other hand, it has also been demonstrated that some glycosyl exchange reactions in the purine series take place even in the absence of catalyst, when reactions are performed at elevated temperatures ("thermal transglycosylation").[6-8]

Transglycosylation reaction may involve transfer of the sugar moiety from one nitrogen atom to another within the same heterocyclic base (intermolecular transglycosylation). In some cases, when the substrate used and the resulting product are of similar thermodynamic stability, glycosyl migration reaction may be reversible and both regioisomers remain in a dynamic equilibrium; otherwise transglycosylation represents a practically irreversible process. It should be underlined at this point, that the term "intramolecular" refers to the observed effects of glycosyl migration reaction, not to its mechanism.

This type of transglycosylation may be well illustrated by rearrangement of 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-N^6-benzoyladenine to the respective 9-ribosylated regioisomer (irreversible 3→9 transglycosylation).[5d] Intramolecular transglycosylation has found some practical applications in isomerization of fully protected nucleosides. For example, 7-(2-acetoxyethoxy)methyl-N^2-acetylguanine, a side product in synthesis of the antiherpetic drug acyclovir, may be easily converted to its biologically active 9-substituted regioisomer (reversible 7⇄9 transglycosylation).[6-8]

The intermolecular transglycosylation, originally developed by Shimizu and Miyaki,[5b] is an exchange process in which the glycosyl portion is transferred from one heterocyclic base to another. In this useful synthetic approach, a starting nucleoside serves as the donor of the glycosyl residue, when an appropriate heterocyclic base is its acceptor:

nucleoside (sugar donor)	+	heterocyclic base (sugar acceptor)	→	new nucleoside

This approach has been often used for the synthesis of new nucleosides.[9-13] For example, heating of fully acetylated cytidine with an excess of N^2-acetylguanine in the presence of mercuric bromide gave a mixture of both 7- and 9-regioisomers of tetraacetylguanosine.[9] The yield of intermolecular transglycosylation can be considerably improved when silylated components and more effective catalysts (e.g. trimethylsilyl trifluoromethanesulfonate) are applied.

A counter approach to the synthesis of nucleosides *via* exchange of glycosyl moiety is called "transpurination".[12] This method may be applied not only in the purine series, but also

for glycosylation of other heterocyclic compounds.[14] In the transpurination method, the starting nucleoside plays the role of a base donor, while a fully protected sugar component is the base acceptor:

nucleoside (base donor)	+	sugar component (base acceptor)	→	new nucleoside

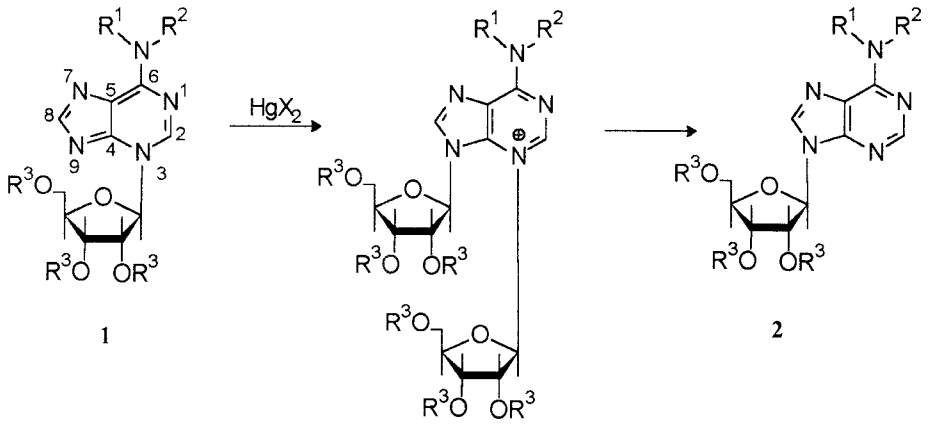
The transpurination reactions was for the first time observed by Lichtenthaler and Kitahara,[15] who described migration of hypoxanthine from ribose to glucose when 2',3'-O-isopropylideneinosine reacted with 1-α-bromo-2,3,4,6-tetra-O-acetylglucose. More recently, this reaction has found application in the synthesis of antiviral acyclonucleosides from guanosine.[6,8]

The exchange procedures of nucleoside synthesis, intermolecular transglycosylation and transpurination are sometimes called "transnucleosidation methods". Both reactions should find numerous applications in the synthesis of biologically active nucleoside analogs, because in these methods inexpensive and easily accessible natural nucleosides may be used as starting materials.

2. 3→9 Transglycosylation

As has been shown by Shimizu and Miyaki,[5] direct glycosylation of N^6-benzoyladenine or N^6,N^6-dimethyladenine by the mercury procedure leads to 3-glycosylated adenines (protected derivatives of isoadenosine in the ribo series, general structure **1**). When heated in the presence of Lewis acids, the kinetic glycosylation products of this type undergo rearrangement to adenosine derivatives, i.e. to 9-glycosylated compounds (general structure **2**).[5]

A plausible mechanism for the formation of 3-glycosylated derivatives of adenine by the mercury procedure and for the subsequent transglycosylation to the 9-substituted products has been proposed and discussed in details by Watanabe, Hollenberg and Fox.[1] Thus, initial glycosylation at position 3 results in an electronic imbalance within the purine system, and this imbalance may be considered as a driving force for the transglycosylation reaction. In the presence of sugar acyloxonium cations, generated either from starting sugar components (nucleoside synthesis) or resulting from dissociation of the N-glycosyl bond in **1** (trans-glycosylation of isolated compounds catalyzed by acids), the N9 atom attacks C1 of the sugar to form a 3,9-diglycosyladenine quaternary salt (**3**). The intermediate **3** is unstable both for



1 3 2

R^1 = H, CH_3, C_6H_5CO R^2 = H, CH_3

R^3 = C_6H_5CO, CH_3CO X = Cl, Br, CN

SCHEME 1

electronic and steric reasons, and cleavage of the former N-glycosyl bond (N3-C1') leads to 9-glycosyladenine (**2**) with the liberation of acyloxonium ion.

The mechanism of 3→9 transglycosylation in the adenine series seems to be well documented. Its intermolecular character has been definitely proven by using radiolabelled derivatives of adenine.[5] Furthermore, the effect of substituents in the heterocyclic portion is in line with the proposed mechanism. The presence of electron-donating groups in positions 2 and 6 reduces the transglycosylation rate, whereas electron-withdrawing substituents in these positions facilitate conversion of **1** to **2**. Thus, tri-O-benzoylisoadenosine (**1**; R^1=R^2=H) and its N^6,N^6-dimethyl derivative (**1**; R^1=R^2=CH_3) undergo 3→9 transglycosylation less readily than N^6-benzoyl-tri-O-benzoylisoadenosine (**1**; R^1=C_6H_5CO, R^2=H).[5] Similarly, introduction of electron-withdrawing groups in position 8 lowers the electron density at N9, which considerably shifts the transglycosylation equilibrium towards isoadenosine derivatives, as it has been shown by Tindall et al. in the case of 8-bromoadenine.[16]

The above presented explanation for 3→9 transglycosylation mechanism using the mercury procedure is equally convincing for the nitromethane - $Hg(CN)_2$ procedure, for the

silyl modification of the Hilbert-Johnson method as well as for the fusion reaction.[1] Numerous examples for conversion of this type in the series of adenine and its analogs are presented in the literature.[1-3]

3→9 Transglycosylation apparently represents an irreversible process: in general, 9-glycosylated products of type **2** are thermodynamically more stable then their 3-glycosylated regioisomers (**1**). For example, N^6-acetyl-2',3',5'-tri-O-acetyladenosine does not undergo thermal isomerization or transpurination with 2-acetoxyethyl acetoxymethyl ether,[8] which is a further evidence that 9-glycosylated adenine is far more stable than any of its possible regioisomers. However, as mentioned above, the 3→9 transglycosylation equilibrium may be shifted towards isoadenosine derivatives due to the effects of substituents.

From the stereochemical point of view, 3→9 transglycosylation of adenine derivatives generally proceeds in line with Baker's rule,[17] i.e. derivatives of 3-(tri-O-acyl-β-D-ribofuranosyl)adenine (**1**) undergo transglycosylation to the respective β-anomers (**2**). Exclusive formation of β-nucleosides can be rationalized by anchimeric assistance of the 2'-acyloxy group and subsequent formation of sugar acyloxonium cations.[1] In some cases, however, substantial amounts of α-glycosides have been detected in the final reaction mixtures, which may be attributed to the reaction conditions. Thus, the ratio of α/β anomers depends on the synthetic method applied, the nature of catalysts, and solvent polarity.[3]

Nevertheless, it is also quite possible that 3→9 transglycosylation in the 2'-acyloxy series always proceeds stereoselectively, with retention of the β-configuration. The observed formation of 1',2'-*cis*-nucleosides can be explained as a result of a "*post*-migration" anomerization, i.e. a 1',2'-*trans*-nucleoside, directly resulted from 3→9 transglycosylation, undergoes then anomerization in the presence of the catalyst. A similar anomerization after transglycosylation, catalyzed by p-toluenesulfonic acid, was recently reported in the β-D-ribofuranosylindazole series.[14]

Apparently 3→9 transglycosylation reactions of adenine derivatives has not been studied in detail for isolated compounds since the pioneering work of Shimizu and Miyaki.[5]

3. 7⇄9 Transglycosylation

As presented above, initial glycosylation at position 3 and subsequent 3→9 transglycosylation have been satisfactorily proven in the adenine series. The 3→9 sequence of

glycosylation and transglycosylation reactions has also been proposed for purines other than adenine, including 6-oxopurines, e.g. guanine and hypoxanthine.[1,5] Ribosylation of guanine, however, very often results in the formation of both 7- and 9-substituted regioisomers.[18,19] Consequently, in the case of guanine, the general mechanism for glycosylation of purines[1,5] assumes the following sequence of events: i) initial glycosylation at N3; ii) formation of either 3,9- or 3,7-disubstituted intermediates; iii) decomposition of the latter compounds leading to the mixture of 7- and 9-regioisomers. The only experimental evidence that supports the discussed mechanism came from benzylation of N^2-acetylguanine, what reportedly gave trace amounts of 3-benzyl compound and some bigger amounts of its 7- and 9-isomers (yields 0.2, 22 and 16%, respectively).[5d] On heating in dimethylformamide, 3-benzyl-N^2-acetylguanine hydro-bromide underwent rearrangement to 7- and 9-substituted products. It seems to be very doubtful that this experiment proves the participation of the N3 atom in glycosylation and transglycosylation of guanine.

More recently, it has been shown that a regiocontrolled synthesis of 7-glycosyl and 9-glycosyl derivatives of guanine could be accomplished under appropriate conditions.[20] As it was reported, kinetically controlled conditions in the glycosylation of trisilylated N^2-acetyl-guanine were in favor of the 7-isomer, whereas application of 2-O-benzoylated sugar components and thermodynamically controlled reaction led mainly to the 9-glycosylguanine. Any compound of the putative 3-glycosyl structure was not detected in that study.

Furthermore, Dudycz and Wright[21] demonstrated that ribosylation of persilylated 2-bromohypoxanthine, N^2-acetylguanine and N^2-(*p*-n-butylphenyl)guanine gave the respective 7-ribonucleosides as single products after a short reaction time. These kinetic products of glycosylation underwent then rearrangement to more stable 9-isomers, which could be finally obtained in the yield exceeding 70%. More importantly, they isolated the corresponding 7,9-diribofuranosylpurines as unstable minor products, which decomposed into the mixtures of 7- and 9-ribosides. The authors postulated that the diribosides were reaction intermediates in 7⇄9 transglycosylation of 6-oxopurines. However, initial 3-glycosylation could be still possible and "faster N-3 → N-7 isomerization could account for this observation".

Other details about glycosyl migration reactions in the purine series came from the study of thermal transglycosylation. As has been shown in our laboratory,[6-8] some fully protected 6-oxopurine ribo- and acyclonucleosides readily undergo isomerization to a mixture of 7- and 9-nucleosides when heated at a temperature exceeding 190°C for a short period of time (5-10

min). The reaction takes place in the absence of catalysts, when starting nucleosides are melted without solvents (SCHEME 2).

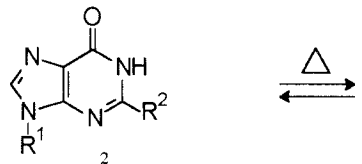
In the case of the 6-oxopurine nucleosides shown in SCHEME 2 transglycosylation is reversible: no matter which isomer (9-isomers: compounds **4**, **6**, **8**, or 7-isomers: **5**, 7, **9**) is used as a substrate, after a few minutes of heating both isomers are in a dynamic equilibrium.[7] This equilibrium is slightly shifted towards 9-isomers, which means that in the series of 6-oxopurines 7-nucleosides are "more kinetic products", whereas 9-isomers are "more thermodynamic products". However, as can be evaluated from this study, their thermodynamic stabilities are rather similar.

Steric or electronic factors may shift the equilibrium of transglycosylation (SCHEME 3). For example, the tetraacetyl derivative of 3-methylguanosine (**10**)[22] undergoes a quantitative conversion to the corresponding 7-ribo compound (**11**) at 230° for 3 min, but a reverse process is not possible.[23] A similar irreversible 9→7 transglycosylation has been reported in the case of (2-acetoxyethoxy)methyl analog of the hypermodified nucleoside wyosine (**12a** → **13a**).[24] It is worth while to note that the observed shift of the thermal isomerization equilibrium towards 7-isomers is in line with the stability of the N7-glycosyl bonds versus the exceptional lability of 9-glycosylated derivatives in the series of 3-alkylpurine nucleosides.[25]

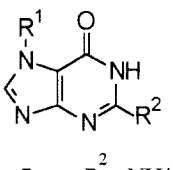
Thermal 7⇄9 transglycosylation is apparently an intermolecular reaction. Four pairs of the respective 9- and 7-regioisomers (**4a, 5a**; **4c, 5c**; **8a, 9a**; **8c, 9c**) were obtained when an equimolar mixture of diacetylacyclovir (**4c**) and triacetyl 5-methyl-4-demethylwyosine (**8a**)[26] was heated at 230° for 10 min.[27]

Interestingly, the discussed thermal glycosyl migration proceeds smoothly in both ribo- and acyclonucleoside series. The formation of sugar acyloxonium cations, as anticipated in the case of 2'-O-acyloxyfuranose derivatives (compounds **a, b** in SCHEME 2), does not considerably change the reaction rate in comparison to that of acyclonucleosides (compounds **c, d, e**). In the latter case, generation of carboxonium ions rather than acyloxonium ions should be expected.[1]

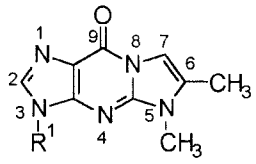
The discussed thermal 7⇄9 isomerization has found application as a convenient synthetic method in the chemistry of 6-oxopurines. It may be useful for conversion of isomers when direct glycosylation results in a mixture of 7- and 9-regioisomers, and only one of them is desirable. Similarly, naturally occurring 9-nucleosides can be readily transformed into the respective 7-isomers. This simple method is especially convenient in the synthesis of



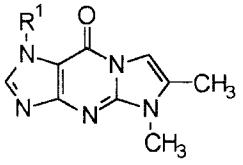
4 a-e; R^2 = NHAc
6 a, c; R^2 = H



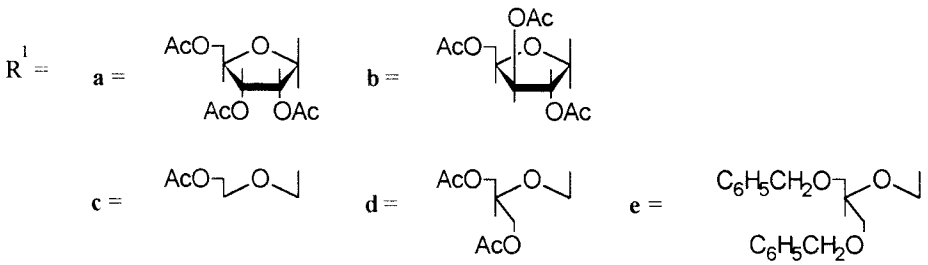
5 a-e; R^2 = NHAc
7 a, c; R^2 = H



8 a, c



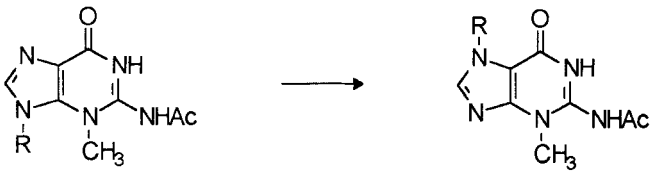
9 a, c



SCHEME 2

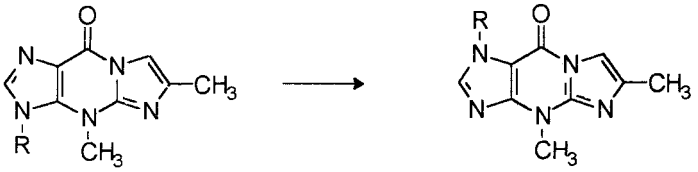
biologically active acyclonucleosides.[6,8,28] However, the following limitations of this approach must be taken into account: i) the yield of the required isomer is limited by the isomeric ratio at the equilibrium state; ii) the melting point of the substrate should not exceed 230-240°; iii) only one kind of acyl protecting groups should be used in order to avoid undesirable transacylation.[7]

In certain cases some minor products of the thermal 7⇄9 transglycosylation may be detected in the reaction mixture, like the corresponding protected purine base resulting from a thermal cleavage of the N-glycosyl linkage and, in the ribo series, small amounts of α-isomers. The degree of anomerization depends on the nature and purity of nucleosides subjected to transglycosylation, and is generally similar to that observed in glycosylation by the fusion



10 **11**

R = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl



12 a, b **13 a, b**

a : R= (2-acetoxyethoxy)methyl
b : R = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl

SCHEME 3

method.[29,30] Again, anomerization in this case may be explained as a *post*-migration event (*vide ante*).

Obviously, 7⇄9 transglycosylation can also be accomplished at lower temperatures in solvents, but requires the presence of a catalyst. For example, a reversible conversion of 9-(tri-O-benzoyl-β-D-ribofuranosyl)-N^2-acetylguanine into its 7-isomer was performed by Shimizu and Miyaki in the presence of $HgBr_2$ at 160°.[5d] Considerably milder conditions, i.e. $AlCl_3$ in dichloromethane at room temperature, were applied for an irreversible 3→9 transglycosylation (9→7 in the purine numeration system) of tri-O-acetylwyosine (SCHEME 3; **12b→13b**).[31] Recently, Seela and Winter have reported another irreversible 7→9 glycosyl transfer.[32] On refluxing in toluene in the presence of $HgBr_2$, 7-[2-deoxy-3,5-di-(4-O-toluoyl)-β-D-ribofuranosyl]-6-methoxypurine underwent conversion to a 1 : 1 mixture of the respective 9α and 9β anomers. This experiment shows two significant characteristics of the 7⇄9 transglycosylation: i) the anchimeric assistance of 2'-acyloxy groups is necessary for the

stereocontrolled conversion and, even more importantly, ii) methylation at O6 entirely shifts the transglycosylation equilibrium towards 9-regioisomers, i.e. reversible 7⇄9 glycosyl migration occurs only in the series of 6-oxopurine nucleosides.

The discussed isomerization apparently takes place in the case of some nucleoside analogs modified in the aglycon portion, which may be exemplified by 7→9 glycosyl migration in the 1-deazapurine series.[33,34] Furthermore, the 7⇄9 transglycosylation process must be involved in the synthesis of 3-deazaguanosine, as can be deduced from the mixture of 1- and 3-ribosylated products (positions corresponding to 9 and 7 in the purine series, respectively) resulting from condensation of trimethylsilyl 6-aminoimidazo[4,5-*c*]pyrimidine-4-one with 2,3,5-tri-O-acetyl-D-ribofuranosyl bromide.[35,36]

Glycosylation at N7 has also been reported in the adenine series. Montgomery and Thomas demonstrated the utility of removable blocking groups at N3 of adenine in the preparation of 7-glycosyladenines.[37a] In this example, again, the presence of a 3-substituent is responsible for the exclusive formation of 7-glycosides in glycosylation and transglycosylation reactions, similarly to that observed for 3-benzylhypoxanthine,[37b] theophylline,[38] 3-methylguanine,[23] and wyeine[24,31].

As the latter reaction can be easily rationalized by a greater thermodynamic stability of 3,7-disubstituted purines versus 3,9-disubstitution, the report of Ryan, Acton and Goodman[39] on ribosylation of adenine is still somehow confusing. They noted the formation of both 7- and 9-isomers of (β-D-ribofuranosyl)adenine in reaction of N^6-benzoyladenine with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide, catalyzed by $HgBr_2$ in benzene. That result is in apparent contradiction to the generally accepted 3→9 sequence of glycosylation in the adenine series. In a similar way, but applying the silyl procedure, Vorbrüggen and Höfle[40] obtained all positional isomers of adenosine, i.e. 1-, 3-, 7- and 9-nucleosides, when N^6-benzoyladenine was ribosylated in the presence of trimethylsilyltriflate. Under thermodynamically controlled conditions all kinetic products (1-, 3- and 7-ribosylated compounds) underwent further rearrangement to the final 9-riboside. The formation of various kinetic products in the latter reaction may be due to the presence of different silyl derivatives reacting with sugar acyloxonium ions. Thus, glycosylation of the 1,N^6-*bis*-(trimethylsilyl) intermediate leads preferentially to 3- and 7-nucleosides, whereas 9,N^6-*bis*-silylation of the starting purine favors the 1- and 3-glycosyl regioisomers.[3,40] This observation points to an important fact that in

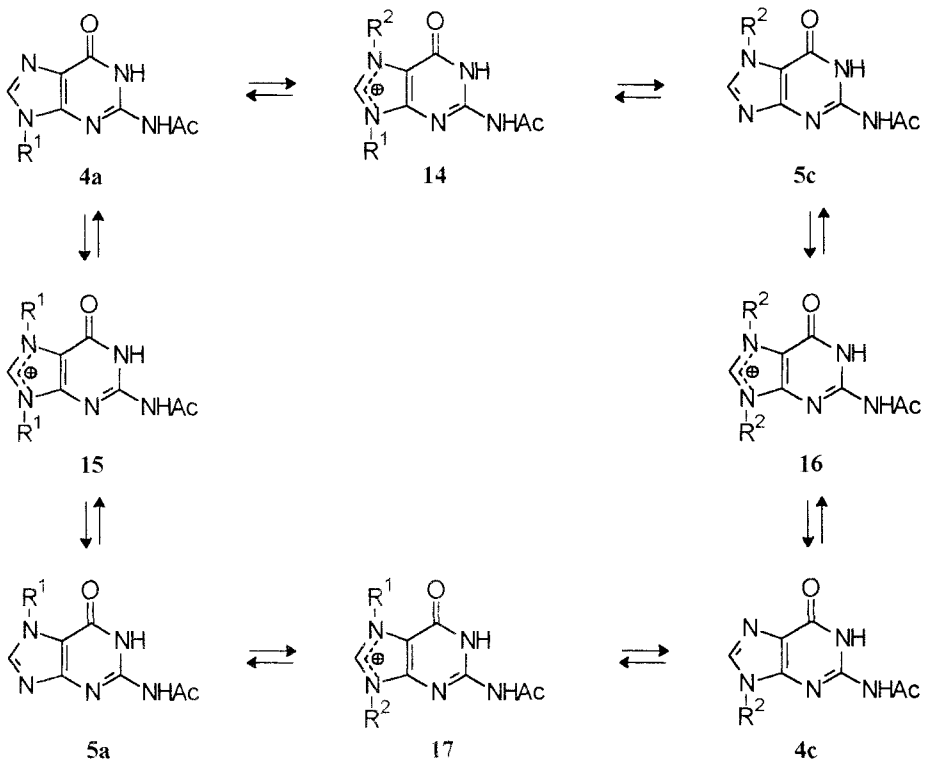
certain cases silylation may change the electronic structure of the starting nucleobase, in this way affecting the sequence of glycosylation.

The examples presented above unambiguously show that the 7⇄9 transglycosylation in the purine series is as equally conceivable as the better known and generally accepted 3→9 process. Whereas the 3→9 glycosyl migration has been well documented for adenine and its derivatives, the 7⇄9 transglycosylation has been generally noted in the series of 6-oxopurines. In the absence of substituents which may affect the glycosyl migration equilibrium, the 3→9 transglycosylation is practically irreversible, while the 7⇄9 glycosyl migration of 6-oxopurines represents a reversible reaction.

Although participation of the purine N7 atom in glycosyl migration reactions has already been proven, the sequence of glycosylation of 6-oxopurines has to be fully elucidated. Namely, it should be clearly shown whether 6-oxopurines are glycosylated in the sequence 7→9, or *via* a very unstable 3-glycosyl intermediate, i.e. in the sequence 3→7→9. The former possibility apparently results from the study of Dudycz and Wright[21] (*vide ante*). The latter one has been also considered by the same authors as being in line with the previously proposed mechanism.[1,5]

In order to study the sequence of glycosyl exchange process in the case of guanine, an approach was applied, in which two substituents of the glycosyl type, i.e. 2,3,5-tri-O-acetylribofuranosyl and (2-acetoxyethoxy)methyl, were present in the reaction medium.[41] It should be mentioned at this point that application of 2-acetoxyethyl acetoxymethyl ether[42] as a model of peracylated sugar components appears to be a very convenient way to study glycosyl exchange reactions. The approach, recently used to elucidate the mechanism of irreversible 2→1 transglycosylation of β-D-ribofuranosylindazoles,[14] offers the following advantages: i) the (2-acetoxyethoxy)methyl group behaves quite similarly to 2,3,5-tri-O-acetyl-β-D-ribofuranosyl substituent in glycosyl exchange reactions (*vide ante)*; ii) the acyclic substituent does not introduce new centers of asymmetry; iii) acyclonucleoside products are readily distinguishable from nucleosides of cyclic sugar by chromatographic means. Therefore, this method may be recommended for study on regioselectivity of glycosyl migration processes in chemistry of nucleosides and related compounds.

As has been previously reported, the transpurination reaction of tetraacetylguanosine (**4a**) with an excess of 2-acetoxyethyl acetoxymethyl ether performed in refluxing chlorobenzene in the presence of p-toluenesulfonic acid gave a mixture of 9-[(2-acetoxyethoxy)methyl]-N^2-



R^1 = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl
R^2 = (2-acetoxyethoxy)methyl

SCHEME 4

acetylguanine (**4c**; diacetylacyclovir) and its 7-isomer (**5c**)[8,43] (SCHEME 4). The 7-isomer can be transformed to the desired 9-isomer applying 7⇄9 thermal transglycosylation.[6-8,28] Recently the regioselectivity of this reaction was improved by using more effective catalysts.[44]

For a kinetic study this reaction was repeated under milder conditions and its progress was carefully monitored by HPLC. Interestingly, when tetraacetylguanosine (**4a**) was subjected to transpurination, 7-[(2-acetoxyethoxy)methyl]-N^2-acetylguanine (**5c**) was found as a single product after 2 min of reaction. In a counter experiment, reaction of fully acetylated 7-(β-D-ribofuranosyl)guanine (**5a**) with 2-acetoxyethyl acetoxymethyl ether gave 9-acyclonucleoside (**4c**) as a kinetic product. After 90 min, both reactions resulted in an almost identical

distribution of products: prevailing amounts of 9- and 7-acyclonucleosides (**4c** and **5c**, respectively) and smaller amounts of 9- and 7-ribosides (**4a**, **5a**).

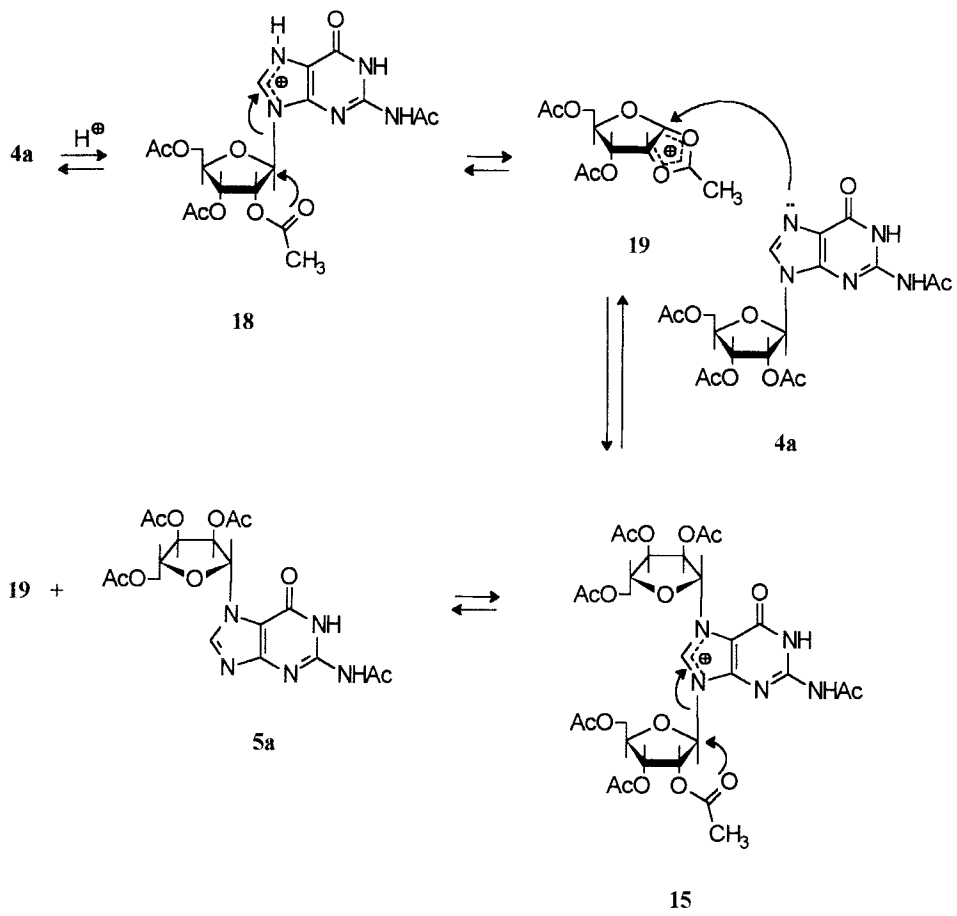
The observed reaction pathway may be explained as shown in SCHEME 4. Horizontal arrows denote transpurination reactions (exchange of glycosyl substituents), whereas the vertical ones represent "intramolecular" 7→9 transglycosylation. Any diagonal conversion is not possible, e.g. diacetylacyclovir (**4c**) cannot be obtained directly from tetraacetylguanosine (**4a**), but either *via* formation of the 7-acyclonucleoside (**5c**), or *via* 7-isomer of guanosine (**5a**). The respective 7,9-diglycosylguanine quaternary salts (**14-17**) are reaction intermediates for each single conversion.[41]

The results of this experiment leads to some important conclusions. First of all, the sequence of glycosylation 3→7→9 in the guanine series seems to be very doubtful. If tetraacetyl-guanosine (**4a**) had been glycosylated at N3 with the formation of 3,9-disubstituted intermediate, the latter compound would decompose to a 9-substituted product (*vide ante*), and not to the observed 7-isomer (**5c**). Argumentation of this type also applies to 7-isomers subjected to glycosyl exchange reactions. Therefore, only N7 and N9 atoms participate in transglycosylation reactions in the case of guanine and perhaps other 6-oxopurines.

Secondly, the presented data support the previously suggested mechanism of 7⇄9 transglycosylation,[8,21] which may be depicted as shown in SCHEME 5 for tetraacetylguanosine (**4a**).

A chain process is initiated by protonation at N7 (structure **18**), which facilitates the cleavage of the N-glycosyl bond with liberation of sugar acyloxonium ion (**19**). The sugar cation can be generated in the presence of Lewis acids[1] as well as without catalysts at high temperature (thermal transglycosylation). In the case of 2'-O-deoxy or acyclonucleosides, the participation of O4' rather than 2'-acyloxy group and the formation of a carboxonium cation should be anticipated. A nucleophilic attack of N7 of another molecule **4a** at C1 of the sugar ion (**19**) leads to the 7,9-diribofuranosyl intermediate (**15**). Decomposition of this intermediate gives the 7-riboside (**5a**) with the liberation of sugar ion (**19**), which may then react with a next molecule of free nucleoside, etc., until a dynamic equilibrium of this reversible reaction is achieved.

The proposed hereby mechanism is generally in line with suggestions of Dudycz and Wright.[21] However, 7-glycosyl compounds are not always the kinetic products of glycosylation in the guanine series, as may be understood from their study. As shown in the transpurination



SCHEME 5

experiment (SCHEME 4), the site of initial glycosylation evidently depends on the structure of substrates. Thus, the 9-substituted substrate (**4a**) gives a 7-glycosylated kinetic product, whereas 7-substituted guanine (**5a**) undergoes direct glycosylation at N9. These findings lead to a more general hypothesis that synthesis of guanine nucleosides proceeds *via* initial glycosylation of the unsubstituted (i.e. of hybridization sp^2) nitrogen atom of imidazole ring (either N7 or N9), no matter what is the starting substituent covalently bound to the other nitrogen (N9 or N7, respectively).[41,45] Indeed, the 6-oxopurines subjected to ribosylation in the study of Dudycz and Wright[21] were initially silylated, presumably also at N9. Therefore, the corresponding 7-ribosides were exclusively formed as kinetic products.

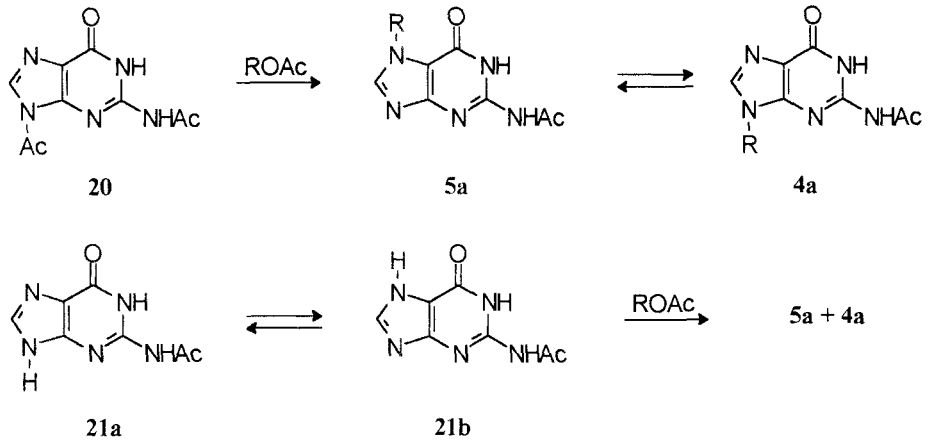
This rule of regioselectivity has already been confirmed for starting substituents such as 2,3,5-tri-O-acetyl-β-D-ribofuranosyl and (2-acetoxyethoxy)methyl,[41] as well as for acetyl groups and even proton.[45] As it has been shown recently, ribosylation of 9,N^2-diacetylguanine (**20**) and N^2-acetylguanine (**21**) in the presence of p-toluenesulfonic acid and tetraacetylribose gave almost identical mixture of 7- and 9-ribosides (**5a** and **4a**, respectively) after a prolonged reaction time (SCHEME 6).[45] However, the 7-isomer (**5a**) was the kinetic product in ribosylation of diacetylguanine (**20**), whereas the 9-isomer (**4a**) was formed later as a result of 7⇄9 transglycosylation. In the case of monoacetylguanine (**21**), both isomers (**4a**, **5a**) were formed simultaneously. These results are in line with the proposed rule of regioselectivity. In the first reaction, a nucleophilic attack of N7 at the sugar ion must take place since N9 of the substrate has been already blocked by the 9-acetyl group, whereas the formation of both regioisomers in the second reaction reflects the observed N^9H (**21a**) ⇄ N^7H (**21b**) tautomerism of monoacetylguanine.[45]

Presumably, this rule of regioselectivity may be applicable not only to guanine, but to other 6-oxopurine derivatives as well, and for other covalently bound starting substituents commonly met in various methods of nucleoside synthesis (SCHEME 7).

At the end of this part it should be emphasized that, similarly as it was shown for the 3→9 glycosylation in the adenine series, some structural modifications in the aglycon portion may affect the rate, sequence and site of glycosylation of 6-oxopurines. For example, hypoxanthine generally undergoes glycosylation and transglycosylation according to the 7⇄9 pathway, while glycosylation of xanthine leads to a mixture of 3-, 7-, 9-monosubstituted and 3,7-disubstituted products.[46,47] Quite similarly, it has been shown that the N3 atom of uric acid participates in glycosylation of its trimethylsilyl derivative.[48] The nature of the starting sugar and its protecting groups may also have an effect on the course of transglycosylation, e.g. 2-O-benzoylation rather than 2-O-acetylation is in favor of the 9-isomer in synthesis of guanosine.[20]

4. General Remarks

Transglycosylation reactions of purine nucleosides have been investigated for isolated nucleosides only in a few cases. Much of the discussion thus far has been based on the data obtained from glycosylation reactions in the purine series and comparison with similar reaction of pyrimidine derivatives[1-3] and related heterocycles.[49] In certain cases mechanism of transglycosylation can only be deduced from the structure of the products resulting from

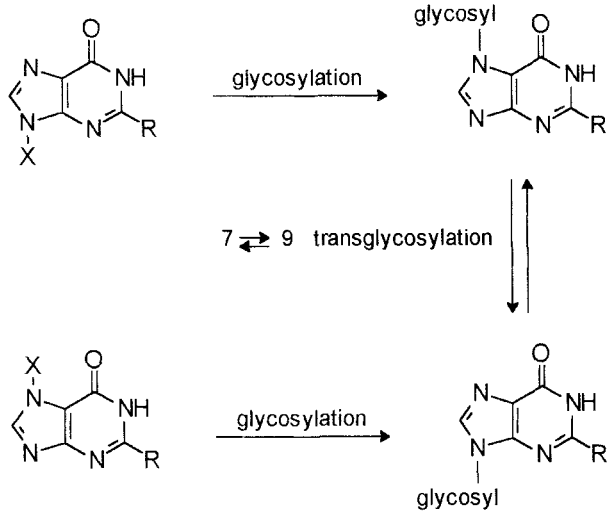


20 **5a** **4a**

21a **21b**

R = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl

SCHEME 6



R = H, NHAc, NHiBu, etc.
X = H, HgBr, HgCl, Ag, $(CH_3)_3Si$, Ac,
2,3,5-tri-O-acetyl-β-D-ribofuranosyl,
(2-acetoxyethoxy)methyl, etc.

SCHEME 7

glycosylation reactions. Nevertheless, the presently available information on transglycosylation of purine nucleosides allows for formulating the following conclusions:

1. Transglycosylation reaction apparently represents an intermolecular process.

2. The reaction proceeds regioselectively *via* unstable diglycosylpurine intermediates: the formation of a new N-glycosyl bond takes place before the former one has been cleaved. Another possible mechanism of transglycosylation, assuming a simple acid-catalyzed dissociation of the N-glycosyl bond leading to a sugar cation and a base anion with reassociation to form a regioisomer of the substrate, can be excluded as it has not been supported with experiments.

3. The presence of sugar cations is necessary to initiate a chain reaction of glycosyl exchange. Therefore, the reaction has to be catalyzed by Lewis acids which facilitate an initial cleavage of N-glycosyl linkage with liberation of the sugar ion, or this may also be achieved in the absence of catalysts at high temperatures (thermal transglycosylation).

4. In the purine series, only the unsubstituted nitrogen atoms, i.e. of hybridization sp^2, are nucleophilic centers which react directly with the sugar ions. However, in the case of some modified purine nucleosides, other exocyclic atoms of strong nucleophilic character may also take part in transglycosylation.

5. In the case of unsubstituted purine, the order of thermodynamic stability of its all possible N-glycosides, proposed by Shimizu and Miyaki,[5d] is as follows: $9 > 7 > 1 > 3$.

6. There are two main mechanistic pathways of glycosylation and transglycosylation for the most common derivatives of purine: the $3 \rightarrow 9$ sequence for adenine and related compounds, and the $7 \rightleftarrows 9$ sequence for guanine and other 6-oxopurine derivatives. Adenine and its derivatives undergo initial glycosylation at N3, and then the irreversible $3 \rightarrow 9$ transglycosylation. In the "guanine type" transglycosylation, the structure of kinetic glycosylation products depends on the site of substitution of substrates. 9-Substituted 6-oxopurines give 7-glycosylated regioisomers as kinetic products of glycosylation, and *vice versa*, 7-substituted substrates are initially glycosylated at N9. The $7 \rightleftarrows 9$ transglycosylation of the "guanine type" is reversible.

7. Structural modifications, especially introduction of substituents imposing strong electronic and steric effects into the aglycon portion, may drastically change the course of glycosylation and transglycosylation. Any changes of this type can affect the yield of products, equilibrium of transglycosylation and even the initial and ultimate sites of glycosylation. That is why some modified nucleosides do not belong to either the "adenine type", or to the "guanine type".

8. Transglycosylation in the 2'-acyloxy series proceeds presumably as a stereocontrolled reaction with retention of 1',2'-*trans*-configuration. Anomerization, observed in certain cases, may be explained as a "*post*-migration" event.

9. In the case of tautomerism of substrates, each tautomeric form reacts individually with sugar ions, and transglycosylation is responsible for the final distribution of products.

Some of the conclusions presented above should be understood just as the author's suggestions or a hypothesis which still requires further experimental verification. For better understanding of the glycosyl migration phenomenon the concluding remarks concern not only transglycosylation, but also glycosylation reactions. I hope that mechanistic proposals presented in this short review may be helpful in planning new experiments, not only in the chemistry of purine, but in the case of related heterocycles as well.[49]

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