Proc. Indian Acad. Sci. (Chem. Sci.), Vol. 99, Nos 1 & 2, August 1987, pp. 119–128.

Nucleoside antibiotics: Conformation and biological activity

ANIL SARAN
Chemical Physical Group, Tata Institute of Fundamental Research, Homi Bhabha Road, Bombay 400 005, India

Abstract. Minor modifications in pyrimidine and purine nucleosides have a profound effect on their biological activity. These modified nucleosides which exhibit a wide variety of antiviral, antibacterial, antitumor or cancerostatic properties are collectively called as nucleoside antibiotics. Conformational properties of these antibiotics have been investigated by quantum mechanical PCILO method. The results indicate that the nucleoside antibiotics and their parent nucleosides have very similar conformational preferences and this is specially so in the situations that occur in aqueous media. This result has important biological implications: these antibiotics can easily get incorporated in growing chains of RNA or DNA by mimicking their parent nucleosides and then bring about the inhibition of RNA or DNA or protein synthesis.

Keywords. Nucleoside antibiotics; conformation; biological activity; PCILO; modified nucleosides.

1. Introduction

Nucleoside antibiotics constitute a class of biologically active compounds which result from minor modifications or substitutions in the pyrimidine and purine nucleosides. The modifications can occur either in the sugar ring or in the base. As a result of this, nucleoside antibiotics exhibit a wide variety of antibacterial, antiviral, antitumor and cancerostatic properties (Bloch 1975a). Quite a few of these antibiotics have been tested clinically on animals and humans in a bid to search for a potential drug against cancer and viral diseases (Bloch 1975b).

Examples of sugar-ring modifications are shown in figure 1. In arabinosyl nucleosides (figure 1a), the 2′-hydroxyl group is on the same side as that of the C5′ and on opposite side as that of the 3′-hydroxyl group. The base can be either adenine or cytosine and the resulting modified nucleosides: Ara-A and Ara-C are both cytocidal agents. Both of them have been extensively studied as inhibitors of mammalian cells in culture, tumor cells and viruses. They get phosphorylated and incorporated as terminal residues into DNA *in vitro*. Ara-A gets incorporated into the 3′-terminal end of tRNA (Suhadolnik 1970, 1979). The replacement of 3′-hydroxyl group in adenosine by a proton and an amino group results in 3′-deoxy adenosine (cordycepin) and 3′-amino-3′-deoxy adenosine (figure 1b), respectively. Cordycepin is a cytostatic agent and a strong inhibitor of RNA polymerase. 3′-amino-3′-deoxyadenosine exhibits antitumor activity and its 5′-triphosphate is a strong inhibitor of RNA and DNA syntheses in Ehrlich ascites tumor cells. Cordycepin gets incorporated as the terminal residue in RNA, while 3′-amino-3′-deoxy adenosine after getting incorporated becomes the 3′-terminal residue in tRNA (Suhadolnik 1970, 1979). The nucleoside antibiotic resulting from the

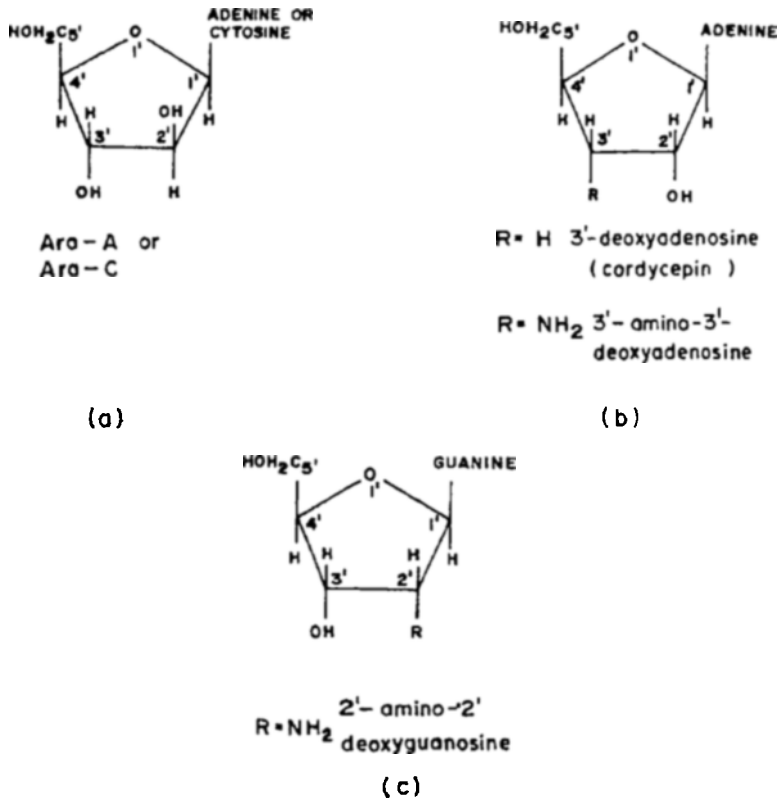

Figure 1. Nucleoside antibiotics resulting from sugar modifications.

replacement of the 2′-hydroxyl group by an amino group in guanosine is 2′-amino-2′-deoxy-guanosine (figure 1c). This antibiotic shows antitumor activity against HeLa cells and sarcoma 180 and also inhibits RNA and protein synthesis in E. Coli KY3591 (Nakanishi *et al* 1974, 1976, 1977).

Figure 2 shows some examples of modifications in the base part of the purine nucleosides. Tubercidin (figure 2a) results from the replacement of N(7) in adenosine by a —CH group. Further, the replacement of the hydrogen atom attached to C(7) of tubercidin by a cyano group (−C≡N) or a carboxamide group ($-CONH_2$) gives, respectively, toyocamycin and sangivamycin (figure 2a). Tubercidin possesses strong antitumor activity (Acs *et al* 1964; Bloch *et al* 1967) and is a inhibitor of RNA and DNA viruses (Bloch 1975a, 1975b). Toyocamycin is a strong antimicrobial agent (Matsuoka 1960) having signifcant antitumor activity (Sareyoshi *et al* 1965). Sangivanmycin is a strong antileukemic agent (Cairns *et al* 1967). All of them get phosphorylated to their 5′-triphosphates and then incorporated into RNA (Suhadolnik *et al* 1968a, b; Suhadolnik 1970). They also replace adenosine at the 3′-termini of tRNAs (Uretsky *et al* 1968). Formycin (figure 2b) has a 'C–C' sugar base linkage instead of the usual 'C–N' linkage. This antibiotic very efficiently substitutes for adenosine in many enzymatic reactions and also gets incorporated as the 3′-terminal residue of tRNA by replacing adenosine (Ward *et al* 1968, 1969a, b). The replacement of the amino group at C(6) in formycin by an oxygen atom results in formycin B. Both formycin and formycin B inhibit the influenza A_1 virus (Suhadolnik 1970). The above mentioned antibiotics are only a few examples of base modification in purine nucleosides. There are,

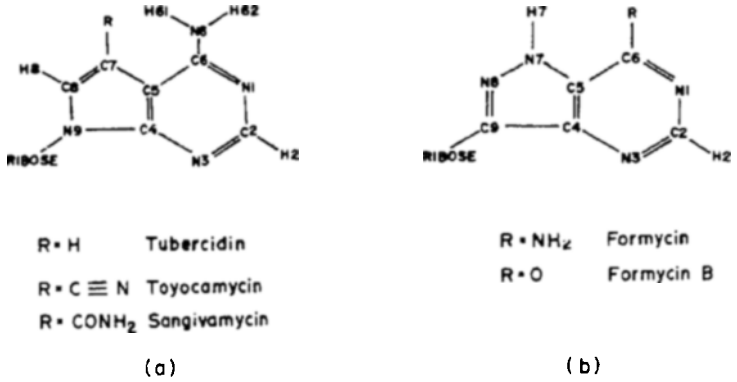

Figure 2. Nucleoside antibiotics resulting from purine base modifications.

however, a number of other examples which are well characterized and documented (Suhadolnik 1979).

Some examples of modifications in the base part of pyrimidine nucleosides are shown in figure 3. The replacement of C(6) in uridine and cytidine by a nitrogen atom results in 6-aza uridine (6-azaU) and 6-aza cytidine (6-azaC) (figures 3a, b), respectively, while in 3-deazauridine (3-deazaU) and 3-deazacytidine (3-deazaC) (figures 3c, d) it is the atom N(3) of the pyrimidine nucleosides which has been substituted by a carbon atom. 6-azaU and 6-azaC are both cancerostatic agents (Skoda 1963), whereas 3-deazaU and 3-deazaC exhibit cytostatic properties and inhibit the growth of several RNA viruses (Robins *et al* 1969). 5-substituted uridines and deoxyuridines (figure 4) have attracted considerable attention because of their antiviral and antitumor activity (Heidelberger 1965; Torrence *et al* 1978). 5-vinyl-2′-deoxyuridine (figure 4a) is not only an antiviral agent (Cheng *et al* 1976) but can also replace the parent nucleoside: thymidine in DNA of some organisms (Jones and Walker 1975). 5-ethynyl-2′-deoxyuridine (figure 4a) exerts strong activity against herpes simplex and vaccinia virus in culture and leukemia L1210 cells in culture (Sharma *et al* 1976). 5-amino uridine (figure 4b) is reported to have a wide range of biological activity inhibiting the growth of tumors and viruses (Gale *et al* 1972; Egert *et al* 1978). 5-aza cytidine which has C(5) atom of cytidine replaced by a nitrogen is a very potent antileukemic agent. It is readily incorporated into RNA and DNA and inhibits protein synthesis in bacterial, viral and mammalian cells (Sorm and Veseley 1964; Evans and Hanka 1968; Daskocil *et al* 1967). The above mentioned examples are only some of nucleoside antibiotics, the complete list of these antibiotics is available in the literature (Suhadolnik 1970, 1979).

We have been interested in the study of the conformations of some of these nucleoside antibiotics by using the PCILO method (Saran *et al* 1977; Mitra and Saran 1978; Saran and Mitra 1979; Saran and Chatterjee 1980a, b; Saran and Patnaik 1981, 1982, 1986; Patnaik and Saran 1984). The aim of these studies has been to understand why minor modifications or substitutions in pyrimidine and purine nucleosides leads to antibiotic activity of the modified nucleosides. In this review we would like to present the significant results which we have obtained on tubercidin (Saran and Mitra 1979), toyocamycin and sangivamycin (Saran and Chatterjee 1980a), cordycepin and 3′-amino-3′-deoxyadenosine (Saran and Patnaik 1981), 2′-amino-2′-deoxyadenosine (Patnaik and Saran 1984), 6-azauridine and 6-azacytidine (Mitra and Saran 1978), 3-deazauridine and 3-deazacytidine

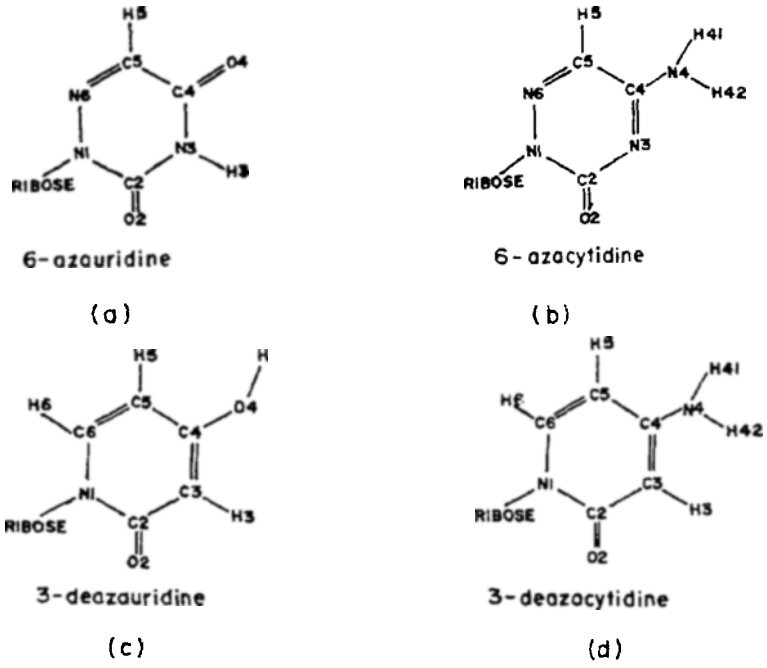

Figure 3. Nucleoside antibiotics resulting from pyrimidine base modifications.

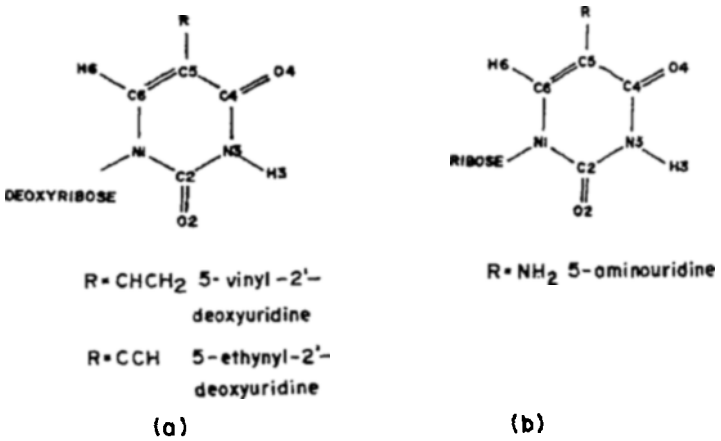

Figure 4. Nucleoside antibiotics resulting from pyrimidine base modifications.

(Saran and Chatterjee 1980b), 5-vinyl- and 5-ethynyl-2′-deoxyuridines (Saran and Patnaik 1982) and 5-aminouridine (Saran and Patnaik 1986). Besides these, arabinosyl nucleosides (Saran *et al* 1974) and formycins and showdomycin (Saran *et al* 1977) have also been investigated. However, these investigations are not as detailed as the other ones mentioned above.

2. Results and discussions

The method utilized in these investigations is the PCILO method (Pullman and Saran 1976; Jordan *et al* 1971). The torsion angles χ_{CN} (Sundaralingam 1960) and $\Phi_{C4'-C5'}$, $\Phi_{C5'-O5'}$, $\Phi_{C3'-O3'}$, and $\Phi_{C2'-O2'}$, (Saran *et al* 1972) as indicated in figure 5

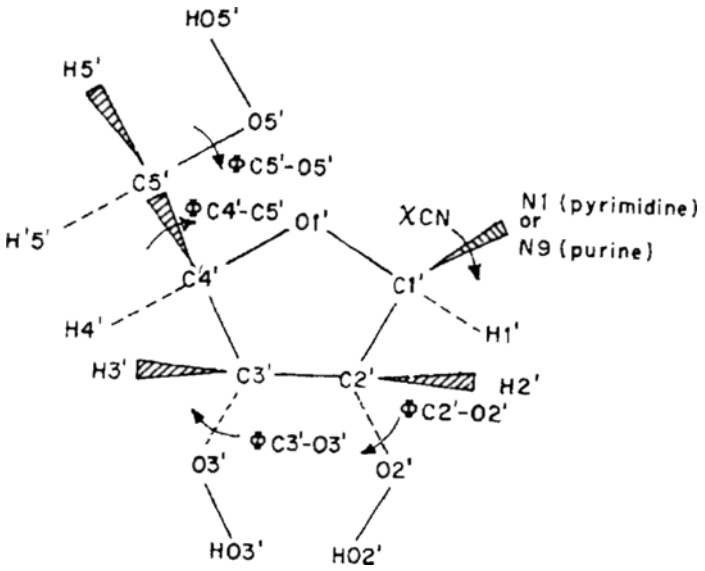

Figure 5. Torsion angles involved in nucleosides or nucleoside antibiotics.

determine the conformation of purine and pyrimidine nucleosides. These torsion angles are defined as:

$$\chi_{CN} = O(1')-C(1')-N(9)-C(8) \text{ or } O(1')-C(1')-N(1)-C(6)$$

$$\Phi_{C4'-C5'} = C(3')-C(4')-C(5')-O(5')$$

$$\Phi_{C5'-O5'} = C(4')-C(5')-O(5')-H(O5')$$

$$\Phi_{C3'-O3'} = C(2')-C(3')-O(3')-H(O3') \text{ and}$$

$$\Phi_{C2'-O2'} = C(1')-C(2')-O(2')-H(O2')$$

with the *cis*-planar arrangement of the terminal bonds being taken as zero for the torsion angle. The values of $\chi_{CN} = 0° \pm 90°$ and $180° \pm 90°$ correspond, respectively, to *anti* and *syn* regions (Sundaralingam 1960) while the values of $\Phi_{C4'-C5'} \approx 60°$, 180° and 300° correspond to *gauche-gauche* (*gg*) , *gauche-trans* (*gt*) and *trans-gauche* (*tg*) conformations around the exocyclic C(4')-C(5') bond (Saran *et al* 1972; Pullman and Saran 1976) respectively. Besides these, the sugar ring puckering can be either C(2')-endo or C(3')-endo.

There are different possibilities of intramolecular hydrogen bonding between the sugar and the base and these are:

(i) O(5')–H(O5') --- N(3) of purine or
O(2) of pyrimidine base,

with the conditions: $\Phi_{C5'-O5'} = 60°$ and $\Phi_{C4'-C5'} = 60°(gg)$,
and

(ii) O(2')–H(O2') --- N(3) or
O(2)

with the condition: $\Phi_{C2'-O2'} = 60°$

For the C(2′)-endo sugar pucker, both intramolecular hydrogen-bonding (i) and (ii) are possible while in the case of C(3′)-endo sugar pucker the second intramolecular hydrogen-bonding is not possible because of the fact that the participating atoms are farther apart than in the C(2′)-endo sugar pucker (Saran and Chatterjee 1980a, b; Saran 1981). When these intramolecular hydrogen-bonds are allowed, the theoretical computations predict the most preferred conformation of the molecule as the one in which there is an intramolecular hydrogen-bonding. However, such intramolecular hydrogen-bonding is very unlikely to be preserved in aqueous solution. This is due to the fact that in aqueous solution the two hydrogen-bonding sites of the nucleoside or nucleoside antibiotics would rather be involved in two intermolecular hydrogen-bonds with water molecules than in one intramolecular hydrogen-bond. The situation in which both H(O5′) and H(O2′) are oriented away from the base, precludes the possibility of any of the intramolecular hydrogen-bonds and thus mimics the situations prevailing in the aqueous medium. This is achieved in theoretical calculations by prefixing the value of $\Phi_{C5'-O5'}$ and $\Phi_{C2'-O2'}$ equal to 180° and the conformations then obtained represent those occurring in the aqueous solution. The excellent agreement between theoretical predictions and the experimental observations in aqueous solutions on 8-azaadenosine (Saran *et al* 1978), tubercidin (Saran and Mitra 1979), 6-azauridine and 6-azacytidine (Mitra and Saran 1978), cordycepin (Saran and Patnaik 1981) and propranolol (Kulkarni *et al* 1979) has provided strong support to the above hypothesis. Since most of the biochemical reactions occur in aqueous medium, the results of the theoretical computations carried out on nucleoside antibiotics with the above mentioned conditions have very important biological significance. The important results of our studies have been summarized in tables 1 and 2.

2.1 *Nucleoside antibiotics derived from purine nucleosides*

The results on nucleoside antibiotics derived from purine nucleosides in table 1 indicate that conformational preferences of these antibiotics are very similar to their respective parent nucleosides. Highly localized global minima have been observed in the cases where the possibility of intramolecular hydrogen-bonding exists. For example, the conformation of the molecule is *syn-gg* in the case of intramolecular hydrogen-bonding through O(5′)-H(O5′) whereas in the case of O(2′)-H(O2′) it is *anti-gg*. However, in the absence of these intramolecular hydrogen bonds, the conformational preferences are highly flexible showing *syn-gg* $\rightleftharpoons$ *anti-gg* equilibrium with low barrier (~ 2–3 kcal/mole) between the *syn* and *anti* regions. Ara-A (Saran *et al* 1974) and formycins (Saran *et al* 1977) also show large conformational flexibility when no intramolecular hydrogen-bonding is allowed.

2.2 *Nucleoside antibiotics derived from pyrimidine nucleosides*

Table 2 lists the results on nucleoside antibiotics derived from the pyrimidine nucleoside as well as the parent nucleosides and here also the conformational preferences of nucleoside antibiotics are very similar to those of the parent nucleosides and this similarity is specially profound in the case where no intramolecular hydrogen-bonding is allowed. Both *anti-gg* and *syn-gg* regions are

Table 1. Preferred conformations of nucleoside antibiotics derived from purine nucleosides.

Sugar pucker	Intramolecular hydrogen bonding with	Tubercidin (Saran and Mitra 1979)	Toyocamycin sangivamycin (Saran and Chatterjee 1980a)	Cordycepin 3′-amino-3′-deoxyadenosine (Saran and Patnaik 1981)	Adenosine (Pullman and Berthod 1973; Berthod and Pullman 1971)	2′-amino-2′-deoxyguanosine (Patnaik and Saran 1984)	Guanosine (Patnaik and Saran 1984)
C(2′)-endo	O(5′)–H(O5′) O(2′)–H(O2′)	*syn-gg* *anti-gg*	*syn-gg* *anti-gg*	*syn-gg* *anti-gg*	*syn-gg* *anti-gg*	*syn-gg* *anti-gg*	*syn-gg* *anti-gg*
	None	*syn-gg* *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*
C(3′-endo)	O(5′)–H(O5′)		*syn-gg*	*syn-gg*	*syn-gg*	*syn-gg*	*syn-gg*
	None		*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*	*syn-gg* ⇌ *anti-gg*

Table 2. Preferred conformations of nucleoside antibiotics derived from pyrimidine nucleosides.

Sugar pucker	Intramolecular hydrogen bonding with	6-azauridine* (Mitra and Saran 1978) 3-deazauridine (Saran and Chatterjee 1980b)	Uridine (Pullman and Berthod 1973; Berthod and Pullman 1971)	6-azacytidine* (Mitra and Saran 1978) 3-deazacytidine (Saran and Chatterjee 1980b)	Cytidine (Pullman and Berthod 1973; Berthod and Pullman 1971)
C(2′)-endo	O(5′)–H(O5′)	*syn-gg*	*syn-gg*	*syn-gg*	*syn-gg*
	O(2′)–H(O2′)	*anti-gg*	*anti-gg*	*anti-gg*	*anti-gg*
	None	*anti-gg*, *syn-gg*	*anti-gg*, *syn-gg*	*anti-gg*, *syn-gg*	*anti-gg*, *syn-gg*
	O(5′)–H(O5′)	*syn-gg*	*anti-gg*	*syn-gg*	*syn-gg*
C(3′-endo)	None	*anti-gg*, *syn-gg*	*anti-gg*, *syn-gg*	*anti-gg*, *syn-gg*	*anti-gg*, *syn-gg*

* 6-azauridine and 6-azacytidine have not been investigated in as much detail as 3-deazauridine and 3-deazacytidine for the case in which no intramolecular hydrogen-bonding is allowed, but very similar results to those of 3-deazauridine and 3-deazacytidine are expected.

favourable with a slightly higher energy barrier (~ 3 to 5 kcal/mole) in between the *syn* and *anti* regions as compared to the antibiotics derived from purine nucleosides. The results on 5-vinyl- and 2′-ethynyl-2′-deoxyuridines show remarkably similar conformational preferences to those of the parent nucleoside: thymidine (Saran and Patnaik 1982). This is also true for 5-aminouridine (Saran and Patnaik 1986).

3. Biological significance

The results presented above clearly indicate that the nucleoside antibiotics have very similar conformational preferences to those of the parent nucleoside. This similarity is remarkably profound in the case where no intramolecular hydrogen-bonding is allowed as in aqueous solution. Since all biochemical reactions occur in aqueous media, the important implication of the above mentioned result is that these nucleoside antibiotics can very easily mimic the parent nucleosides and get incorporated in growing chains of RNA or DNA. This deduction is in agreement with experimental observations. Tubercidin, toyocamycin and sangivamycin get incorporated in tRNA by replacing the 3′-terminal adenosine residue and after incorporation they do not allow the normal functioning of the tRNA in terms of esterification of amino acids (Suhadolnik *et al* 1968a, b; Uretsky *et al* 1968). The activity of cordycepin and 3′-amino-3′-deoxyadenosine results from the fact that after incorporation into RNA, which has been experimentally observed (Suhadolnik 1970, 1979), they become terminal residues of RNA and the RNA synthesis stops. 2′-amino-2′-deoxyguanosine also gets incorporated in growing chains of RNA producing defective RNA which in turn inhibit protein synthesis. The experimental observations of Gassen *et al* (1972) indicate that 3-deazauridine gets substituted in the UUU codon of mRNA which specially interacts with phenylala-

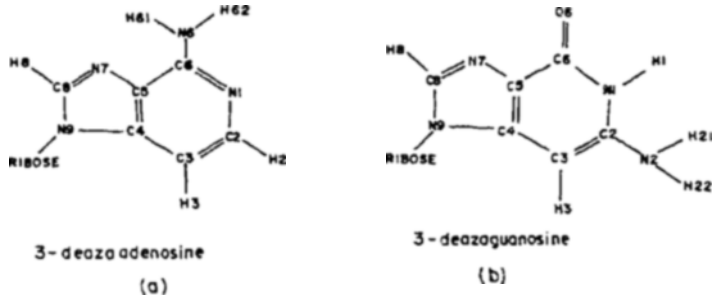

Figure 6. 3-deaza purine nucleosides.

nine of tRNA from yeast. The experimental observations on 5-vinyl-2′-deoxyuridine (Jones and Walker 1975) and 5-aminouridine (Egert *et al* 1978) are all in agreement with the deduction arrived at from theoretical studies (Saran and Patnaik 1982, 1986).

4. Conclusion

In conclusion it can be said that nucleoside antibiotics have very similar conformational preferences to those of the parent nucleoside from which they are derived. This similarity is highly profound in the situations that prevail in aqueous solution with the result that these antibiotics get incorporated in RNA and DNA by mimicking their parent nucleosides and then bring about the inhibition of RNA, DNA or protein synthesis. On the basis of these results, it has been possible to correlate the biological activity of these nucleoside antibiotics to the striking similarity of their conformational preferences to those of their parent nucleosides in the situations that prevail in aqueous solutions. Our theoretical studies on 3-deazaadenosine and 3-deazaguanosine shown in figure 6, indicate that these nucleoside analogs have very different conformational preferences as compared to their parent nucleoside (Saran and Chatterjee 1984). These two analogs have been experimentally shown to be biologically inactive (Cook *et al* 1975; Ikehara and Fukui 1974). The results on 3-deazaadenosine and 3-deazaguanosine clearly demonstrate that the converse of the correlation stated above for the biological activity of nucleoside antibiotics also holds true.

References

Acs G, Reich E and Mori M 1964 *Proc. Natl. Acad. Sci. USA* **52** 493

Berthod H and Pullman B 1971 *Biochim. Biophys. Acta* **232** 595

Bloch A 1975a *Ann. N.Y. Acad. Sci.* **255** 576

Bloch A (ed.) 1975b *Chemistry, biology and clinical uses of nucleoside analogs* (New York: New York Acad. Sci.)

Bloch A, Leonard R J and Nicol C A 1967 *Biochim. Biophys. Acta* **138** 10

Cairns J A, Hall T C, Olson K B, Khuang C L, Horton J and Sadduk R K 1967 *Cancer Chemother. Rep.* **51** 197

Cheng Y C, Domin B A, Sharma R A and Bobek M 1976 *Antimicrob. Agents Chemother.* **10** 119

Cook P D, Rousseau R J, Mian A M, Meyer R B Jr, Ivanovics G, Streeter D G, Wikouski J T, Stout M G, Simon L N, Sidwell R W and Robins R K 1975 *J. Am. Chem. Soc.* **97** 2916, and references quoted therein

Doskocil J, Paces V and Sorm F 1967 *Biochim. Biophys. Acta* **145** 771
Egert E, Lidner H J, Hillen N and Gassen H G 1978 *Acta Crystallogr.* **B34** 2204
Evans J S and Hanka L J 1968 *Experientia* **24** 972
Gale E F, Cundtiff E, Reynolds P E, Richmond M H and Wasing M J 1972 *Molecular basis of antibiotic action* (New York: Wiley)
Gassen H G, Schetters H and Mathaei H 1972 *Biochim. Biophys. Acta* **272** 560
Heidelberger C 1965 *Prog. Nucleic Acid Res. Mol. Biol.* **4** 1
Ikehara M and Fukui T 1974 *Biochim. Biophys. Acta* **338** 512
Jones A S and Walker R T 1975 *Nucleic Acids Res.* (Spec. Publ. No. 1) S1
Jordan F, Gilbert M, Malriue J P and Pincelli U 1971 *Theor. Chem. Acta* **15** 211, and references quoted therein
Kulkarni V M, Vasanth Kumar N, Saran A and Govil G 1979 *Int. J. Quantum Chem., Quantum Biol. Symp.* **6** 153
Matsuoka M 1960 *J. Antibiot.* **13** 121
Mitra C and Saran A 1978 *Biochim. Biophys. Acta* **518** 193
Nakanishi T, Iida T, Tomita F and Furaya A 1976 *Chem. Pharm. Bull.* **24** 2955
Nakanishi T, Tomita F and Suzuki T 1974 *Agric. Biol. Chem.* **38** 2465
Nakanishi T, Tomita F and Furaya A 1977 *J. Antibiot.* **30** 743
Patnaik L N and Saran A 1984 *J. Biol. Phys.* **12** 12
Pullman B and Berthod B 1973 *Conformation of biological molecules* (eds) E Bergmann and B Pullman (New York: Academic Press) p. 209
Pullman B and Saran A 1976 *Prog. Nucl. Acid Res. Mol. Biol.* **18** 215
Robins M J, Currie B L, Robins R K and Bloch A 1969 *Proc. Am. Assoc. Cancer Res.* **10** 73
Saran A 1981 *Int. J. Quantum Chem.* **20** 439
Saran A and Chatterjee C L 1980a *Int. J. Quantum Chem., Quantum Biol. Symp.* **7** 123
Saran A and Chatterjee C L 1980b *Biochim. Biophys. Acta* **607** 490
Saran A and Chatterjee C L 1984 *Int. J. Quantum. Chem.* **25** 743
Saran A and Mitra C 1979 *Indian J. Biochem. Biophys.* **16** 304
Saran A, Mitra C K and Pullman B 1977 *Int. J. Quantum. Chem., Quantum Biol. Symp.* **4** 43
Saran A, Mitra C and Pullman B 1978 *Biochim. Biophys. Acta* **517** 255
Saran A and Patnaik L N 1981 *Int. J. Quantum Chem.* **20** 357
Saran A and Patnaik L N 1982 *Int. J. Quantum Chem., Quantum Biol. Symp.* **9** 247
Saran A and Patnaik L N 1986 *Int. J. Quantum Chem., Quantum Biol. Symp.* **13** 121
Saran A, Pullman B and Perahia D 1972 *Biochem. Biophys. Acta* **287** 211
Saran A, Pullman B and Perahia D 1974 *Biochim. Biophys. Acta* **349** 189
Sareyoshi M, Tokuzen R and Fukuoka F 1965 *Gann* **56** 219
Sareyoshi M, Tokuzen R and Fukuoka F 1965 *Gann* **56** 219
Sharma R A, Perman J, Bloch A and Bobek M 1976 *Chem. Abstr.* **172** (MEDI) 70
Skoda J 1963 *Prog. Nucl. Acid. Res.* **2** 197
Sorm F and Veseley J 1964 *Neoplasma* **11** 123
Suhadolnik R J 1970 *Nucleoside antibiotics* (New York: Wiley-Interscience)
Suhadolnik R J 1979 *Prog. Nucl. Acid Res. Mol. Biol.* **22** 193, and references quoted therein
Suhadolnik R J, Uematsu T and Uematsu U 1968a *Biochim. Biophys. Acta* **149** 41
Suhadolnik R J, Uematsu T, Uematsu U and Wilson R J 1968b *J. Biol. Chem.* **243** 2761
Sundaralingam M 1960 *Biopolymers* **7** 821
Torrence P F, Spencer J W, Bobst A M, Descamps J and De clerq 1978 *J. Med. Chem.* **21** 228
Uretsky S C, Acs G, Reich E, Mori M and Altberger L 1968 *J. Biol. Chem.* **243** 306
Ward D C, Cerami A, Reich E, Acs G and Altberger L 1969a *J. Biol. Chem.* **244** 3243
Ward D C, Fuller W and Reich E 1969b *Proc. Natl. Acad. Sci. USA* **62** 581
Ward D C and Reich E 1968 *Proc. Natl. Acad. Sci. USA* **61** 1494