Interaction of adenosine, guanosine and inosine with ruthenium hydride complexes

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Complexes of adenosine, guanosine and inosine with some ruthenium hydride complexes have been prepared and studied by UV, visible, IR, ^{1}H NMR and ^{13}C NMR spectroscopies. The ligands have been found to coordinate through their exocyclic groups and the N(7) atom to the $RuHCl(PPh_3)_3$ unit and through only exocyclic groups to the $RuHCl(CO)(PPh_3)_3$ unit.

Keywords: ruthenium(II) complexes, adenosine, guanosine, inosine

The nucleic acid constituents play an important role in biological systems.[1-7] In almost all biological processes involving nucleic acids metal ions are known to bind with these acids. The presence of metal ions at various reactive sites of DNA influences the physical properties and chemical reactivity of the polynucleotide chains, which are fundamental units of biological systems.[8]

Keeping in view an exploration of the nature of metal-nucleic acids interactions in biological systems, the present study was undertaken to find the sites of bonding when the metal ion is already crowded with bulky ligands that could create steric restraints. The heteroatoms in nucleic acids provide a great variety of binding sites. Soft acids generally coordinate to the nitrogen atoms of the base moieties.[9-11] In the present investigation the preferential coordination sites of adenosine (ADS), guanosine (GNS) and inosine (INS) with some Ru(II) hydride complexes have been determined.

Experimental

Synthetic procedure

All the reagents used were analytical grade. ADS, GNS, INS and $[Ru(Cl)H(CO)(PPh_3)_3]$ were obtained from Aldrich Chemical Company, Inc. USA. Solvents were dried before use under dry nitrogen gas. The light petroleum used had b.p. 60 & 80 °C. $[Ru(Cl)H(PPh_3)_3]$ was prepared according to the literature.[12] Chloride and phosphorus were determined gravimetrically. Carbon, hydrogen and nitrogen were analysed by a Perkin-Elmer model 240C elemental analyser. IR spectra (KBr) were recorded with a Perkin-Elmer 783 spectrophotometer and electronic spectra ($CHCl_3$) with a Shimadzu UV 190 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a JEOL FX 90 FT spectrometer using TMS in DMSO-d_6 as internal standard.

Preparation of complexes

(a) A 1:1 ratio of the required ligand precursor (ADS/GNS/INS) suspended in methanol (25 mL) was mixed with a solution of $[Ru(Cl)H(PPh_3)_3]$ in dichloromethane (25 mL) and stirred at room temperature under dinitrogen. The volatiles were removed *in vacuo*. The residue was washed with hexane and filtered off. Yields were 60%.
(b) The appropriate ligand precursor (ADS/GNS/INS), suspended in methanol (25 mL), was added to a solution of $[Ru(Cl)H(CO)(PPh_3)_3]$ (0.500 g) in dichloromethane (5 mL) in 1:1 ratio under continuous stirring under dinitrogen. The mixture was then refluxed for 30 min, allowed to cool, filtered off and the resulting solid was washed with methanol and finally with petroleum ether and dried under reduced pressure. Yields were 80 to 90%.

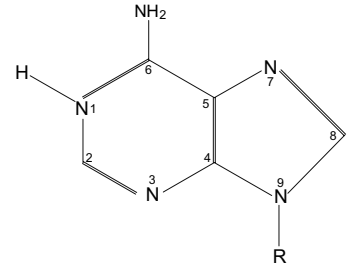
Results and discussion

The analytical data of the complexes are reported in Table 1. The new complexes were obtained by the replacement of one of the three coordinated PPh_3 molecules of $[Ru(Cl)H(PPh_3)_3]$ or $[Ru(Cl)H(CO)(PPh_3)_3]$ by ADS/GNS/INS. The synthesised complexes are stable in alcoholic solution as well as in aerobic conditions.

Adenosine

IR spectra studies

The potential binding sites of ADS (Fig. 1) are the pyrimidine N(1) and N(3) and the imidazole N(7) ring nitrogen atoms, the N(6) nitrogen of the exocyclic NH_2 group and the hydroxyl oxygens of the ribose group. The most preferred binding site of adenine is the N(9) atom.[13] Bonaccorsi *et al.*[14] have predicted that the N(7) position is the weakest binding site of adenine. In ADS, the ribose substituent blocks the N(9) site so that when ADS acts as a unidentate ligand it binds through the N(7) atom while N(1) and N(7) atoms are used for bidentate binding.[15] N(3) is not a probable coordinating site because of the steric hinderance created by the ribose group.[16] Thus the probable sites of metal ion binding are N(1), N(7) and C_6–NH_2 in ADS. The hydroxyl oxygens of the ribose are also probable binding sites of ADS especially in the absence of water.[17]



R is the Ribose group.

Fig. 1

Table 1 Analytical results (%) for the complexes

Complexes	Ru		Cl		P		C		H		N	
	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd
$RuHCl(C_{10}H_{13}N_5O_4)[P(C_6H_5)_3]_2$	10.95	10.88	3.73	3.81	6.77	6.67	59.55	59.45	4.72	4.77	7.64	7.54
$RuHCl(C_{10}H_{13}N_5O_4)[P(C_6H_5)_3]_2$	10.74	10.69	3.82	3.75	6.48	6.55	58.50	58.53	4.74	4.69	7.36	7.41
$RuHCl(C_{10}H_{12}N_4O_5)[P(C_6H_5)_3]_2$	10.83	10.86	3.86	3.81	6.60	6.66	59.25	59.39	4.60	4.66	6.12	6.02
$RuHClCO(C_{10}H_{13}N_5O_4)[P(C_6H_5)_3]_2$	10.48	10.56	3.72	3.70	6.50	6.47	59.05	58.97	4.60	4.63	7.40	7.32
$RuHClCO(C_{10}H_{13}N_5O_5)[P(C_6H_5)_3]_2$	10.35	10.38	3.61	3.64	6.32	6.36	58.07	58.00	4.54	4.56	7.28	7.20
$RuHClCO(C_{10}H_{12}N_4O_5)[P(C_6H_5)_3]_2$	10.50	10.55	3.66	3.70	6.52	6.46	59.02	58.90	4.49	4.52	5.95	5.85

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The [Ru(Cl)H(ADS)(PPh$_3$)$_2$] complex

The νOH vibration (3410 cm^{-1}) of the ribose fragments do not show any shift in the complexes indicating non-participation of the ribose in complexation. Several νC=C, νC=N and ring vibrations of ADS, appearing in the range 1650–1300 cm^{-1}, undergo substantial shifts and splitting in the spectrum of the complex. The band at 1470 cm^{-1} in free ADS disappears in the spectra of the complex. The shifts towards high frequency region for the bands appearing at 1537 cm^{-1} and 1572 cm^{-1} in ADS to 1564 cm^{-1} and 1595 cm^{-1} respectively in the spectrum of the complex suggest a decrease in electron in the pyrimidine ring, due to the binding of Ru(II) to the imidazole ring. The ν C(5)–N(7)–C(8) band also shows a shift to higher (1338 to 1370 cm^{-1}) frequency in the complex. The Ru(II) complex exhibits a shift in the frequency of ν N(7) bands of ADS with respect to free ADS indicating the participation of the N(7) atom in complexation.

The δNH$_2$ band appearing at 1670 cm^{-1} in the spectrum of ADS undergoes substantial shifts towards lower frequency (1630 cm^{-1}) in the complex, showing coordination through the C$_6$–NH$_2$ group of ADS because the δNH$_2$ band shows a higher frequency shift on hydrogen bonding.[15] The NH$_2$ vibrations show significant shifts in the spectrum of the complex.

Thus, IR studies show that [Ru(Cl)H(ADS)(PPh$_3$)$_2$] forms a chelate with ADS binding through its C(6)–NH$_2$ group and the N(7) atom.

The [Ru(Cl)H(CO)(ADS)(PPh$_3$)$_2$] complex

The IR spectra of ADS do not show any substantial shifts for νOH (3410 cm^{-1}) of the ribose fragments in the complexes. The δNH$_2$ band at 1670 cm^{-1} in the spectrum of ADS shifts to lower frequency (1620 cm^{-1}) in the complex showing coordination through the C$_6$–NH$_2$ group of ADS. Other vibrations related to NH$_2$ vibrations exhibit significant shifts in the spectra of the complex suggesting binding through the C$_6$–NH$_2$ group of ADS as this binding site eases the steric hindrance introduced by the ribose substituent at the N(9) atom.

Shimokawa *et al.*[18] have suggested that the amino group of ADS is the preferred binding site for Zn(II), Cd(II) and Hg(II) ions. Mansy *et al.* [19] and Robins[20] also reported reactions of ADS with *cis*- and *trans*-[PtCl$_2$(NH$_3$)$_2$] in which the sites N$_1$, N$_7$ and NH$_2$ were considered to be involved in bonding. Chatterjee *et al.*[21] have observed that the C$_6$–NH$_2$ group favours over N$_1$ as coordinating site in an ADS-Au(III) complex. In the present study also the C$_6$–NH$_2$ group is the favoured binding site of ADS in [Ru(Cl)H (CO)(ADS)(PPh$_3$)$_2$] because of the steric restraints due to the crowded ligands around the metal ion.

NMR spectra studies

The binding sites of the bases with Ru(II) were determined using ^{13}C NMR and ^{1}H NMR spectroscopy. (CD$_3$)$_2$SO was used as the solvent because the ligands and the synthesised complexes were soluble in it. It has been observed that the proximity of a given atom to the site of coordination is indicated by the magnitude of the change in its chemical shift. The ^{13}C NMR data for the ligands and their complexes are reported in Table 2. The NMR peak assignments have been taken from the literature.[22,23] In the complexes it is evident from Table 2 that the ribose group does not participate in complexation.

The [Ru(Cl)H(ADS)(PPh$_3$)$_2$] complex

The ^{13}C NMR spectrum (Table 2) shows downfield shifts in the resonances of C(5) and C(8) while the upfield shift for the C(6) resonance suggests the binding sites as the C(6)–NH$_2$ group and the N(7) atom of ADS. C(2) and C(4) resonances show negligible shifts indicating the non-participation of N(1) and N(3) atoms in coordination.

The ^{1}H NMR data in Table 3 for the ADS-complex show the largest proton shift for the exocyclic NH$_2$ resonances (0.56 ppm downfield) and a downfield shift in the H(8) resonance. The H(2) resonance shows small shifts. These results (due to changes in electron density) show that the C(6)–NH$_2$ group and the N(7) atom are the sites for metallation. ADS has been reported[18,24,25] to bind to different metal ions through both the C(6)-NH$_2$ and N(7). On the basis of ^{1}H NMR data also the exocyclic NH$_2$ is the most suited binding site for Ru(II) binding.

The [Ru(Cl)H(CO)(ADS)(PPh$_3$)$_2$] complex

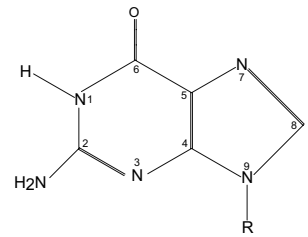
The ^{13}C NMR resonances of the complex show small shifts in C(2), C(4) and C(8) resonances indicating the non-participation of N(1), N(3) or N(7) atoms in binding to Ru(II). Also the ribose group creates steric hindrance to the N(3) atom so that it could not act as a binding site. The only remaining potential binding site is the C(6)–NH$_2$ exocyclic group. This is indicated by larger upfield shifts in the C(6) and C(5) resonances as these carbons are closest to the C(6)–NH$_2$ exocyclic group of ADS. The ^{1}H NMR data in Table 3 for the ADS–complex show the largest shift for the exocyclic NH$_2$ resonances (0.62 ppm downfield). H(8) and H(2) resonances show negligible shifts. On the basis of ^{1}H NMR data also the exocyclic NH$_2$ is the most suitable binding site for Ru(II). Podder *et al.*[21] have also concluded in their study of the interaction of Au(III) with ADS that the exocyclic NH$_2$ coordinates to the metal ion.

Guanosine

IR spectra studies

GNS (Fig. 2) has a number of potential binding sites including the nitrogens of the pyrimidine and imidazole rings and the exocyclic donor atoms along with the ribose group. The ability of various donor atoms to act as sites of complexation depends on several factors[10,26-30] *viz* the relative basicity of the donor atoms, steric interactions between exocyclic groups on the nucleic base or nucleoside and other ligands in the coordination sphere, as well as attractive or repulsive forces acting between the exocyclic groups on the nucleic base or nucleoside and other coordinated ligands. Also the delocalisation of electron density in the heterocyclic rings affects the binding site of metallation.

In neutral solution,[31-33] GNS exists in the keto form. In the keto form, the N(1) atom is protonated whilst the N(3) atom is weakly basic and also faces steric hindrance due to the ribose group. Thus N(1) and N(3) will not be preferred for binding with the metal ions. The NH$_2$ group is not very basic in GNS[31] hence the metallation will also not be probable at the NH$_2$ group. N(7), C(6)=O and the ribose



R is the Ribose group

Fig. 2

Table 2 ^{13}C NMR chemical shifts of the ligands and their complexes

Compounds	δ[a]									
	Base carbon atoms					Ribose carbon atoms				
	C(6)	C(2)	C(4)	C(8)	C(5)	C(1)'	C(4)'	C(2)'	C(3)'	C(5)'
Adenosine	156.2	152.4	149.1	139.9	119.4	88.0	85.9	73.5	70.7	61.7
RuHCl(ADS)[P(C$_6$H$_5$)$_3$]$_2$	152.2	151.9	149.8	145.8	124.8	88.2	86.2	74.0	71.7	61.9
RuHClCO(ADS)[P(C$_6$H$_5$)$_3$]$_2$	152.4	152.0	148.3	139.9	117.6	88.1	85.3	73.8	69.8	61.1
Guanosine	156.9	153.7	151.4	135.7	116.8	86.6	85.3	73.8	70.5	61.5
RuHCl(GNS)[P(C$_6$H$_5$)$_3$]$_2$	154.8	153.9	151.3	140.9	112.0	87.4	85.5	73.9	69.9	61.2
RuHClCO(GNS)[P(C$_6$H$_5$)$_3$]$_2$	154.5	153.8	149.5	136.1	114.3	87.2	85.1	73.3	68.8	61.0
Inosine	157.2	146.6	148.0	138.8	125.0	88.0	85.8	74.2	70.2	61.1
RuHCl(INS)[P(C$_6$H$_5$)$_3$]$_2$	155.0	146.8	148.2	142.2	120.0	88.2	86.0	74.5	70.5	61.3
RuHClCO(INS)[P(C$_6$H$_5$)$_3$]$_2$	154.8	146.5	148.0	139.0	122.2	87.6	85.6	74.1	70.2	61.2

[a]Chemical shifts are measured from (CH$_3$)$_4$Si internal standard at 15.09 MHz.

Table 3 ^{1}H NMR chemical shifts for the complexes

Compound	Δ				
	N(1)–H	NH_2	H(8)	H(2)	H(1)'
Adenosine		6.92	7.91	7.71	5.45
$RuHCl(ADS)[P(C_6H_5)_3]_2$		6.36	7.40	7.79	5.46
$RuHClCO(ADS)[P(C_6H_5)_3]_2$		6.30	7.88	7.76	5.45
Guanosine	10.65	6.44	7.94		5.73
$RuHCl(GNS)[P(C_6H_5)_3]_2$	10.98	6.48	8.28		5.68
$RuHClCO(GNS)[P(C_6H_5)_3]_2$	10.90	6.48	7.98		5.64
Inosine	12.30		8.35	8.10	5.86
$RuHCl(INS)[P(C_6H_5)_3]_2$	13.10		9.10	8.02	5.79
$RuHClCO(INS)[P(C_6H_5)_3]_2$	12.67		8.46	7.84	5.61

[a]Chemical shifts are measured in Me_2SO-d_6 from $(CH_3)_4Si$ internal standard at 89.55 MHz.

group may bind to the metal ion. N(7), being the most basic site, was reported[10,26-30,34,35] to be the preferred binding site.

The [Ru(Cl)H(GNS)(PPh$_3$)$_2$] complex

The IR spectrum of the complex shows changes in the region 1800 –1600 cm^{-1}, suggesting complexation through the C(6)=O bond. The νC(6)=O of free GNS (1700 cm^{-1}) changes to 1600 cm^{-1} in the spectrum of the complex. Also several νC=N and ring vibrations show significant shifts upon complexation, indicating the binding of ring nitrogen to Ru(II).

The [Ru(Cl)H(CO)(GNS)(PPh$_3$)$_2$] complex

In the IR spectrum of this complex, the νC=O band is shifted to lower frequency (1625 cm^{-1}) showing the involvement of the C(6)=O group of GNS in coordinating to Ru(II).

It has been observed[36] that the delocalisation of electrons in these systems is such that the differences between the N and O centres in these molecules are not large, so steric factors are much important. N(1) and/or O(6) of GNS have been found[31,32,37] to be involved in bonding with Hg(II) and Cu(II) ions. In an Ag(I)–GNS complex a five membered chelate structure is attributed[38] with O(6) and N(7) as binding sites. Hadjiliadis *et al.*[39,40] have suggested that the N(7) and N(1) and the O(6) of GNS binds to Pt(II) and N(7) and O(6) to the Pd(II) ion.

NMR spectra studies

The [Ru(Cl)H(GNS)(PPh$_3$)$_2$] complex

The ^{13}C NMR spectrum shows a significant downfield shift in the C(8) resonance while large upfield shifts of the C(5) and C(6) resonances suggest N(7) and C(6)=O as the chelating sites. ^{1}H NMR data show sizable shifts in N(1)–H and H(8) resonances indicating C(6)=O and N(7) as the sites for coordination.

The [Ru(Cl)H(CO)(GNS)(PPh$_3$)$_2$] complex

The ^{13}C NMR spectrum exhibits only small shifts in the resonances of ribose carbons in Table 2, showing non-coordination of the ribose group to Ru(II). For the GNS complex the C(5) and C(6) resonances show upfield shifts in Table 2. Small shifts are observed for other carbon resonances indicating that neither N(7) nor N(1) participates in binding to Ru(II) ion. The large shifts in the C(6) and C(5) resonances indicate that binding of Ru(II) to GNS takes place through the C(6)=O group.

^{1}H NMR data in Table 3 for the GNS complex show the largest shift in the N(1)–H resonance (0.25 ppm). Being nearest to C(6)=O the above shift is consistent with the proposed coordination site.

Inosine

IR spectra studies

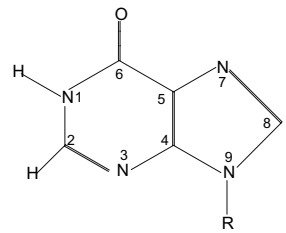
Inosine (Fig. 3) also possesses, along with the ribose group, the N- and O-donor atoms as potential binding sites. INS has been found[38,41-45] to coordinate through N(1), O(6) and N(7) to metal ions. INS is found [46,47] to exist predominantly in the keto form.

The [Ru(Cl)H(INS)(PPh$_3$)$_2$] complex

The IR spectrum of the complex exhibits shifts in C(6)=O vibrations (1700 cm^{-1} to 1608 cm^{-1}) and νC=N and ring vibrations (1610 cm^{-1} to 1585 cm^{-1}) indicating INS to bind through the C(6)=O group and the N(7) atom in chelation.

The [Ru(Cl)H(CO)(INS)(PPh$_3$)$_2$] complex

In the IR spectrum of the complex the band appearing at 1700 cm^{-1} in INS shifts to lower frequency (1620 cm^{-1}) indicating the involvement of the C(6)=O group bonding to Ru(II).



R is the Ribose group

Fig. 3

When metal ions like Co(II), Ni(II), Cu(II) do not interact with C(6)=O, no change in C(6)=O band is observed.[38] But in the case of the Hg complex, a change in the C(6)=O band implicates binding through the C(6)=O group. The transition metals form complexes through the N(7) atom.[42,48-50] Ag(I)–INS[38] and Cu(II)-INS[41] complexes were found to involve the O(6) and N(7) atoms of INS for bonding to form a five membered chelate ring. Theophanides *et al.*[39,40,51] have reported that INS binds to Pt(II) and Pd(II) ions through the N(7) and N(1) atoms and the C(6)=O, depending on pH.

NMR spectra studies

The [Ru(Cl)H(INS)(PPh$_3$)$_2$] complex

The ^{13}C NMR spectrum of the complex shows a significant downfield shift for the C(8) resonance and upfield shifts of the C(5) and C(6) resonances (Table 2), suggesting N(7) and C(6)=O as the binding sites to Ru(II). Also significant shifts in the N(1)–H and H(8) resonances in the ^{1}H NMR spectrum of the complex indicate C(6)=O and N(7) as the sites for coordination of INS to Ru(II).

The [Ru(Cl)H(CO)(INS)(PPh$_3$)$_2$] complex

For the INS complex the largest shifts in ^{13}C NMR resonances are observed for C(5) (2.8 ppm upfield) and C(6) (2.4 ppm upfield) (Table 2), suggesting the binding site for Ru(II) ion is the C(6)=O group. ^{1}H NMR data in Table 3 of the INS complex shows similar shifts as for the GNS complex. The largest shift (0.37 ppm) is for the N(1)–H resonance. The H(8) resonances show negligible shifts. These data also confirm the binding site in INS complex as the C(6)=O group.

Geometry of the complexes

In ^{1}H NMR spectra of the ADS/GNS/INS complexes of {RuHCl$(PPh_3)_3$}, the hydride resonances are observed at δ –26.25 (J_{HP} = 23.4 Hz), δ -26.50 (J_{HP} = 23.8 Hz)and δ -26.40 (J_{HP} = 24.0 Hz) respectively, indicating that hydride is *cis* to $(PPh_3)_2$. In the ADS/GNS/INS complexes of {$RuHCl(CO)(PPh_3)_3$}, the hydride resonances are shifted significantly downfield, to δ –2.40, 2.38 and δ –2.42 respectively, suggesting hydride to be *trans* to the carbonyl. The hydride resonances appear as triplets in the case of all the six complexes, with similar J_{HP} values (23–25 Hz), due to coupling with two equivalent *cis* -triphenylphosphines.

The characteristic IR bands[52] for Ru–P at 410, 414 and 412 cm^{-1} and RuH stretching frequencies at 1938, 1942 and 1940 cm^{-1} respectively for the ADS, GNS and INS complexes of {$RuHCl(PPh_3)_3$}, compared to Ru–P bands at 280, 274 and 278 cm^{-1} and RuH bands at 2012, 2020 and 2018 cm^{-1} for the ADS, GNS and INS complexes of {$RuHCl(CO)(PPh_3)_3$} respectively, appear in the IR spectra of the complexes. The carbonyl stretching frequencies are at 1956, 1952

and 1950 cm^{-1} respectively for ADS, GNS and INS complexes of $\{RuHCl(CO)(PPh_3)_3\}$.

As all the Ru(II) complexes are diamagnetic, [spin paired d^6 Ru(II)], a distorted octahedral geometry could be expected for the new compounds. $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ are the two spin allowed transition expected because the ground state of Ru(II) in an octahedral environment is $^1A_{1g}$. The new Ru(II) complexes exhibit two bands at 500–520 nm and 460–490 nm corresponding to transitions $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ respectively. Therefore, distorted octahedral geometry is proposed for all the new complexes.

Conclusion

In the present work, the binding sites for ADS, GNS and INS have been investigated for two Ru(II) hydride complexes. It is observed that when Ru(II) is less crowded prior to binding with ADS/GNS/INS then the ligands are bidentate, chelating through their exocyclic group C(6)–NH_2 or C(6)=O and N(7) atoms, while in case of more crowded Ru(II) centre with ADS/GNS/INS, the ligands bind through only the exocyclic C(6)–NH_2 group with ADS while for GNS and INS binding is through the C(6)=O group. Thus the binding sites are different from those suggested on the basis of relative basicity of the atoms. This is due to the steric factors exerted by the bulky ligands attached to Ru(II).

As the ligands are coordinated with the exocyclic group which undergoes hydrogen bonding in DNA, this study may relate to the synthesis of antitumour compounds, since it is presumed that the antitumour activity of such compounds is due to the interaction of the C(6)=O group of the guanine constituent of DNA with the compound.[53] Thus the present work suggests it is possible to synthesise compounds that will coordinate through an exocyclic group instead of the nitrogen atoms of nucleic acids or nucleosides if proper factors are taken into consideration.

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