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ALTERNATE g^-g^- CONFORMATION FOR DINUCLEOSIDE PHOSPHATES IN SOLUTION

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An alternative g^-g^- conformation (conformer I') for dinucleosides in solution has been deduced, based on potential energy calculations and nuclear magnetic resonance spectroscopy. This conformation is characterized by larger glycosidic torsional angles ($\chi = 94–111°$) than those of conformer I ($\chi = 8–35°$), although the other torsional angles are similar. There are thus four stable conformers (I, I', II and III) for dinucleosides in equilibrium with the open forms. The structure of conformer I' supports that of the 'vertical' double helix constructed by Olson (W.K. Olson, Proc. Natl. Acad. Sci. U.S.A. 74, (1977) 1775). Our data may suggest the possibility of interconversion between the vertical double helix and the regular double helix of A-form DNA, RNA or A'-form RNA.

1. Introduction

Solution conformation of dinucleoside phosphates, which represent the basic building block of nucleic acids with nearest-neighbor interactions, is important. Because of the dynamic nature of the molecules in solution, the investigation of the solution conformation of dinucleosides has been hampered by a lack of accurate models. Ts'o et al. [1] first proposed a right-handed structure for dinucleosides in solution, using NMR methods of the base protons. Lee et al. [2] and Ezra et al. [3] proposed the g^-g^- ($\omega' = 280°$, $\omega = 285°$) and g^+g^+ ($\omega' = 90°$, $\omega = 80°$) conformers for dinucleosides, using NMR information obtained from the ribose and the base protons. Lee and Tinoco [4] concluded that there are three possible stable conformers I, II and III for dinucleosides in solution using the NMR data of modified dinucleosides containing adenine. These three conformations are further substantiated and refined by semi-empirical potential energy calculations [5] (I, $\omega' = 300°$, $\omega = 291°$; II, $\omega' = 55°$, $\omega = 68°$; III, $\omega' = 60°$, $\omega = 180°$).

Recently, the method of semi-empirical potential energy minimization has been used successfully to compare the stabilities of several proposed conformations for dinucleoside phosphates [5]. This method also has proven to be useful in generating the molecular structures of α-phellandrene, thus yielding the calculated rotatory strengths of the chiral chromophores in agreement with the experimental data [6]. Such an independent approach to molecular structures is a necessary step for the analysis of solution molecular conformations, especially in the case of highly flexible molecules such as dinucleoside phosphates. In the present study, we have found an alternate g^-g^- conformation, designated as conformer I' ($\omega' = 300°$, $\omega = 290°$), for dinucleoside phosphates. Detailed comparison of the structure and potential energy between this conformer (I') and conformer I is discussed. (The conformations of I, II and III of ApA are also listed in table 1 for comparison.)

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Evidence from NMR supporting the existence of this conformer in solution is presented.

2. Methods

The strain energy calculations were carried out on a PDP-10 computer at the National Institutes of Health. The program utilized for the computation, called GEMO, was originally written by Cohen [7], who has kindly made his program available to us.

The original program has been modified for free field input of data, and also for the output of atomic coordinates suitable for direct utilization in the NIH program X-ray. The latter program then utilizes a Calcomp or other plotter to draw the molecular structures (fig. 2).

The conformations of the dinucleosides ApA, ApU, UpA and UpU were optimized by minimizing the energies of the bonds, valence angles, torsional angles and the van der Waal's interactions [5–8]. The total energy of the conformation is expressed as $E_{(conf)} = E_{(l)} + E_{(\theta)} + E_{(\phi)} + E_{(nb)}$, where $E_{(conf)}$ represents the conformational energy, and the terms on the right-hand side of the equation represent bond stretching (or compression) energy, valence angle bending energy, torsional energy and van der Waal's energy, respectively.

The energy functions and parameters are described elsewhere [5–8]. The structure of the bases adenine and uracil are taken as those in the crystal of ApU [9] and are used as fixed (i.e., with constant bond lengths, valence angles and torsional angles) throughout the calculation, so that they give constant contribution to the conformational energy. For the van der Waal's interactions, every pair of atoms separated by more than three bonds is considered. Thus, an unreasonably short contact distance between atoms is avoided in obtaining the energy-minimized structure (table 1). The NMR ring current shifts for the protons of the optimized structures by the neighboring base are calculated by the method of Giessner-Prettre et al. [10] (table 2).

3. Results

3.1. Structure of conformation I′ of dinucleoside phosphates

The structure of the dinucleoside phosphate ApA is shown in fig. 1, and the detailed conformations for conformer I′ of ApA, ApU, UpA and UpU, together with those of conformers I, II and III of ApA are summarized in table 1. It is found that the dinucleosides of different purine-pyrimidine sequences have a common structure of conformation, with both ribose units in the 3′-*endo* conformation, and with the following ranges for the torsion angles: $\chi_1 = 102.5–107°$ (high *anti*), $\phi' = 175.1–184.4°$ (*trans*), $\omega' = 297.8–302.3°$ (*gauche*$^-$), $\omega = 290.8–295.5°$ (*gauche*$^-$), $\phi = 172.9–173.4°$ (*trans*), $\psi = 48.2–54.6°$ (*gauche*$^+$) and $\chi_2 = 94.5–111.7°$ (high *anti*). This structure is similar to that of conformation I [2–5], except for the considerably larger glycosidic torsional angles χ(94.5–111.7°, compared to 8.6–35.2° for I). Direct interconversion between conformations I′ and I can occur, since the energy barrier is small. Only

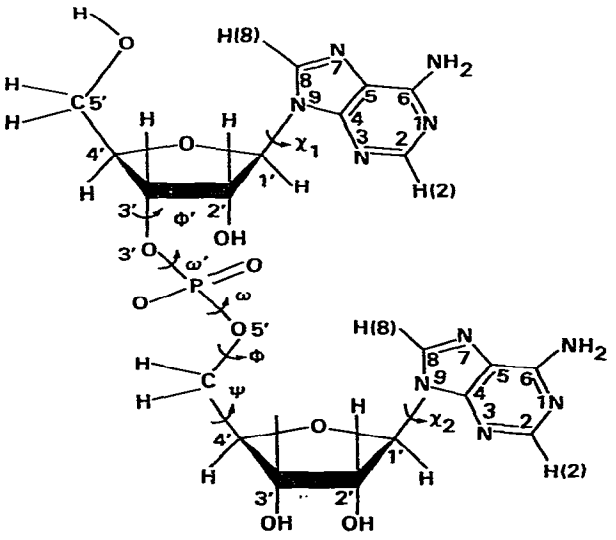

Fig. 1. Structure of the dinucleoside phosphate ApA. The definition of the torsional angles is according to Sundaralingam [11].

Table 1

Torsional angles (and the ribose conformation of conformer I' of dinucleoside phosphates ApA, ApU, UpA and UpU, and those of conformers I, II and III of ApA

	χ_1	Ribose 1	ϕ'	ω'	ω	ϕ	ψ	Ribose 2	χ_2
ApA I'	104.9	3'-*endo*	184.4	302.3	295.5	174.4	54.6	3'-*endo*	94.5
ApU I'	102.5	3'-*endo*	178.2	299.8	291.3	173.7	48.2	3'-*endo*	108.9
UpA I'	107.0	3'-*endo*	175.1	297.8	291.1	172.9	54.5	3'-*endo*	104.9
UpU I'	104.7	3'-*endo*	177.1	299.2	290.8	173.4	50.3	3'-*endo*	111.7
ApA I [a]	15.5	3'-*endo*	184.0	298.7	291.5	172.3	57.1	3'-*endo*	28.2
ApA II [a]	32.2	3'-*endo*	166.8	54.7	69.3	199.5	74.2	3'-*endo*	32.4
ApA III [a]	15.3	2'-*endo*	295.7	61.5	181.5	192.0	66.5	3'-*endo*	99.7

[a] Data taken from ref. 5.

rotation of the glycosidic bonds is required, along with minor adjustments in other torsional angles, and no separation of the stacked bases is involved. The increase in the glycosidic torsional angles in going from I to I' leads to drastic changes in the base-base stacking geometry (fig. 2). Such differences in base-base stacking patterns are also shown clearly in the calculated ring current shifts (table 2).

3.2. Potential energy of conformation I'

The conformational energy for conformer I' (11.3–12.8 kcal/mol) lies within the range of those calculated for conformers I, II and III of dinucleoside phosphates (table 3). When conformation I' is converted to I, there is little change in bond stretching energy. The valence angle bending energy $E_{(\theta)}$ increases by 0.8 to 1.3 kcal/mol, the torsional energy $E_{(\phi)}$ decreases by 0.4 to 0.6 kcal/mol. On the other hand, the van der Waal's attractive energy $E_{(nb)}$ decreases in ApA (0.9 kcal/mol), but increases in the other dinucleosides (0.7 to 1.9 kcal/mol). The conformational energy $E_{(conf)}$ indicates that ApA I' is less stable than ApA I (11.3 vs. 10.0 kcal/mol), while ApU I', UpA I' and UpU I' are each more stable than its corresponding form ApU I, UpA I and UpU I (i.e., 12.2 vs. 12.6, 11.6 vs. 12.0 and 12.8 vs. 13.8 kcal/mol, respectively).

3.3. Evidence from NMR data supporting the existence of conformation I'

3.3.1. Chemical shifts of the base protons in ApA

From the NMR dimerization shifts of the base

Table 2

Calculated ring current shifts (ppm) for conformation I' of ApA, ApU, UpA and UpU

		$H_{1'}$	$H_{2'}$	$H_{3'}$	$H_{4'}$	$H_{5'}$	$H_{5''}$	H_2 or H_5	H_8 or H_6
ApA I'	Ap-	0.121	0.218	0.285	0.086	0.079	0.080	0.003	1.095
	-pA	0.092	0.005	−0.051	−0.017	−0.085	−0.049	1.253	−0.047
ApU I'	Ap-	0.001	0.059	0.032	0.008	0.006	0.007	−0.008	0.116
	-pU	0.083	0.031	−0.039	−0.016	−0.076	−0.045	0.015	0.032
UpA I'	Up-	0.156	0.502	0.326	0.098	0.077	0.085	0.506	1.137
	-pA	0.009	0.003	−0.004	−0.002	−0.009	−0.005	0.072	0.003
UpU I'	Up-	−0.004	0.052	0.028	0.006	0.005	0.006	0.041	0.109
	-pU	0.012	0.004	−0.004	−0.001	−0.009	−0.005	0.005	0.006

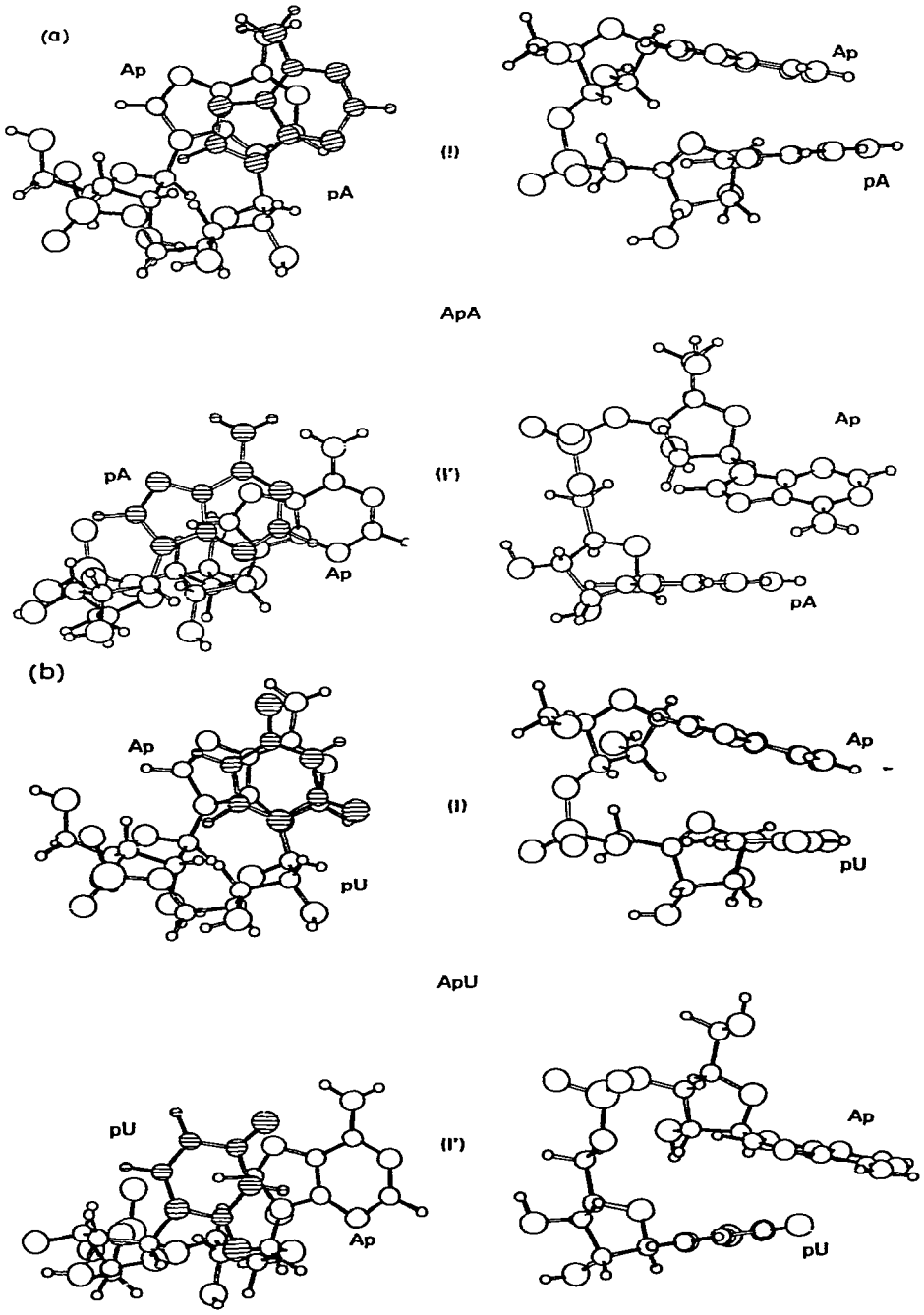

Fig. 2. Structures of conformations I and I' for (a) ApA, (b) ApU, (c) UpA and (d) UpU. The pictures on the right-hand side are drawn parallel to the base of the -pN residue while those on the left-hand side are drawn perpendicular to the base (with shaded circles) of the -pN residue.

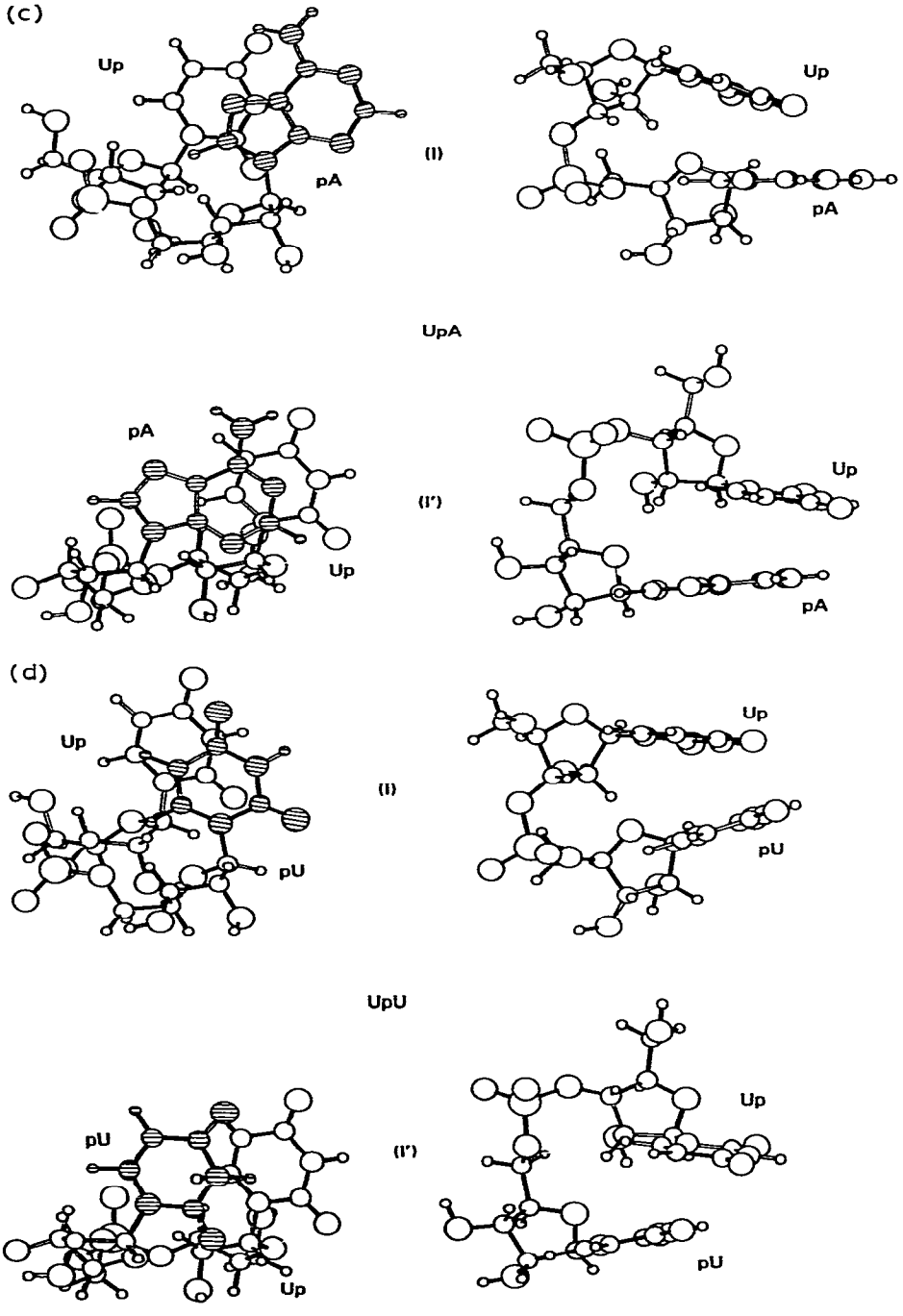
(c)
Up
pA
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Table 3

Conformational energies (kcal/mol) of conformers [a] I, I', II and III of ApA, ApU, UpA and UpU

	$E_{(l)}$	$E_{(\theta)}$	$E_{(\phi)}$	$E_{(nb)}$	$E_{(conf)}$
ApA I	0.03	13.8	9.4	−13.2	10.0
ApA I'	0.02	14.6	9.0	−12.3	11.3
ApA II	0.14	14.3	9.8	−12.1	12.1
ApA III	0.11	11.3	9.7	−9.0	12.1
ApU I	0.03	14.0	9.5	−10.9	12.6
ApU I'	0.06	14.9	8.9	−11.6	12.2
ApU II	0.09	14.1	9.9	−10.7	13.4
ApU III	0.12	11.5	9.6	−8.5	12.7
UpA I	0.04	14.3	9.3	−11.7	12.0
UpA I'	0.04	15.5	8.7	−12.6	11.6
UpA II	0.11	14.1	10.1	−11.5	12.7
UpA III	0.11	11.3	9.7	−9.2	12.0
UpU I	0.06	13.7	9.4	−9.4	13.8
UpU I'	0.08	15.0	8.9	−11.1	12.8
UpU II	0.10	14.2	9.9	−9.5	14.8
UpU III	0.06	11.2	9.3	−7.9	12.7

[a] Data for I, II and III are taken from ref. 5.

protons in dinucleosides, Ts'o et al. [1] proposed a right-handed structure. A similar conclusion was reached later by other researchers [2–5,12]. Nonetheless, the calculated ring current shifts for the base protons in ApA I, II and III are only qualitatively but not quantitively or semiquantitively consistent with the published experimental data [5]. For example, the dimerization shifts of H_8 in Ap- and H_2 in -pA can hardly be accounted for by the predicted values (ref. 5, and table 4 of this paper); and thus an additional conformation such as conformer I' is needed to offset this discrepancy. Since conformation III has the base of the -pA residue overlapping on the ribose instead of the base of the Ap- residue, there is little ring current shift showing up on the base protons. Thus, it is reasonable that the observed dimerization shifts for the base protons in ApA result from the composite of fractions of conformations I, I' and II. The calculated composite ring current shifts at 20°C (assuming 31% for I; 12%, I'; and 7%, II; with the shift values for 100% I and 100% II taken

Table 4

Calculated ring current shifts (ppm) and the observed dimerization shifts (ppm) of the base protons of ApA at 4, 20, 45 and 75°C

	Ap-		-pA	
	H_2	H_8	H_2	H_8
100% (I) [a]	0.947	0.047	−0.122	0.633
100% (I')	0.003	1.095	1.253	−0.047
100% (II) [a]	−0.106	0.082	−0.016	0.579
100% (III) [a]	−0.034	0.178	−0.040	−0.017
Observed values at 4°C [b]	0.355	0.180	0.133	0.285
38% (I)+14%(I')+8% (II)	0.352	0.178	0.128	0.280
38% (I)+ 8% (II)	0.352	0.025	−0.047	0.287
Observed values at 20°C [b]	0.287	0.152	0.114	0.244
31% (I)+12% (I')+7% (II)	0.286	0.152	0.111	0.231
31% (I)+ 7% (II)	0.286	0.021	−0.039	0.237
Observed values at 45°C [b]	0.202	0.133	0.083	0.168
22% (I)+9% (I')+6% (II)	0.202	0.114	0.088	0.170
22% (I)+6% (II)	0.202	0.015	−0.028	0.174
Observed values at 75°C [b]	0.147	0.130	0.068	0.111
16% (I)+7% (I')+5% (II)	0.147	0.089	0.067	0.127
16% (I)+5% (II)	0.147	0.012	−0.021	0.130

[a] Data taken from ref. 5.
[b] Data taken from ref. 4.

from ref. 5) are 0.286, 0.152, 0.111 and 0.231 ppm for H_2, H_8 of Ap- and H_2, H_8 of -pA- respectively. These are in excellent agreement with the corresponding observed values of 0.287, 0.152, 0.114 and 0.244 ppm [4]. Good agreement between the calculated and the experimental chemical shifts for samples at 4, 45 and 75°C is also shown in table 4 when conformation I′ is taken into account. This may suggest that if there be any other base-base stacked conformations for ApA other than I, I′ and II in solution, their populations must be small and insignificant (for example, the left-handed g^-g^- conformation discussed later in section 4). It is also clear that no good agreement between the calculated and the experimental values can be reached without the participation of conformation I′.

3.3.2. Dimerization shifts of $H_{5'}$ and $H_{5''}$ of the -pN residue

It is consistently observed that the NMR signals of $H_{5'}$ of the -pN residue in dinucleosides are shifted downfield to a greater extent than those of the $H_{5''}$ of the same residue upon dimerization [2–4]. This, in addition to the base proton shifts, has been used as evidence supporting the presence of conformation I in solution [2–4]. When interconversion between conformations I and I′ occurs, the rotation of the glycosidic bonds does not significantly alter the relative position of $H_{5'}$ and $H_{5''}$ of -pN with regard to $O_{2'}$ of the Np- residue. The calculated distances from $H_{5'}$ and $H_{5''}$ of -pN to the $O_{2'}$ of Np- are 2.31 and 4.05 Å, respectively, in conformation I′. The corresponding values in conformation I are 2.4 and 4.1 Å. Thus, in both conformations I and I′, $H_{5'}$ of -pN will experience larger diamagnetic (downfield) shift from $O_{2'}$ of Np- upon dimerization because of the shorter distances [2–4].

3.3.3. Torsional angles of the $C_{3'}$-$O_{3'}$, $O_{5'}$-$C_{5'}$ and $C_{5'}$-$C_{4'}$ bonds and the ribofuranose conformation

NMR data have shown that the conformation of the $C_{3'}$-$O_{3'}$, $O_{5'}$-$C_{5'}$ and $C_{5'}$-$C_{4'}$ bonds in dinucleosides are preferentially in the domains of *trans*/*gauche*$^-$, *trans* and *gauche*$^+$, respectively; and both riboses are predominantly in the 3′-*endo* conformation. Conformation I′ has the corresponding torsional angles 178° (*trans*), 173° (*trans*) and 52° (*gauche* +) for $C_{3'}$-$O_{3'}$, $O_{5'}$-$C_{5'}$ and $C_{5'}$-$C_{4'}$ bonds are 3′-*endo* for both riboses. (The corresponding conformational terminologies used for these three bonds by NMR researchers are *gauche*$^-$/*gauche*$^+$ ($\phi' = 180°/300°$) *gauche'*-*gauche'* ($\phi = 180°$) and *gauche*-*gauche* ($\psi = 60°$) [2–5].)

4. Discussions

Using semi-empirical potential energy minimization, we are able to generate conformations of minimal energy for dinucleoside phosphates, which show theoretical chemical shifts consistent with the experimental NMR data. It should be pointed out that the experimental data cited here were measured at 5 mM [4], a concentration at which the intermolecular base-base stacking is negligible, as demonstrated by Ts'o et al. [1] using the method of extrapolation to infinite dilution.

The composite chemical shifts for the base protons in ApA may be affected by the diamagnetic effects of the ribose unit in response to the change of the glycosidic torsional angles upon dimerization [13]. Our calculations, according to the method of Giessner-Prettre and Pullman [13], show that the chemical shifts of the base protons H_2 and H_8 arising from this effect are less than 10% of the observed dimerization shifts by assuming that the glycosidic torsional angles for monomer and dimer are 45 and 10°, respectively (data not shown). Thus, the dimerization shifts of the base protons contributed from this effect are negligible in the present case. Similar calculations (data not shown) for the ribose protons [14] show that only the $H_{1'}$ protons have good agreement between the computed and the observed values, presumably due to the fact that the other ribose protons experience other effects in addition to the ring current effect for chemical shift changes upon dimerization [2–5].

The existence of conformation I′ is further supported by the research of Sarma et al. [15,16]. They studied the conformations of the modified dinucleosides A^spA^s and A^spU^o, in which $C_{2'}$ of the sugar rings cross-links to the adenine C_8 or the uracil C_6 through an S or O atom, and concluded

that these molecules possess a right-handed sugar-phosphate backbone and a left-handed base-base stacking with high *anti* conformation ($\chi = 120°$) for the glycosidic bonds.

Recently, Olson [17] has suggested that single-stranded polynucleotides may possibly have the conformation of left-handed base-base stacking, while still assuming a right-handed sugar-phosphate structure. Further model building indicated that it is possible to construct a 'vertical' double helix using this structure [18]. Conformation I′ of dinucleosides in solution is, indeed, a structure with a right-handed sugar-phosphate backbone (almost the same as that in conformation I, see table 1) but with a left-handed base-base stacking. The comparison between the detailed structure of conformation I′ and that of Olson's vertical double helix [18] is described as: χ, 94–111° (conformer I′)/105–120° (vertical double helix); ϕ', 175–184°/198–210°; ω', 297–302°/268–278°; ω, 291–295°/280–295°; ϕ, 173–174°/178–188°; ψ, 48–55°/58–70°. The agreement between both structures provides experimental as well as theoretical support for the vertical double helix from the conformation of the naturally occurring dinucleosides.

It is also possible that a polynucleotide may assume a left-handed helical conformation with g^-g^- (i.e., $\omega' = 265°$ and $\omega = 275°$) and high *anti* (i.e., $\chi = 120°$) configurations as suggested by Yathindra and Sundaralingam [19]. In order to examine the possibility of this left-handed conformation for dinucleosides in solution, a similar energy minimization was carried out for ApA with ω', ω and χ angles fixed at 265, 275 and 120°, respectively. It is found that this conformer is energetically unfavorable ($E_{(conf)} = 40.2$ kcal/mol) compared to conformers I and I′ ($E_{(conf)} = 10–11.3$ kcal/mol, table 3). The high conformation energy of this conformer is primarily contributed by the unstable torsional angles of ω'(265°), ω(275°) and χ(120°), which yield 35.4 kcal/mol for $E(\phi)$ of this conformer. Also, the valence angle bending energy ($E_{(\theta)} = 15.4$ kcal/mol) and the van der Waal's energy ($E_{(nb)} = -10.7$ kcal/mol) of this left-handed conformer make the molecule less stable than the other conformers (table 3). Thus, the population of this left-handed conformation for dinucleoside in solution is probably minimal and negligible.

Other conformers, which do not have ϕ', ϕ and ψ in *trans, trans* and *gauche*$^+$ conformations, respectively, may be able to fit the dimerization data of the base protons. However, in light of the fact that *trans* and *gauche*$^+$ conformations contribute about 80–90% population for ϕ and ψ in dinucleosides in solution [2–5], such conformers, if any, are apparently the minor species and thus negligible.

Substitution at C_8 of purine or C_6 of pyrimidine of a nucleotide with a bulky group such as Br or S-CH_3 or an aza group is likely to cause a steric repulsion between the exocyclic sugar-phosphate backbone and the base at the *anti* conformation [20–22]. This molecular strain can be relieved by rotating either the glycosidic bond or the $C_{4'}$-$C_{5'}$ and $C_{5'}$-$O_{5'}$ bonds, or both. Such structural modification is likely to lead to an increase in the population of conformation I′ (i.e., $\chi = 100°$) as well as those of *syn*, *g/t* and *g′/t′* conformers [20–22]. (The *g/t* and *g′/t′* rotamers defined by NMR researchers are equivalent to $\psi = -60°$ (*gauche*$^-$) or 180° (*trans*) and $\phi = \pm 60°$ (*gauche*$^+$ and *gauche*$^-$).)

5. Conclusions

We have shown by energy-minimization calculations and NMR spectroscopy that an alternate g^-g^- conformation (I′) exists for dinucleosides in solution. This conformer has much larger glycosidic torsional angles (94–111°) than those of conformer I (8–38°), [5], while the other torsional angles for I′ and I are close to each other, assuming that ϕ', ϕ and ψ are in *trans, trans* and *gauche*$^+$ conformations, respectively. Therefore, there are four stable conformations (I, I′, II and III) for dinucleosides in equilibrium with the open forms in solution [1–5,12]. This can be represented by the following scheme:

$$g^-g^-(\mathrm{I}' \rightleftharpoons \mathrm{I})$$
$$\Updownarrow$$
base-base unstacked forms $\rightleftharpoons g^+g^+(\mathrm{II})$
(open forms = g^+t or III)

Our present study suggests that energy minimization is a necessary procedure for molecular modeling in order to explain solution data such as those obtained using NMR or circular dichroism for flexible molecules.

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