Raman Spectroscopy of Z-Form Poly[d(A-T)]·Poly[d(A-T)]

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ABSTRACT: Helical structures of double-stranded poly[d(A-T)] in solution have been studied by Raman spectroscopy. While the classical right-handed conformation B-type spectra are obtained in the case of sodium chloride solutions, a Z-form Raman spectrum is observed by addition of nickel ions at high sodium concentration, conditions in which the inversion of the circular dichroic spectrum of poly[d(A-T)] is detected, similar to that observed for high-salt poly[d(G-C)] solutions [Bourtayre, P., Liquier, J., Pizzorni, L., & Taillandier, E. (1987) *J. Biomol. Struct. Dyn. 5*, 97-104]. The characterization of the Z-form spectrum of poly[d(A-T)] is proposed by comparison with previously obtained characteristic Raman lines of Z-form poly[d(G-C)] and poly[d(A-C)]·poly[d(G-T)] solutions and of $d(CG)_3$ and d(CGCATGCG) crystals [Thamann, T. J., Lord, R. C., Wang, A. H.-J., & Rich, A. (1981) *Nucleic Acids Res. 9*, 5443-5457; Benevides, J. M., Wang, A. H.-J., van der Marel, G. A., van Boom, J. H., Rich, A., & Thomas, G. J., Jr. (1984) *Nucleic Acids Res. 14*, 5913-5925]. Detailed spectroscopic data are presented reflecting the reorientation of the purine–deoxyribose entities (C2′-endo/anti → C3′-endo/syn), the modification of the phosphodiester chain, and the adenosine lines in the 1300-cm^{-1} region. The role played by the hydrated nickel ions in the B → Z transition is discussed.

Among all synthetic polydeoxynucleotides, poly[d(A-T)] is certainly one of the most polymorphic. A wide variety of different helical structures have been suggested for this polynucleotide, depending on the experimental conditions. Thus, the right-handed A–D geometries and various other models, for example, alternating B (Klug et al., 1979), have been proposed to interpret the data of X-ray diffraction (Davies & Baldwin, 1963; Arnott et al., 1974; Leslie et al., 1980; Drew & Dickerson, 1982; Mahendrasingam et al., 1983), NMR (Shindo et al., 1979; Kypr et al., 1981; Patel et al., 1981; Vorlickova et al., 1983; Sarma et al., 1984; Assa-Munt et al., 1984), circular dichroism (CD) (Sarocchi & Guschlbauer, 1973; Brahms et al., 1976; Vorlickova et al., 1982; Jovin et al., 1983; Thomas & Bloomfield, 1985), Raman spectroscopy (Small & Peticolas, 1971; Thomas & Peticolas, 1983; Thomas & Benevides, 1985; Fodor et al., 1985; Wartell & Harrell, 1986), and infrared spectroscopy (Pilet et al., 1975; Brahms et al., 1976; Adam et al., 1987). The existence of left-handed DNA structures, proposed to interpret the inversion of the CD spectrum of poly[d(G-C)] in high sodium chloride solutions (Pohl & Jovin, 1972), has been proved by X-ray diffraction studies on a $d(C-G)_3$ crystal (Wang et al., 1979). Raman spectroscopy has shown that the structures of the crystallized hexamer and of poly[d(G-C)] in high salt were the same (Thamann et al., 1981), and marker lines of the C3′-endo/syn geometry of guanosines in Z form were proposed. Whereas oligo- and polydeoxynucleotides containing only G-C base pairs quite easily adopt this structure, the introduction of A-T base pairs in regularly alternating $d(G-C)_n$ sequences makes the right → left interconversion more difficult to observe (Rich et al., 1984; Jovin et al., 1988). In the case of poly[d(A-T)] this transition is still more difficult to detect. The stabilization of the Z conformation has been proposed for chemically modified polymers poly[d(2-amino-A-T)] (Howard et al., 1984) and poly[d(A-s^4T)] (Arnott et al., 1980; Jovin et al., 1983). Insertion of $d(A-T)_n$ sequences in plasmids has led to diverging conclusions: subsequent induction of supercoils modifies the structure of the insert and has been interpreted either in terms of Z conformation (McLean et al., 1986) or not (Haniford & Pulleyblank, 1985; Panyutin et al., 1985), depending on the length of the insert and the nature of the flanking sequences. In oligonucleotides a small number of A-T base pairs incorporated in G-C sequences adopt a Z geometry, as shown by X-ray diffraction (Wang et al., 1984; Coll et al., 1986), NMR (Patel et al., 1985), Raman spectroscopy (Benevides et al., 1984), and IR spectroscopy (Taboury et al., 1984a). We have characterized by IR spectroscopy the Z-form marker bands observed for hydrated films of poly[d(A-T)] in the presence of divalent transition-metal ions (Adam et al., 1986a,b). Moreover, in solution we have shown the existence of a new inverted CD spectrum for poly[d(A-T)] obtained in high salt (5 M NaCl) and in the presence of nickel (95 mM $NiCl_2$). This spectrum, which exhibits a positive band at 261 nm, a structured negative band at 292 and 280 nm, and no negative band on the low-wavelength side, has been interpreted in terms of a left-handed geometry of the polymer (Bourtayre et al., 1987). We present here the Raman marker lines of the left-handed geometry of poly[d(A-T)] obtained in solution at the same ionic strength (5 M NaCl/95 mM $NiCl_2$). The conditions that allow the stabilization of the Z form of unmodified poly[d(A-T)] are discussed.

Materials and Methods

2′dA and 2′dT were purchased from P-L Biochemicals; poly[d(A-T)] was purchased from Sigma (lot 55F-05262). The polynucleotide was dissolved in 5 M NaCl directly in the microcell (concentration of 1 OD/μL). A concentrated solution of $NiCl_2$ was added up to a final concentration of 95 mM $NiCl_2$. Samples were exposed to the 514.5-nm line from a Spectra-physics Model 2025 argon laser. The output power used was 400 mW at the source. Raman spectra were recorded on a Dilor Omars 89 multichannel spectrophotometer coupled to an IBM PCAT3 computer. Integration time was usually 8 s. Each spectrum is an average of about 250 integrations. Solvent background correction was performed by

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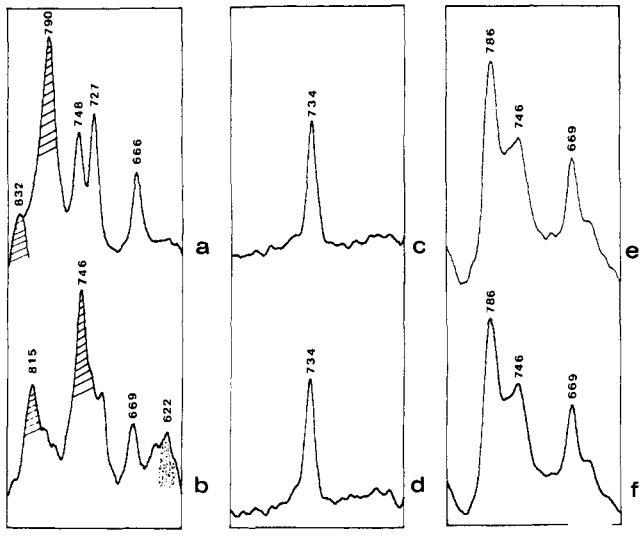

FIGURE 1: Raman spectra in the 600–850-cm^{-1} region: (a) poly[d-(A-T)], 5 M NaCl, B form; (b) poly[d(A-T)], 5 M NaCl/95 mM $NiCl_2$, Z form; (c) 2′dA, 5 M NaCl; (d) 2′dA, 5 M NaCl/95 mM $NiCl_2$; (e) 2′dT, 5 M NaCl; (f) 2′dT, 5 M NaCl/95 mM $NiCl_2$. Hatched, phosphodiester chain stretching vibrations; stippled, purine C3′-endo/syn.

subtracting the solvent spectrum recorded in the same conditions.

Results and Discussion

600–850-cm^{-1} Region. In Figure 1 are shown the Raman spectra between 600 and 850 cm^{-1} of poly[d(A-T)] in 5 M NaCl (Figure 1a) and 5 M NaCl/95 mM $NiCl_2$ (Figure 1b) and of 2′dA (Figure 1c,d) and 2′dT (Figure 1e,f) in the same ionic strength conditions. This spectral region contains on the one hand lines due to the base vibrations and on the other hand lines due to motions of the phosphodiester chain. On the low-salt spectrum (Figure 1a) are observed a thymidine line at 748 cm^{-1}, an adenosine line at 727 cm^{-1}, a line at 666 cm^{-1} involving both adenosine and thymidine, and two lines assigned to motions of the P–O single bonds in the phosphodiester backbone: a symmetric stretching vibration at 790 cm^{-1} and an antisymmetric stretching vibration at 832 cm^{-1}. This spectrum reflects a B-type geometry of the polynucleotide (Thomas & Peticolas, 1983; Thomas & Benevides, 1985; Fodor et al., 1985; Wartell & Harrell, 1986). When nickel is added to the solution, a totally new Raman spectrum is obtained (Figure 1b), which is different from the A-form Raman spectrum of poly[d(A-T)] previously discussed (Thomas & Benevides, 1985). In this spectral region one of the most important marker lines of the Z conformation has been found. The line at 625 cm^{-1} is characteristic of the Z form of poly[d(G-C)] (Pohl et al., 1973; Thamann et al., 1981; Benevides & Thomas, 1983; Nishimura et al., 1984). A similar line has been detected in the Z-form spectra of poly[d-(A-m^5C)]·poly[d(G-T)] (McIntosh et al., 1983) and poly[d-(A-C)]·poly[d(G-T)] (Ridoux et al., 1987). Similarly, in the Raman spectrum of poly[d(A-T)] obtained in the presence of nickel a new line is observed at 622 cm^{-1} (Figure 1b). In parts c and e of Figure 1 are presented the spectra of 2′dA and 2′dT in 5 M NaCl. They are in agreement with previously published spectra of the nucleosides in the solid state (Mathlouthi & Seuvre, 1984; Mathlouthi et al., 1984) and can be interpreted in particular on the basis of recent force-field computations (Letellier et al., 1987a). The addition of nickel ions to either 2′dA or 2′dT in the same high-salt conditions (5 M NaCl) does not perturb the spectra of the nucleosides in this region, as can be clearly seen by comparing parts c and d of Figure 1 on the one hand and parts e and f of Figure 1 on the other. Thus, the modifications in this region of the poly[d(A-T)] spectrum due to the addition of nickel do not reflect a particular interaction with the nickel ion but do reflect changes at the level of the secondary structure of the polynucleotide.

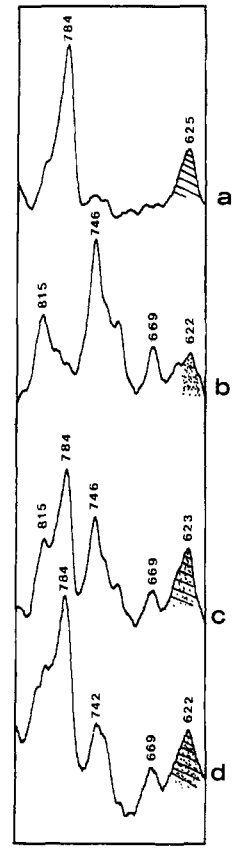

FIGURE 2: Raman spectra in the 600–850-cm^{-1} region of Z conformations: (a) poly[d(G-C)]; (b) poly[d(A-T)]; (c) computed spectrum of (a) plus (b); (d) poly[d(A-C)]·poly[d(G-T)]. Stippled, dA C3′-endo/syn; inverse hatched, dG C3′-endo/syn.

In Z-form poly[d(G-C)] (solutions) and $d(CG)_3$ (crystal) the guanosines are in a C3′-endo/syn geometry, and it is well established that the 625-cm^{-1} line precisely reflects this geometry (Thamann et al., 1981). In the case of poly[d(A-m^5C)]·poly[d(G-T)] and poly[d(A-C)]·poly[d(G-T)] contributions of both guanosines and adenosines in C3′-endo/syn geometry should be expected. Figure 2 presents the Raman spectra of poly[d(G-C)] (Figure 2a), poly[d(A-T)] (Figure 2b), and a computer-stimulated spectrum (Figure 2c) obtained by addition after normalization of the two previous ones. This simulated spectrum is in excellent agreement with the experimental spectrum of Z-form poly[d(A-C)]·poly[d(G-T)] presented in Figure 2d (Ridoux et al., 1987). Thus, the existence of a Raman line around 622 cm^{-1} in the spectrum of poly[d(A-T)] in the presence of nickel can be interpreted as reflecting a C3′-endo/syn geometry of adenosines.

The 625-cm^{-1} line of the Z-form spectrum of poly[d(G-C)] is assigned to a breathing motion of the guanine coupled through the C1′–N9 glycosidic bond to a deoxyribose vibration (Letellier et al., 1986). In the B geometry of the polynucleotide this vibrational mode was located at 682 cm^{-1}. A recent normal coordinate analysis based on the GF Wilson matrix method, concerning adenosine and thymidine residues involved in polynucleotides, shows that B geometry the adenosine breathing motion coupled through the C1′–N9 bond to a deoxyribose vibration is involved partly in the 727-cm^{-1} and

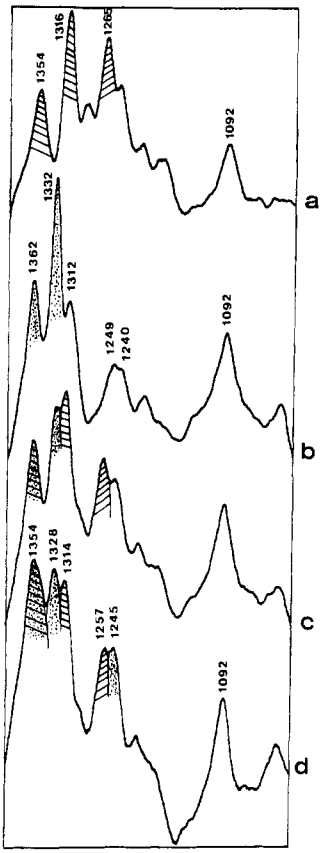

FIGURE 3: Raman spectra in the 1000–1400-cm^{-1} region of Z conformations: (a) poly[d(G-C)]; (b) poly[d(A-T)]; (c) computed spectrum of (a) plus (b); (d) poly[d(A-C)]·poly[d(G-T)]. Inverse hatched, dG C3′-endo/syn; stippled, dA C3′-endo/syn; hatched, dC.

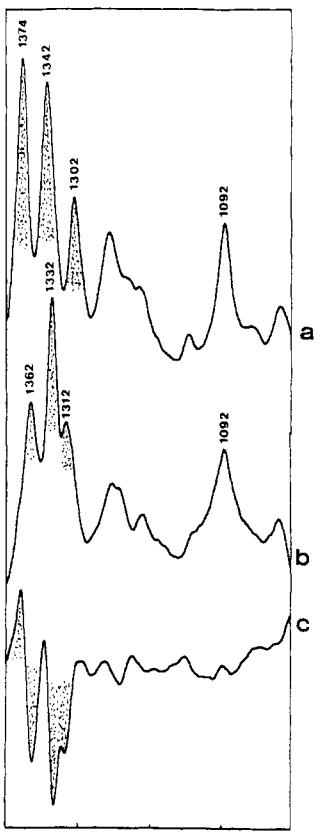

FIGURE 4: Raman spectra in the 1000–1400-cm^{-1} region of poly[d(A-T)]: (a) 5 M NaCl, B form; (b) 5 M NaCl/95 mM $NiCl_2$, Z form; (c) difference spectrum of (a) minus (b). Stippled, dA.

partly in the 666-cm^{-1} lines (Letellier et al., 1987b; Ghomi et al., 1988). The latter contribution is overlapped in the spectrum by a thymidine line. In Z geometry, the calculation has predicted a shift of the 666-cm^{-1} line to lower wavenumbers, around 623 cm^{-1}. The experimental result is in excellent agreement with the computation: we observe (Figure 1b) a decrease of the relative intensity of the 727-cm^{-1} line and a new line at 622 cm^{-1}. The reorientation of the purine residues under the B → Z transition is thus reflected on the Raman spectrum in a similar way for adenosines as for guanosines.

The B → Z reorientation also induces modifications in the phosphodiester chain geometry, as initially shown by X-ray diffraction of the $d(C\text{-}G)_3$ crystals (Wang et al., 1979). The antisymmetric and symmetric stretching vibrations of the P–O bonds in the phosphodiester chain are respectively observed at 832 and 790 cm^{-1} in the B-form spectrum of poly[d(A-T)] (Figure 1a). In the Z-form spectrum these lines are shifted to 815 and 746 cm^{-1} (Figure 1b). The 746-cm^{-1} line overlaps then a thymidine line, which in the B form was observed at 748 cm^{-1}. These shifts of the phosphodiester chain lines are very similar to those previously observed for poly[d(A-C)]·poly[d(G-T)] (Figure 2d) and poly[d(G-C)] (Figure 2a). In the case of poly[d(G-C)] in the B form, a cytosine ring breathing line located at 784 cm^{-1} overlaps the symmetric stretching phosphate line. Under the B → Z transition the phosphate line is shifted to 742 cm^{-1} while the intense cytosine line remains unaffected at 784 cm^{-1}. The comparable behavior of the phosphodiester chain lines for these three polynucleotides may reflect a similarity of their backbone in Z geometry.

1000–1400-cm^{-1} Region. In Figure 3 are presented the Raman spectra of left-handed Z-form structures of poly[d(G-C)] (Figure 3a) and poly[d(A-C)]·poly[d(G-T)] (Figure 3d) as well as the spectrum of poly[d(A-T)] recorded in the presence of nickel (Figure 3b). Spectrum c has been computed by addition of equivalent contributions of spectra a and b after normalization, using the phosphate 1092-cm^{-1} line as a standard, so as to simulate a 1/1 A-T/G-C base pair ratio. This curve can be satisfactorily compared with the experimental spectrum of poly[d(A-C)]·poly[d(G-T)] presented in Figure 3d, which comforts us to consider that the structure of poly[d(A-T)] obtained in the presence of nickel is indeed a Z form. We must recall that the modifications of the poly[d(A-T)] spectrum are in excellent agreement with earlier predictions of Benevides et al. (1984) concerning a "Raman spectrum of a hypothetical Z DNA containing only A-T base pairs in alternating sequence". These authors had proposed some characteristics obtained by subtracting from the spectrum of a Z octamer d(CGCATGCG) that of a Z hexamer d(CGCGCG).

The geometry of these crystals has been previously determined as Z form by X-ray diffraction (Fujii et al., 1985; Wang et al., 1979). The difference spectrum should have been that of A-T pairs in Z form. The authors concluded that the main differences between the B- and Z-form spectra should be expected in the 1200–1500-cm^{-1} region. The shifts and the difference intensity profiles we present here concerning the group of lines between 1300 and 1400 cm^{-1} are in excellent agreement with their predictions. This region contains in particular several adenosine lines extremely sensitive to the secondary structure of the DNA. In Figure 4 are presented the classical spectrum of B-form poly[d(A-T)] (Figure 4a), the spectrum recorded in the presence of nickel (Figure 4b), and the difference spectrum (Figure 4c). The difference spectrum has been obtained after normalization of the spectra presented in parts a and b using the phosphate symmetric stretching vibration line located at 1092 cm^{-1} as a standard.

Important changes in the Raman spectrum can be easily detected concerning both positions and relative intensities of three lines located at 1302, 1342, and 1374 cm^{-1} in the case of the B geometry. These lines have been respectively assigned to adenosine vibrations, as far as the first two are concerned, and to adenosine and thymidine vibrations for the latter one. (Prescott et al., 1984; Wartell & Harrell, 1986). In the presence of Ni^{2+}, three strong lines are also detected, but at 1312, 1332, and 1362 cm^{-1} (Figure 4b). The adenosine line observed at 1374 cm^{-1} in the B form involves an important contribution of the C1′–N9 glycosidic bond torsion (Letellier et al., 1987b). When a right- → left-handed transition is simulated with an anti → syn reorientation of the purine deoxyribose entities, the normal coordinate analysis predicts a shift of this line to lower wavenumbers. This is true not only for adenosine but also for guanosine (Letellier et al., 1986) and has been observed experimentally by Raman spectroscopy for poly[d(G-C)] (Benevides & Thomas, 1983) and poly[d(A-C)]·poly[d(G-T)] (Ridoux et al., 1987) and by IR spectroscopy on hydrated polynucleotide films (shift of the 1374-cm^{-1} band to lower wavenumbers; Taillandier et al., 1984; Taboury et al., 1985; Adam et al., 1986a). The shift of the adenosine line in the poly[d(A-T)] spectrum when nickel is added (Figure 4a,b) from 1374 to 1362 cm^{-1} is thus indicative of a C2′-endo/anti → C3′-endo/syn reorientation of the adenosine, in agreement with the detection of the syn Raman marker line at 622 cm^{-1} previously discussed.

Conditions of the B–Z Transition. The induction of the Z geometry of poly[d(A-T)] has been observed at 5 M NaCl/95 mM $NiCl_2$. Z poly[d(A-T)] has not been obtained simply by increasing the ionic strength of the solution, as for poly[d(G-C)]. An attempt to obtain the left-handed structure by addition of the nickel chloride alone is unsuccessful and is followed by immediate precipitation of the polynucleotide. Thus, the combined effect of high sodium chloride and specific metal ions is necessary. The B → Z transition occurs in a very narrow range of nickel concentrations (between 85 and 95 mM $NiCl_2$). Different interaction sites are available on the DNA, strongly electronegative phosphate groups on the one hand and nucleophilic sites on the bases, such as the N7 of purines, on the other. A recent work has shown that, as far as the induction of the B → Z transition is concerned, these different interaction sites are not identically efficient (Ho et al., 1987). Thus, in the case of a d(CGCGCG) crystal, ruthenium hexaammine is less efficient than cobalt hexaammine in inducing the Z form although there are more potential sites available for the larger ruthenium complex than for the cobalt analogue. The authors proposed that the ruthenium complex would exhibit the same affinities for the phosphates as for the convex surface and that binding to the phosphates would be ineffective in stabilizing or would even destabilize the Z form. Similarly, in the case of poly[d(A-T)]–Ni^{2+} it seems that interactions on purine N7 sites are most important to induce the B → Z conformational change.

We have previously shown by IR spectroscopy in several studies concerning poly[d(G-C)], poly[d(A-C)]·poly[d(G-T)], and poly[d(A-T)] that divalent transition-metal ions such as nickel or cobalt interact with the N7 site of purines (guanosines, adenosines, or both) (Taboury et al., 1984b; Adam et al., 1986b). It is known that binding of bulky ligands on the N7 site of purines [for a review, see Jovin et al. (1988)] stabilizes the syn geometry of the nucleoside. We propose that binding of nickel on the N7 of adenines plays this role. Other interactions of the nickel could be expected at the level of the phosphate groups; therefore, the presence of an important concentration of sodium ions may shield the phosphate charges and lead the subsequently added nickel ions to interact preferentially with the bases.

In solution the nickel entity that will interact with the DNA is a complex hydrated ion, $Ni(H_2O)_6^{2+}$ (Liquier et al., 1984). The water molecules bound to nickel have been detected by IR spectroscopy performed on hydrated poly[d(A-T)]–Ni^{2+} films (Adam et al., 1986a). The organization of the water molecules may play a capital role in the stabilization of the helical geometries of DNAs (Kopka et al., 1983; Wang et al., 1984). A simple decrease of the water activity has even been proposed as the main factor accounting for the induction of B → A or B → Z transitions (Taboury et al., 1984b; Saenger et al., 1987). The nickel complex hydrated ion that interacts with poly[d(A-T)] modifies the organization of water molecules around the B helix, which may play a favorable role to induce the B → Z transition and stabilize the Z conformation.

In conclusion, we propose that the Z form of poly[d(A-T)] may be obtained thanks to interactions of a nickel ion on the N7 of adenosines. This interaction would play a double role: stabilization of the syn geometry of adenosines and reorganization of the water distribution along the DNA. This interaction would be made possible thanks to the screening of the strongly negatively charged phosphate groups by the presence of a high sodium concentration. This work shows that in appropriate conditions any regularly alternating purine–pyrimidine sequence can adopt a Z geometry. As recently proposed (Jovin et al., 1988), the Z form seems to have quite universal characteristics, which may possibly be considered as not sequence specific. Such characteristics can be pointed out by markers provided here by Raman spectroscopy: (1) Raman lines characteristic of the Z DNA backbone (phosphodiester chain vibrations) located around 746 and 815 cm^{-1}; (2) syn geometry of the purines evidenced by a breathing mode coupled to the deoxyribose vibration around 622 cm^{-1}; (3) characteristic profile in the 1300–1400-cm^{-1} region with, in particular, a shift of the 1374-cm^{-1} purine line to lower wavenumbers correlated with the anti → syn reorientation of the nucleosides under the B → Z transition.

We hope that these markers may allow the investigation in solution by Raman spectroscopy of more complex systems such as protein–DNA reconstituted entities.

Registry No. Ni, 7440-02-0; poly[d(A-T)], 26966-61-0.

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