SEQUENCE-SELECTIVE BINDING OF TRANSITION METAL COMPLEXES TO DNA EINAR SLETTEN pdf

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Einar Sletten 3; Einar Sletten 3 and N. Ã…. () Sequence-Selective Binding of Transition Metal Complexes to DNA, in Metal Complex-DNA Interactions (eds N.

Bearing in mind that the model used is rather crude all of the sugar backbone replaced by methyl groups , further discussion of more subtle sequence-specific differences is not warranted. The relative rates of sequence oxidation were determined by densitometric assay of the ODN cleavage bands. The amount of charge on a certain G was calculated from the coefficients of the guanine fragment orbitals. Quantitative densitometric assay was used to determine the relative amounts of cleavage products. The experimental results were compared to IP values calculated for 16 sets of base-paired G- and GG-containing 5-mers. A plot of the log of the relative reactivity krel toward photo-induced one-electron oxidation versus calculated IP is shown in Figure 1. Reprinted with permission from J. Copyright American Chemical Society. The authors propose that the accessibility of H2O to the reaction site determined by the steric blocking by the methyl group plays the dominant role for the observed sequence-selectivity, rather than electronic effects. Dodecamer 12 base pair sequences adopting a normal B-DNA double-helical conformation, are assumed to complete a full turn of a right-handed helix. The structure of such a mini-helix is probably sufficiently close to that of real DNA to serve as a realistic model for determining preferred metal binding sites. The effects of adding paramagnetic metal ions to an aqueous solution of DNA fragments may be monitored by observing the decrease in spin-lattice T1 and spinspin T2 relaxation times related to line-broadening for protons close to the metal centres. Paramagnetic metal ions may be classified according to their electronic correlation times, i. In this case geometric information about metal binding sites is most effectively obtained by measuring proton spin-lattice relaxation times T1. Paramagnetic relaxation arises in NMR spectroscopy when an unpaired electron spin interacts with a nuclear spin. The large magnetogyric ratio of the electron compared to that of the proton makes the dipolar coupling to the electron spin a very effective means of relaxation for the nuclear spin. In the simplest possible case, a ligand molecule exchanges between a paramagnetic environment e. The effect of paramagnetic metal ions located at specific binding sites on DNA is observed as differential linebroadening of proton signals close to the binding site. Often, in 1D spectra of oligonucleotide molecules containing ten base pairs or more, key proton resonances may be severely overlapped, preventing an accurate assessment of the influence of 10 Sequence-Selective Binding to DNA the added metal ions. For diamagnetic metal ions no unpaired spin the formation of a chemical bond is usually found to cause changes in the chemical shifts of proton resonances of hydrogen atoms in the proximity of the metal binding site. G4 open squares , G10 filled squares. The circles represent the overlapping G2 and G12 resonances7 the minor groove see discussion below. The amount of broadening was consistent with inner sphere coordination to G-N7. The binding to guanine by 3d transition metals was not surprising, considering the differences in thermodynamic stability of the corresponding complexes of the nucleoside and nucleotide monomers. It is evident that the exposed terminal residues both in sequence II and the previous sequence I, although offering favourable accessibility, are not the preferred binding sites. One may also notice that the A5-H2 and A7-H2 protons, residing in the minor groove, are completely unaffected. A systematic search for a selectivity pattern was initiated by designing three self-complementary sequences: The H8 and H6 proton resonances of purine and pyrimidine residues are labelled according to their sequential assignment8 distinct sequence-selective pattern: The adenine A-H8 resonances, plotted as references, are not influenced by the paramagnetic ions. In contrast, the terminal G1-H8 in duplex II see above shows almost no line-broadening. VI , where the metal ions are coordinated only to the terminal guanine G1-N7 position, with no metal ions binding to nonterminal guanine positions. This is in contrast to our studies, which show a clear sequence-selective binding pattern for 3d metal ions with no special NMR Spectroscopic Studies 13 Figure 1. One may notice that only Gs in the context G-purine exhibit maximum broadening. A close inspection of Table 1. The residues which show maximum

broadening are marked in bold and underlined. Restriction enzyme recognition sequences are marked in italic Sequence 1. At higher metal ion concentrations most 1H NMR resonances undergo varying degrees of broadening. It must be stressed, however, that only relative broadening effects for each sequence are taken into account. The effects of varying the X-residue are clearly shown in Figure 1. As a caveat we should mention that minute paramagnetic impurities in DNA samples used for NMR structure determination seriously affect the validity of the structural analysis since calculations of protonâ€" proton distances are based on the magnitude of cross-peak intensities. Consequently, spin-spin T1 relaxation time measurements will give more reliable information on metal binding sites than line-broadening T2 data. The affinities for G3 and G4 are identical within experimental errors, while the affinity of G5 in the context GT is, as expected, significantly lower.

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1 Sequence - Selective Binding of Transition Metal Complexes to DNA Einar Sletten and Nils Ã… ge Ã¸ ystein Fr Introduction.

The reaction mixtures exhibited no, or only slight, upfield highly sequence dependent. A long-term goal is to design metal complexes that can bind selectively to chosen sequences Large variations in the efficacy of anticancer platinum drugs of DNA. Previously, a general selectivity pattern for 3d are exhibited depending on the type of malignancy. This may transition-metal binding to the guanine residues in double- be related to differences in the genetic expression, and it is helical oligonucleotides was proposed based on proton NMR tempting to speculate that the drugs may bind to DNA in a line-broadening studies. This sequence selectivity is not Bergen Norway observed for single-stranded oligonucleotides unpublished Fax: This finding supports our proposed selectivity [c] Prof. Sadler rule, which is based on NMR experiments. It is apparent that School of Chemistry adjacent residues exert a minor influence. A Supporting information for this article is available on the WWW under simple electrostatic interaction between a positive metal ion http: They conclude that the wide result which does not agree with the proposed selectivity rule and very electronegative minor groove, as found in T4A4 , for labile metal ion complexes. Recently, Hambley has provides an excellent site for divalent cation localization, summarized the present status on platinum binding to while the narrow minor groove of A4T4 is not nearly as DNA. Apparently, the are discussed in relation to ab initio calculations of HOMOs rule of sequence selectivity, which was proposed for labile of several G-containing 5-mer duplexes with B-form geom- metal ion complexes and which is based on 1H NMR and etry published by Saito et al. However, the mechanism of chelate formation does not necessarily follow the sequence selectivity of the initial formation of monofunctional adducts. The chemicals used for HPLC purification: Sodium perchlorate and sodium cleotides, both NMR spectroscopic and chromatographic dihydrogen phosphate were from Merck. The metal salt MnCl2 was from methods have been used to determine kinetic parameters. NMR spectra were recorded on the following instru- des. In these reactions, an initial monofunctional adduct is ments: Each instrument was fitted with a pulsed gradient formed that subsequently ring-closes to form a bifunctional module and a 5 mm inverse probehead. The instruments were used for the chelate. In a reaction 1 H NMR spectra. The mixtures containing each of or t1 increments. The products of II proper coherence and the 15N spins were decoupled during acquisition. The pH of the samples was 6 and the sodium beginning of the reaction, this was gradually increased to 32 transients. A perchlorate concentration was mm. The concentration of metal ions relaxation delay of 2 s was used. Data collected for initial concentration of 0. The apodization function used in both dimensions for the 2 D and subsequently after every 20 min for the next two hours followed by data was a pure squared-cosine-bell, and an exponential window function longer intervals for the next 10 h. The same procedure was followed for kinetic studies of II with the original value, except for FIDs that were recorded with increments in exception of somewhat higher initial sample concentration 1. HPLC oligo purification and separation of reaction mixtures: NMR sample Typical spectra demonstrating the variation in intensities for the NH and purification was carried out with a Waters LC instrument using NH2 signals of Pt dien are shown for I after 30 min and 4 h, respectively Millennium 32 software. The separations were carried out at ambient Figure 1. The dodecamer I was first run through a column length: Final Figure 2 show three main peaks with increasing elution times: The with Chelex resin Biorad to remove paramagnetic impurities. Chelex resin treatment effectively equalized for seqence I and are reversed for sequence II. A 60 min Biotech and eluted with sodium phosphate buffer 10 mm, pH 6. The samples volume of each eluted sample was 1. The eluents were A: TEAA and acetonitrile were removed by freeze-drying the sample twice, once at pH 12 and once at pH 3. Complete assignments of the exchangeable and non- exchangeable proton resonance signals for duplex I are listed in the Supporting information Table S 1. Paramagnetic metal ions may be classified according to their electronic correlation times, that is as relaxation probes that give rise to broad lines or as paramagnetic

shift probes with less line-broadening. Line-broadening is expressed as the line- width at half-height as a function of metal concentration. In kinetically labile metal complexes at low metal-to-nucleotide ratios, paramagnetic shift effects are difficult to detect. Of special interest is the effect on the G-H 8 protons that are adjacent to the expected N 7 binding site of guanine residues. The pH line broadening versus r are shown in Figures 3 b and 3 c, values of the NMR samples were in the range 5. A comparison of the plots for the three duplexes Data analysis: Rate constants for the reactions were determined by a shows some interesting differences. How- data were fitted using first- and second-order rate equations see ever, the most interesting observation is the variation in Supporting Information. For this diamagnetic system, the chemical shifts for G-H 8 protons were monitored as a function of Proton assignments of the duplexes: The dodecamers added zinc salt. Plots of chemical shift versus r are shown in Figure 4, method of sequential connectivity of NOESY cross-peaks for and a similar trend to that for the paramagnetic system is right-handed double-helical DNA. The magnitude of the observed. As usual, terminal based on variations in chemical shifts is not possible since this imino signals were found to be very broad, even at low variation is related to two major and several minor binding Chem. Typical [1H, 15N] duplex I using the formula published by Eriksson et al. A new set of Pt NH2 and Pt NH cross- peaks emerged during the reaction, while the intensities of the initial cross-peaks diminished. Determination of rate constants was based on the intensities of Pt NH cross-peaks since the emerging Pt NH2 cross-peaks were severely overlapped. The time courses for reactions of each of the three duplexes are shown in Figure 5. The rate constants, which were determined for the individual guanines, can be accounted for by a two-step kinetic model Scheme 1. Direct evidence for preassociation that precedes covalent binding has recently been published by Farrell and co-workers for the reaction of cisplatin with surface-immobilized oligonucleotides. Several factors may account for Figure 5. Experimental concentrations NMR data and theoretically the apparent discrepancy between our study and that of the fitted curves for the reaction between a 0. It intervals during the reactions. However, due to the severe would be of interest to monitor the kinetics of 15N-labeled overlap of resonance signals from several species, these cisplatin by 2 D 1H, 15N NMR spectroscopy and make spectra could not be fully assigned. Direct platination of a palindrome duplex at a Pt: Proton 1 D spectra were recorded at 1 h time species. The concentrations of the samples were relatively low provide spectra with a sufficient signal-to-noise ratio to detect 0. The chemical shift assign- nated residue. In con- in the Supporting Information. A summary of the Pt-induced trast, the spectrum of fraction 2 contains two significant cross- shifts of G-H 8 protons is given in Table 2. The asterisks indicate the platinated guanine residue. Chemical shift differences, Dd, measured as d I-Pt dI. In this fraction, the adjacent G5 residue is assumed to be platinated. The signals by high-field NMR spectroscopy. The use of self-complemen- in box P of b and c are cross-peaks between the NH2 groups of Pt dien tary sequences greatly simplifies the spectral analysis due to and H 8 of the guanosine to which Pt dien is coordinated. These structural changes mode. Examples labile platination of double-helical DNA oligonucleotides Chem. The mode of binding of In principle, platinum complexes should preferentially metal ion complexes to different DNA oligomers is mainly attack the more electron-donating sites in DNA duplexes. For the most studied platinum complex, ion complex. The helical parameters twist, tilt, DNA followed by annealing to the complementary strand to roll etc. We have shown unpublished data variations within the B-family of structures have been that single-strand metalation does not follow the rule of determined with reasonable precision. A comparison of considerable contribution from p-orbital interactions to the reaction rates shows that the selectivity for covalent platina- Pt N bond energy. However, when the reaction mixtures were aged over most electron-donating sites in duplex DNA. The occurrence of Pt N bond cleavage may attacks at these sites. Qualitatively, these results agree with influence the results of kinetic analyses that are based on our rule for sequence-selective binding of metal ions to HPLC techniques, in which aliquots of the reaction mixture duplexes based on NMR spectroscopic data. The fact that are collected at several time points and quenched with a large sequence-selective structural variation in DNA has a pro- amount of potassium chloride. The use of self-complementary sequences has enabled us to A downfield shift for G-H 8 of around 0. Usually,

platination of G-N 7 induces a large in ring current effects. Initially, these data were interpreted as representive was observed. Variations in the chemical shift pattern structure of DNA double helices that are induced by for G-H 8 of platinated nucleotides have been analyzed in platination. If large DNA distortion and protein recognition detail by Kozelka, Chottard, and Fouchet[31] and more are major determinants of the efficacy of platinum anticancer recently by Marzilli et al. We are grateful to Dr. An important aim is to provide an experimental method that Jpn. In this work we have [5] a H. The results for labile [8] A. Van der Veer, J. A Elizondo- and a series of oligodeoxyribonucleotides. Guo, labile metal ion adducts. The relative difference in binding P.

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Metal ions and metal complexes have long been recognized as critically important components of nucleic acid chemistry, both in regulation of gene expression and as promising therapeutic agents. Understanding how metal complexes interact with DNA has become an active research area at the interface between chemistry, molecular biology and medicine.

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