Notes

Steric Parameters for Metal Binding Sites on Nucleobases

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Introduction

The binding of metal species to nucleic acids may influence various biological functions, including those related to structural motifs induced by coordination.[1] The endocyclic nitrogens of the common nucleobases (Figure 1) are of particular interest with respect to metallo-chemotherapeutics, such as the antitumor drug cisplatin (*cis*-diamminedichloroplatinum(II)), since these sites are considered to be key molecular targets for such compounds.[2]

For isolated nucleobases, factors which favor one such site over another include basicity[3] and steric considerations.[4] With respect to basicity, preferential binding (in particular to the N7 position of guanine) has been quantitatively rationalized through pK_a values,[3] and relative coordination strengths of different binding sites have also been rationalized on the basis of electrostatic potential energy distributions.[5] Steric influences prior to, during and after coordination[6] are dictated by the nature of the metal complex (usually by the carrier ligand) and by the features of the binding site itself, such as the neighbouring exocylcic substituent(s) in the case of the nucleobases.[5,7] The relative steric demands of such binding sites have been considered by some workers to be difficult to quantify.[4] In an attempt to achieve this goal, we have extended to nucleobase ligands the repulsive energy methodology developed by Brown et al.[8] Thus each nucleobase endocyclic nitrogen site is probed by a $Cr(CO)_5$ moiety to which it is hypothetically bound (Figure 2).

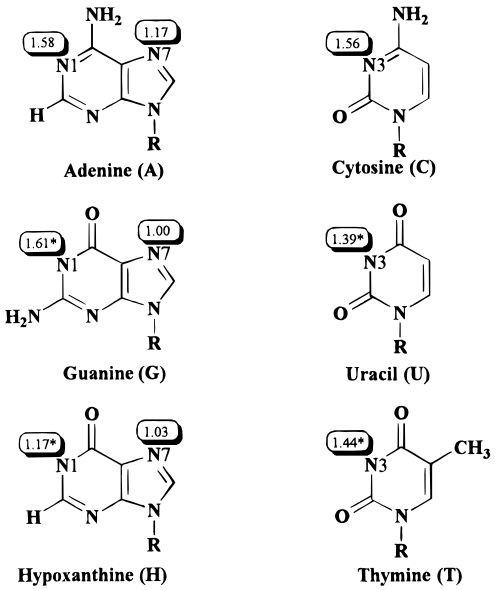

Figure 1. I_S values for potential metal binding sites on the common nucleobases. An asterisk denotes the value for a deprotonated site. For this study R = CH_3.

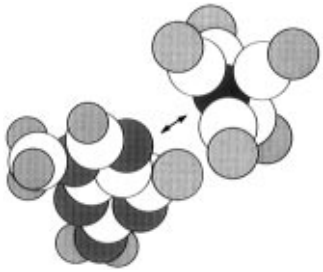

Figure 2. Disk representation of the approach of the steric probe $Cr(CO)_5$ to the N7 position of 9-methylguanine. Pattern coding: light gray (small), hydrogen; light gray (large), oxygen; dark gray, nitrogen; white, carbon; black, chromium.

There are a number of criteria for choosing the $Cr(CO)_5$ moiety, not the least being that it is a good representative of a transition metal species in terms of the degree of crowding about the metal center.[8a] The resulting steric parameter, the ligand repulsive energy, E_R, represents the gradient of the van der Waals repulsive energy for the energy-minimized structure with respect to the Cr−N distance, scaled by the equilibrium Cr−N distance.

Results and Discussion

For the common nucleobases studied here, these E_R values are presented in Table 1.

The numbers shown in Figure 1, associated with each site assessed, represent a steric index, I_S, which may be defined as follows:

$$I_S = E_R[\text{N(nucleobase)}]/E_R[\text{N7(guanine)}]$$

N(nucleobase) = N1(guanine, hypoxanthine, or adenine), N3-(cytosine, thymine, or uracil), or N7(guanine, hypoxanthine, or adenine).

The above definition is predicated upon the N7 of guanine presenting the lowest relative steric hindrance to the probe of all the sites compared in this study.

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Table 1. Ligand Repulsive Energies Presented by Nucleobase Binding Site to the Metal Species $Cr(CO)_5$ (Estimated uncertainty ± 1 kcal/mol)

base	site	E_R (kcal/mol)
9-MeG	N1[a]	58
	N7	36
9-MeH	N1[a]	42
	N7	37
9-MeA	N1	57
	N7	42
1-MeC	N3	56
1-MeT	N3[a]	52
1-MeU	N3[a]	50

[a] Deprotonated.

An examination of the I_S values presented in Figure 1 allows the following observations to be made. With respect to the N7 of the purines (which are both intuitively the least sterically hindered and being the most accessible on a DNA duplex[2a]) the I_S values are comparable for both guanine and hypoxanthine, but approximately 17% higher for adenine. This is in agreement with experimental evidence[4,7] which suggests a greater steric influence on metal coordination at N7 of an exocyclic amino compared to an exocyclic oxo substituent. The sterically equivalent sites, N1 of guanine and N3 of cytosine, have comparable I_S values which are approximately 60% higher than the value for N7 of guanine. If attention is focused on the N1 position of adenine, the I_S value for this site is comparable to the values for the N1 site of guanine and the N3 site of cytosine, in spite of the absence of a concomitant exocyclic oxygen (replaced by hydrogen in the case of adenine). This is further evidence for the larger steric influence of the amino substituent and is consistent with the oxo substituent having only a relatively modest steric effect.[7b] The same conclusion with respect to exocyclic oxo may be reached by comparing the I_S values of the N1 position of hypoxanthine with the N1 of adenine. For the $Cr(CO)_5$ moiety, the steric influence of one oxo substituent ortho to a binding site (e.g. N1 of hypoxanthine) is equivalent to that of an amino substituent one atom removed from a binding site (e.g. N7 of adenine). The N3 of uridine and the N3 of thymine have intermediate I_S values, as might be expected.

In the purine systems, when N9 carries a substituent, the N3 position is rarely accessed by metal species due to the severe steric constraints.[2a] Attempting to probe the N3 position by the method presented here results in an anomalous outcome reflected in inflated values of E_R and structural distortions; more specifically, the planarity of the nucleobase moiety is compromised, and its orientation with respect to the $Cr(CO)_4$ (radial) plane is no longer close to 90°. Thus it is possible that this method could be exploited to identify structural requirements for which coordination is precluded by steric factors. This could be useful in the design of metal complexes as site-specific reagents.[9]

The steric parameters presented here for metal binding sites on nucleobases have sensible relative values and are in accord with deductions from reported experimental data where steric effects are considered to be operative. Thus they demonstrate the feasibility of quantifying relative steric effects in such systems and buttress the suggestion by Brown et al.[8b] that the E_R concept can be extended to ligands of nearly any kind. These workers also suggest that a variety of metal centers may also be considered. In this context, the metal species could equally well be varied (for example, a series of modified platinum complexes) with a particular nucleobase binding site held constant. One would expect the steric parameters derived from such investigations to find particular application in quantitative structure activity/property relationship investigations (QSAR[10]/QSPR[11]) since, unlike the frequently employed molecular volume as a steric parameter,[12] the E_R values represent steric effects at the interface of the interaction and would be expected to carry little "transport" information relating to the hydrophobicity[13] or water solubility[6] of the metal complex.

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Supporting Information Available: Text giving computational details including a table of MM+ added force field parameters for $Cr(CO)_5$/nucleobase complexes (3 pages). Ordering information is given on any current masthead page.

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