Steric Aspects of the Binding of Monofunctional Platinum(II) Complexes to Sites on Nucleobases: Metal Complex "Flatness" as a Structural Element of Speciation

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Through the use of an established repulsive energy methodology, the endocyclic nitrogens of the common nucleobases have been probed by monofunctional $Pt^{II}(A)_3$ moieties, where A ≡ NH_3 and $(A)_3$ ≡ diethylenetriamine (dien) and N^1,N^1,N^4,N^7,N^7-pentamethyldiene (pmdien). These three complexes have been selected to represent, respectively, a gradual buildup of bulk on either side of the coordination plane. The values of the resulting steric parameters, E_R and I_S, are compared between the three complexes and benchmarked to previously reported values for the spherically symmetrical $Cr(CO)_5$ probe. This study indicates that steric effects for coordination to nucleobases of "flatter" metal species are more subtle than those for more encompassing species and are determined predominantly by the distribution of their neighboring exocyclic substituents rather than their individual nature (e.g., amino, oxo, or methyl). A means of quantifying metal complex flatness with respect to the coordination of metal species to endocyclic nitrogens of nucleobases is suggested. For the $Pt(NH_3)_3$(nucleobase) and Pt(dien)(nucleobase) systems, a quantitative relationship has been established between steric effects and conformational flexibility, in terms of rotation about the Pt−N bond. These results suggest that, in the absence of external constraints such as crystal packing forces, the base/coordination plane dihedral angle may be inferred from steric considerations. Over a wide range of Pt/N_4 dihedral angle, rotation about the Pt−N bond is, surprisingly, less sterically demanding when the flanking substituent is an amino rather than an oxo group.

Introduction

The success of certain platinum complexes as chemotherapeutic agents is attributed to their ability to target the endocyclic nitrogen atoms of nucleobases, particularly the N7 position of purines.[1] Although platinum−nucleic acid chemistry in general has received an enormous amount of attention since the discovery of these drugs, the delineation of the steric effects inherent in such interactions is a relatively neglected area of study. This is notwithstanding the acknowledged importance of such effects both from a physicochemical and from a biological point of view.[2] One reason for this neglect has been the lack of a suitable methodology for quantifying steric effects in systems such as these.

We have recently demonstrated the feasibility of extending the repulsive-energy strategy developed by Brown et al.[3] to the quantification of steric effects associated with the binding of metal species to nucleobases.[4−6] This was achieved by computing the ligand repulsive energies (E_R values) between the spherically symmetrical $Cr(CO)_5$ moiety (as a representative steric probe) and the various endocyclic nitrogen atoms. The relative steric demands of the nucleobase coordination sites toward this steric probe were found to be dictated by the nature of the exocyclic substituent(s) adjacent to a binding site. For example, with respect to $Cr(CO)_5$ coordination to N7 of purines, the exocyclic amino substituent adjacent to the N7 position of 9-methyladenine and the 6-oxo substituent adjacent to the N7 position of 9-methylguanine (and 9-methylhypoxanthine) clearly discriminate on the basis of their relative steric bulk, with the former being 17% more restrictive than the latter.[4] We have also recently attempted to relate steric parameters derived from the above methodology to various biological indicators with respect to the interaction between monofunctional platinum species of the type *cis*-$[Pt(NH_2R)_2Cl]$ (R = alkyl) and the N7 position of guanine.[5]

These studies have now been extended to the delineation of the steric aspects of the binding of monofunctional platinum(II) complexes to all available endocyclic nitrogen sites on the common nucleobases.

Square-planar platinum(II) species are nonspherically symmetrical and "flatter" than $Cr(CO)_5$-type species. These features might be expected to result in less steric discrimination by such complexes between different binding sites. The degree of flatness of a metal species, with respect to its coordination to

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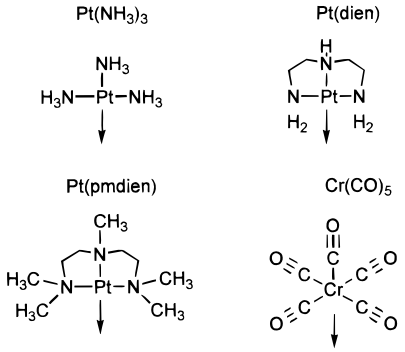

Figure 1. Structural representation of the four probes employed in these studies. The arrow represents the approach to a nucleobase target site.

Figure 2. Views of the $Pt(A)_3$ and $Cr(CO)_5$ steric probes along their direction of approach to a nucleobase target site showing the gradual buildup of the bulk.

various binding sites, is difficult to define per se and is related to the extent and distribution of bulk on either or both sides of the coordination plane. In square-planar complexes, this is primarily determined by the nature of the carrier ligand.[7] In delineating the steric aspects of such interactions, the steric features of the target site, especially where flanking exocyclic substituents present a pocket for the metal species, are also important considerations. For example, probing the N3 position of N9-substituted purines with the $Cr(CO)_5$ moiety indicates that this metal species is too encompassing to access this site without severe distortions;[4,8] hence, binding is likely to be precluded. However, flatter metal species, such as $Pt^{II}(NH_3)_3$, have been shown to be accommodated at this position.[9] Questions arise as to the degree to which the bulk on either or both sides of the coordination plane, together with the nature of the binding site itself, influences (or precludes) coordination to a given site and whether relative metal complex flatness can be regarded as a unique structural element of speciation, which can be isolated quantitatively.

The three monofunctional probes $Pt^{II}(A)_3$, where $A \equiv NH_3$ and $(A)_3 \equiv$ diethylenetriamine (dien) and $N^1,N^1,N,^4N,^7N^7$-pentamethyldiene (pmdien) (Figure 1), represent respectively a gradual buildup of bulk on either side of the coordination plane (Figure 2). These systems, together with the "non-flat" $Cr(CO)_5$, which is used as a benchmark, have been employed to sterically probe the 12 different nucleobase binding sites depicted in Figure 3. A means for characterizing and quantifying the notion of metal complex flatness for a particular system is suggested by these investigations.

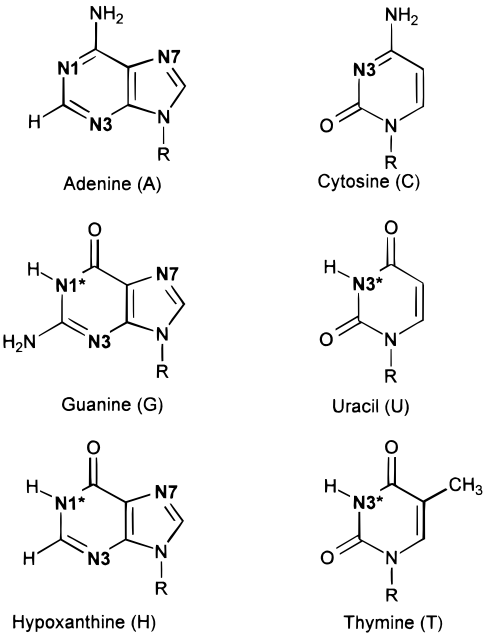

Figure 3. Potential metal binding sites on the common nucleobases; an asterisk denotes a site deprotonated prior to coordination. For this study $R = CH_3$.

Of course, it must also be appreciated that, unlike $Cr(CO)_5$ adducts, square-planar complexes of nucleobases generally have a degree of conformational flexibility about the metal−nitrogen bond. The ability of the platinum species to rotate about the platinum−nitrogen bond is a mechanistic feature of the interaction which has unique steric implications. Indeed, this is an important consideration in rationalizing the biological consequences of the interaction of such species with nucleic acids.[10] In this regard for these platinum systems, the relationship between the computed E_R values and nucleobase/coordination plane dihedral angles, B/PtN_4,[11] has also been explored.

Methods

Structures of Cr and Pt complexes with nucleobases were optimized using the molecular mechanics facilities of HyperChem, version 4,[12] running on a COMPAQ Pentium 5100 computer.

Structure Optimization. The structures of the chromium complexes, $Cr(CO)_5$(nucleobase), were optimized using the MM+ force field modified as described previously.[4] The structures of the platinum series, $[PtA_3$(nucleobase)], were optimized using the modified AMBER force field. Parameters developed for the modeling of these monoadducts (Table 1) as well as those derived by Yao et al.[13] for the modeling of bisadducts and by Yuriev and Orbell[5] for the modeling of $[PtL_2$(9-EtG)Cl] monoadducts were added.

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Table 1. AMBER Parameters for the Geometry Optimization of Complexes with the General Formula [Pt(A)$_3$(Nucleobase)]

bond	r_0[a] (Å)	K_r[b] (kcal mol^{-1} Å^{-2})
PT−NA[c]	2.035	366
PT−NC[d]	2.038	366
angle	θ_0 (deg)	K_θ[e] (kcal mol^{-1} rad^{-2})
PT−NC−CA[f]	122.35	20
PT−NC−CQ[g]	116.00	20
PT−NC−CB[h]	126.15	20
PT−NC−C[i]	116.75	20
PT−NA−CA[j]	119.90	20
PT−NA−C[k]	119.15	20
HC−CA−NA[l]	115.00	35
HC−CA−NC[l]	119.10	35
N#−PT−N3T[m]	90.00	42
N#−PT−N3C[m]	180.00	42
N3T−PT−N3T	180.00	42
torsional angle[n]	ϕ_0 (deg)	n	$V/2$ (kcal mol^{-1})
N3*[o]−PT−NC−C*[p]	90	2	0.25
N3*[o]−PT−NA−C*[q]	90	2	0.25

[a] These bond lengths were derived by averaging Pt−N bond-length values from 49 crystal structures of platinum complexes. The CSD Refcodes are available as Supporting Information. [b] The stretching force constant was set analogous to Pt−N(7) of guanine. See ref 13. [c] NA/N1 position of guanine and hypoxanthine, N3 position of thymine and uracil. [d] NC/N1 position of adenine, N3 position of cytosine, N3 position of purines. [e] The bending force constants were set by analogy to the corresponding angles for guanine complexes. See ref 13. [f] Pt−N3−C2 angles of guanine and hypoxanthine, Pt−N1−C6 angle of adenine, and Pt−N3−C4 angle of cytosine. [g] Pt−N1−C2 and Pt−N3−C2 angles of adenine. [h] Pt−N3−C4 angles of guanine and hypoxanthine and Pt−N3−C4 angle of adenine. [i] Pt−N3−C2 angle of cytosine. [j] Pt−N1−C2 angles of guanine and hypoxanthine. [k] Pt−N1−C6 angles of guanine and hypoxanthine. [l] H2−C2−N1 and H2−C2−N3 angles of hypoxanthine, respectively. [m] N#/NA and NC atom types. [n] Torsional parameters involving platinum were set analogous to ref 13. [o] N3*/N3C and N3T atom types. See ref 5. N3C is a Pt-bound carrier ligand nitrogen, trans to nucleobase. N3T is a Pt-bound carrier ligand nitrogen, cis to nucleobase. [p] C*/CQ, CA, CB, and C atom types. [q] C*/CA and C atom types.

A Monte Carlo conformational search was carried out by varying the rotation of the nucleobase plane with respect to the Cr(CO)$_4$ radial plane and the PtN$_4$ coordination plane in the respective Cr and Pt complexes. During the conformational search, structures were minimized to a δ root-mean-square (rms) gradient of 0.1 kcal mol^{-1} Å^{-2}. The lowest energy structures were then additionally minimized to a δ rms gradient of 0.001 kcal mol^{-1} Å^{-2}.

The optimized [PtA$_3$(nucleobase)] complexes compare favorably to experimentally determined structures with respect to their geometric features.[8] These calculations do not suggest significant angular distortions in the platinum systems. The typical rms deviation of an optimized structure from a crystal structure is 0.1−0.2 Å. The accuracy of reproduction of the nucleobase orientation with respect to the coordination plane is generally very good. However in some cases, the simulation resulted in a marked difference in the B/PtN$_4$ dihedral angle between predicted and experimental structures[14] (up to 15°). This may be attributed to the influence of crystal packing forces in the experimental structures.[7c,15]

Repulsive Energy Calculation. Repulsive energies were calculated according to an established methodology where each nucleobase endocyclic nitrogen site is probed by the metal moiety to which it is hypothetically bound. The resulting steric parameter, termed 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 metal−nitrogen distance, scaled by the equilibrium metal−nitrogen distance.[3−6] More specifically, the general strategy may be described as follows:

(1) The lowest energy structure for the metal complex is obtained.

(2) For a given complex, r_{Me-N} is varied by ±0.08 Å, with all of the other internal coordinates frozen, to create a set of structures.

(3) Using the nonbonded parameters of a modified MM+ force field for the metal−nucleobase complex, the repulsive portion of E_{vdW} for each structure is computed according to:

$$E_{vdW}(\text{rep}) = \sum D_0 \exp\left[\gamma \frac{r_0 - r}{r_0}\right]$$

(4) The repulsive energy is calculated according to:

$$E_R = -r_e \frac{\partial E_{vdW}(\text{rep})}{\partial r_{Me-N}}$$

where D_0 represents the potential well depth, γ is a scaling factor (typically 12.5), r is the interatomic distance in the energy-minimized structure, r_0 is the unstrained interatomic distance, r_{Me-N} is a varied metal−nitrogen distance, and r_e is the metal−nitrogen distance in the energy-minimized structure.

Results and Discussion

Stereochemical Considerations. Consistent with experimental findings[16] and other theoretical investigations,[13,17] the optimized lowest energy conformations of the Pt(NH$_3$)$_3$ and Pt(dien) adducts exhibit B/PtN$_4$ dihedral angles over the range of 62−87°.[18a]

In general, with respect to the approach of a square-planar platinum complex to a nucleobase binding site, a perpendicular orientation between the platinum coordination plane and the nucleobase plane may be assumed to represent the least steric repulsion between the complex carrier ligand(s) and the nucleobase exocyclic substituent(s). Upon coordination, movement away from the perpendicular may be affected by forces such as intramolecular hydrogen bonding[19] and torsional strain.[8] Although such rotation increases steric repulsion, the overall structural strain is relieved.[18]

The steric bulk of the methyl substituents on the carrier ligand nitrogens of the Pt(pmdien) adducts significantly lowers their conformational flexibility, compared to the Pt(NH$_3$)$_3$ and Pt(dien) analogues. Conformational sampling of these systems results in rotamers with essentially perpendicular orientation of nucleobases and two alternative arrangements of exocyclic functional groups with respect to the coordination plane. Because the steric bulk of the carrier ligand (involving en bridges and methyl groups) is not symmetrically distributed on both sides of the coordination plane, these two conformations are not structurally equivalent. Indeed, ^{1}H NMR studies confirm[20] that because of the steric bulk of the terminal methyl

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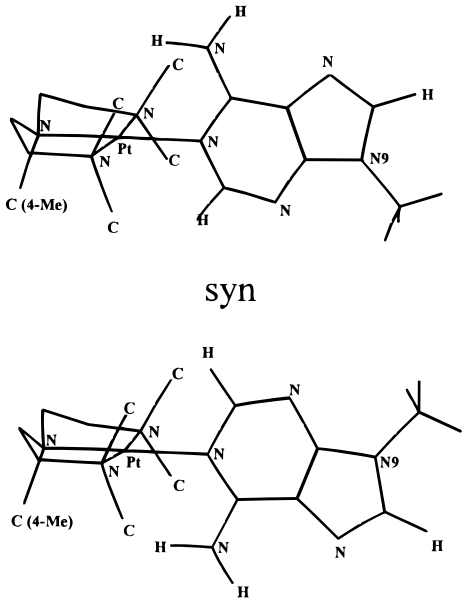

Figure 4. Stereochemical convention for Pt(pmdien)(nucleoconstituent) rotamers. In this example: N1-bound 9-methyladenine.

groups rotation about the Pt−N bond is significantly hindered and the rotamer peaks are well resolved. To classify these conformations, a stereochemical convention is required. In this work, an *absolute* convention[8] is used and is based on the orientation of either a N9 substituent in purines or a N1 substituent in pyrimidines with respect to the coordination plane (Figure 4). Thus, a syn rotamer is defined as one for which a N9 or N1 substituent is on the designated bulkier side of the coordination plane (for the pmdien ligand, the same side as the 4-methyl group); an anti rotamer is defined vice versa. This convention is similar to the NMR convention.[20] However, it allows rotamers to be classified without reference to the direction of the monitored proton, which may vary for different nucleobases. The absolute convention may also be applied to modeling studies and extended to systems not yet investigated by NMR, including hypothetical structures. Finally, this convention allows *systematic* classification of adducts, independent of nucleoconstituent complexity or binding site.

Repulsive Energy Considerations. Repulsive-energy values, E_R(Cr) for the binding of the $Cr(CO)_5$ reference probe, E_R(Pt) for the three selected platinum moieties, and $E_R(Pt)_{90}$ for the $Pt(NH_3)_3$ and Pt(dien) systems, are given in Table 2. The $E_R(Pt)_{90}$ values are computed in the same way as E_R(Cr) and E_R(Pt) except that the structures are minimized under the constraint that the Pt coordination plane is held at 90° with respect to the nucleobase plane. The $E_R(Pt)_{90}$ values for a perpendicular approach of the metal complex to the nucleobase have been included as part of our investigation into the relationship between steric effects and rotational flexibility about the Pt−N bond. Table 3 gives the calculated steric indices,[4] I_S and I_S', for the various binding sites based on the E_R(Cr), E_R(Pt), and $E_R(Pt)_{90}$ values of Table 2. For a given metal species and a defined approach, I_S and I_S' are calculated from the E_R (Cr and Pt) and $E_R(Pt)_{90}$ values, respectively, of Table 2 according to $I_S = E_R[N(\text{nucleobase})]/E_R[N(\text{nucleobase})]_{min}$.

It is immediately apparent from the above data that, compared to the magnitudes of the E_R values for the $Cr(CO)_5$ probe, those for $Pt(NH_3)_3$ and Pt(dien) are almost an order of magnitude lower and are not subject to the same clear steric discrimination

Table 2. Ligand Repulsive Energies Presented by Nucleobase Binding Sites to the Metal Species (kcal/mol[a])

		$Cr(CO)_5$	$Pt(NH_3)_3$		Pt(dien)		Pt(pmdien)	
base	site	E_R(Cr)	E_R(Pt)	$E_R(Pt)_{90}$	E_R(Pt)	$E_R(Pt)_{90}$	syn	anti
9-MeG	N1[b]	58	6.85	5.22	6.76	5.03	39.7	39.1
	N3	(76)[c]	6.35	6.09	8.55	8.55	47.5	47.6
	N7	36	6.76	2.94	6.68	2.89	34.6	32.8
9-MeH	N1[b]	42	6.89	4.44	6.66	4.04	35.7	35.2
	N3	(67)[c]	5.46	5.34	7.63	7.74	43.1	46.9
	N7	37	6.54	2.93	7.07	2.89	34.8	32.6
9-MeA	N1	57	6.22	4.49	6.80	4.14	35.5	35.3
	N3	(71)[c]	5.46	5.24	6.63	6.47	43.1	44.4
	N7	42	4.78	3.05	4.53	2.84	33.9	32.7
1-MeC	N3	56	7.01	4.99	6.19	4.72	38.4	38.8
1-MeT	N3[b]	52	5.94	4.81	6.28	4.59	38.7	38.8
1-MeU	N3[b]	50	5.93	4.66	7.68	4.55	38.8	38.6

[a] Estimated uncertainty ±2%. [b] Deprotonated site. [c] These values have higher uncertainty because of structural distortions in these adducts.

Table 3. Comparative Steric Indices,[4] I_S[a] and I_S',[b] Calculated from the E_R(Cr), E_R(Pt), and $E_R(Pt)_{90}$ Values of Table 2

		$Pt(NH_3)_3$		Pt(dien)		Pt(pmdien)	
site	$Cr(CO)_5/I_S$	I_S	I_S'	I_S	I_S'	syn	anti
N7(A)	1.17	1.00	1.04	1.00	1.00	1.00	1.00
N7(G)	1.00	1.41	1.00	1.48	1.02	1.02	1.01
N7(H)	1.03	1.37	1.00	1.56	1.02	1.03	1.00
N1(A)	1.58	1.30	1.53	1.50	1.46	1.05	1.08
N1(H)[c]	1.17	1.44	1.52	1.47	1.42	1.05	1.09
N1(G)[c]	1.61	1.43	1.78	1.49	1.77	1.15	1.20
N3(C)	1.56	1.47	1.70	1.37	1.66	1.15	1.19
N3(U)[c]	1.39	1.24	1.59	1.70	1.60	1.15	1.18
N3(T)[c]	1.44	1.24	1.64	1.39	1.61	1.15	1.19
N3(A)	1.97[d]	1.14	1.79	1.46	2.28	1.27	1.36
N3(G)	2.11[d]	1.33	2.08	1.89	3.01	1.40	1.46
N3(H)	1.86[d]	1.14	1.82	1.68	2.73	1.27	1.43

[a] I_S = optimized approach. [b] I_S' = perpendicular approach. [c] Deprotonated site. [d] These values are associated with sterically induced distortions in the adducts and may be less reliable.

based on the nature of the adjacent exocyclic substituent(s). As discussed above, these general outcomes are to be expected, given the less encompassing nature of the platinum systems under investigation.

With respect to the Pt(pmdien)(nucleobase) rotamers, it has been found that, although not equivalent structurally, both conformations are very similar energetically and have similar values of E_R(Pt). These are given in Table 2, where they are classified on the basis of the proposed absolute stereochemical convention. For the bulky Pt(pmdien) probe, the E_R magnitudes increase so as to approach the $Cr(CO)_5$ reference values.

N7 of Purines. For a perpendicular approach of a metal species to a binding site, one might expect an adjacent amino substituent to offer more initial steric hindrance than an oxo substituent. However, it is evident from the $E_R(Pt)_{90}$ and I_S' values that, for all three Pt species considered, the N7 positions of adenine, guanine, and hypoxanthine are essentially equivalent in this regard.

For $Pt(NH_3)_3$ and Pt(dien) adducts, the E_R and I_S values for coordination to the N7 position of adenine are actually smaller than those for coordination to the N7 positions of guanine and hypoxanthine. This, perhaps surprising, outcome appears to be related to the ability of the adenine system to achieve more relief of overall steric strain by rotation about the Pt−N7 bond than that achieved by guanine or hypoxanthine. This may be

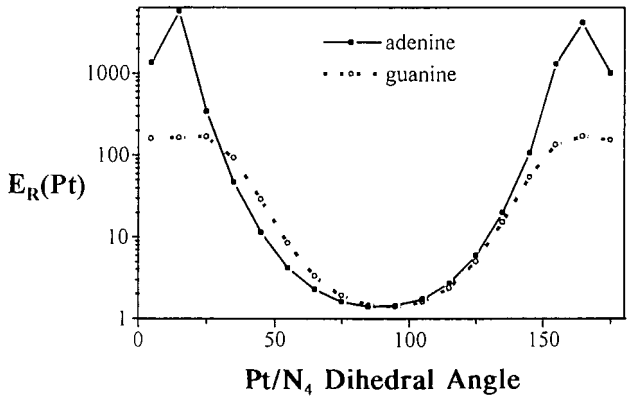

Figure 5. Rotational profiles of the Pt(dien)(nucleobase) adducts with N(7)-bound 9-methylguanine and 9-methyladenine.

understood by considering the variation in the calculated repulsive-energy values as the B/PtN$_4$ dihedral angle changes. Figure 5 depicts this function for Pt(dien) coordination to the N7 position of adenine and guanine nucleobases. Because of differences in the relative steepness of the curves, the E_R values for the adenine system fall lower than those for the guanine over a B/PtN$_4$ dihedral angle range of approximately 30−80°. In the optimized lowest energy conformations of these systems, the dihedral angles of 65° and 68°, respectively, lie within this range.

N1 of Purines. From the $E_R(Pt)_{90}$ and I_S' values for the Pt(NH$_3$)$_3$ and Pt(dien) probes and from the E_R(Pt) and I_S values for the Pt(pmdien) probe (for which the orientation is necessarily constrained to the perpendicular), it is evident that the N1 positions of adenine and hypoxanthine are essentially sterically equivalent with respect to a perpendicular approach, with no discrimination between amino and oxo groups in a putative initial attack, reflecting the situation for a perpendicular approach to the N7 of purines.

The E_R and I_S values for the binding of Pt(NH$_3$)$_3$ to the N1 position of adenine are smaller than those for the coordination to the N1 position of hypoxanthine. This, again, demonstrates an ability to achieve more relief of overall steric strain by rotation about the Pt−N bond when the flanking substituent is an amino rather than an oxo group. As discussed previously for coordination to the N7 position of purines, this also arises because of the different relative profiles of the calculated repulsive energy as a function of the Pt/PtN$_4$ dihedral angle. For Pt(dien) binding to the N1 position of adenine and hypoxanthine, the E_R and I_S values are not significantly different. This probably is due to the influence of the bulk of the en bridges[7a,b] on the flexibility about the Pt−N1 bond. In this regard, the relationship between the steric demands of a carrier ligand or an exocyclic substituent(s) or both and the flexibility of rotation about the Pt−N1 bond is further demonstrated by the values for the respective deviations of B/PtN$_4$ dihedral angles from the perpendicular, Δ(B/PtN$_4$), for the optimized adducts of Pt(NH$_3$)$_3$ and Pt(dien) with N1 of adenine and hypoxanthine:

	Pt(NH$_3$)$_3$		Pt(dien)	
	N1(A)	N1(H)	N1(A)	N1(H)
Δ(B/PtN$_4$)	30	24	22	22

The N1 position of guanine is different from that in adenine and hypoxanthine in that it is flanked by two exocyclic substituents. Accordingly, a perpendicular approach of the Pt(NH$_3$)$_3$ and Pt(dien) probes results in significantly enhanced values of $E_R(Pt)_{90}$ and I_S' for the N1 position of guanine compared to that of hypoxanthine, because of the initial greater steric hindrance of the amino group. However, it is interesting to note that for Pt(NH$_3$)$_3$ and Pt(dien) the E_R and I_S values for coordination to the N1 position of guanine and hypoxanthine are not significantly different.

N3 of Purines. The data of Tables 2 and 3 suggest that, unlike Cr(CO)$_5$,[4] the three Pt species may be accommodated at the N3 positions of the 9-methylpurines, with no structural distortions. The only noticeable structural feature distinguishing these systems from other adducts is the change in their "rocking angles".[18b] However, as is the case with Cr(CO)$_5$,[4] for the N3 positions of purines, the values of $E_R(Pt)_{90}$ are significantly higher than those for all other sites. Furthermore, these values are closer to the repulsive energies in the optimized structures [the E_R(Pt) values] than those of all other sites. These two observations are attributed to significantly increased steric hindrance and decreased, although still existent for Pt(NH$_3$)$_3$ and Pt(dien), flexibility about the Pt−N bond associated with these sites.

As expected, more steric hindrance is encountered at the N3 position of 9-methylguanine for both the perpendicular and the optimized approach for the three Pt systems. This is due to the steric hindrance of the bulky amino substituent, which cannot be effectively relieved by significant rotation about the Pt−N bond.

N3 of Pyrimidines. The coordination of Pt(NH$_3$)$_3$ and Pt(dien) to the N3 positions of cytosine, uracil, and thymine, as well as to the N1 position of guanine, presents a picture similar to that of the above N3 "slot positions" of the purines. As expected, both syn and anti rotamers of the bulkier Pt(pmdien) probe prefer the less sterically demanding[4] slot positions of the pyrimidines over those of the purines.

Benchmarking. An informative way of examining the data presented in Table 2 is provided in Figure 6. In these plots of the 12 nucleobase binding sites, the three sets of E_R(Pt) values are each correlated with the corresponding E_R(Cr) benchmark values for a "nonflat" metal species. These plots demonstrate how a gradual increase of the bulk on either side of the coordination plane leads to more similarity between the platinum and chromium steric probes. We suggest that the correlation coefficients for plots such as these may provide a means of quantifying relative metal complex flatness with respect to a given system. This may assist in determining whether such a structural attribute has a specific importance in the biochemistry of metal species. Such investigations are continuing.

Binding Site Clustering and Classification. For the Pt(pmdien) system, a clustering of coordination sites according to their steric demands is evident (Figure 6c). Accordingly for all systems, coordination sites are grouped in Table 3 with respect to the relative magnitude ranges of the I_S values for Pt(pmdien). Such clustering suggests that although flatter metal species are not highly sensitive to the nature of neighboring exocyclic substituents (oxo, amino, or methyl), as is the encompassing Cr(CO)$_5$ reference probe, these species are more sensitive to their number and arrangement. These different types of binding sites are as follows: (1) one exocyclic group, two atoms removed from the site (i.e., N7 position of purines), (2) one exocyclic group and a hydrogen atom, adjacent to the site (i.e., N1 position of hypoxanthine, N1 position of adenine), (3) two exocyclic groups, adjacent to the site (i.e., N1 position of guanine, N3 position of pyrimidines), (4) one bulky methyl substituent, two atoms removed from the site and a hydrogen atom, adjacent to the site (i.e., N3 position of hypoxanthine, N3 position of adenine), and (5) one bulky methyl substituent,

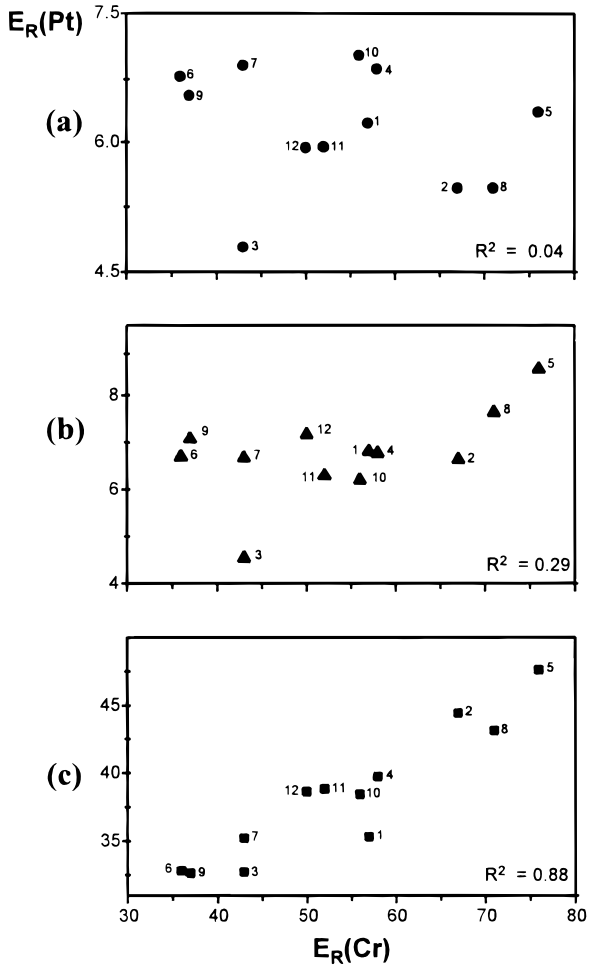

Figure 6. Correlation between E_R(Cr) and E_R(Pt) for the three platinum moieties: (a) Pt(NH_3)$_3$, (b) Pt(dien), (c) Pt(pmdien). Binding site codes: (1) N1(A), (2) N3(A), (3) N7(A), (4) N1(G), (5) N3(G), (6) N7(G), (7) N1(H), (8) N3(H), (9) N7(H), (10) N3(C), (11) N3(T), (12) N3(U).

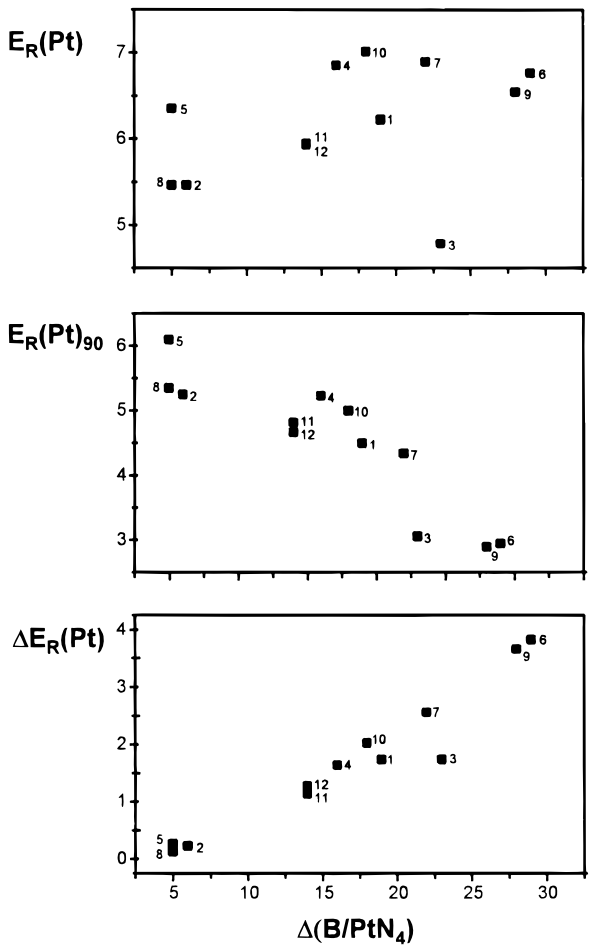

Figure 7. Relationships between repulsive energies and dihedral angles for the Pt(NH_3)$_3$(nucleobase) systems. (a) Optimized molecular systems. (b) Molecular systems optimized with the restriction of nucleobases to the perpendicular orientation with respect to platinum coordination plane. (c) $\Delta E_R(Pt) = E_R(Pt) - E_R(Pt)_{90}$. Binding codes are the same as those for Figure 6.

two atoms removed from the site and an exocyclic group, adjacent to the site (i.e., N3 position of guanine).

Complex Classification. The above investigations also suggest that, qualitatively, three types of metal complexes may be identified with respect to how the attribute of metal complex flatness influences the steric aspects of monofunctional binding to endocyclic nitrogens on nucleobases. These are as follows:

(i) Complexes represented by $Cr(CO)_5$, which are characterized by spherical symmetry and which can be described as nonflat. Such encompassing species discriminate[4] on the basis of the *nature* of the exocyclic substituent(s) (amino, oxo, or methyl) adjacent to the coordination site.

(ii) Complexes such as Pt(pmdien) which are not spherically symmetrical but have severely restricted rotation about the Pt−N bond because of the extent and distribution of bulk on either side of the coordination plane. These clearly discriminate on the basis of the *number* and *arrangement* of neighboring exocyclic substituents, vide supra.

(iii) Complexes such as Pt(NH_3)$_3$ and Pt(dien), which may rotate about the Pt−N bond by up to 30° from the perpendicular. Such complexes tend to but will not necessarily discriminate on the basis of the number and arrangement of exocyclic substituents in the vicinity of the binding site. Antitumor platinum compounds such as *cis*-[(NH_3)$_2$$PtCl_2$] (cisplatin, *cis*-DDP), when binding monofunctionally,[21] would be expected to be of this type.

Adduct Flexibility. To further explore the relationship between steric effects and adduct conformational flexibility (via rotation about the Pt−N bond), the correlation among E_R(Pt), $E_R(Pt)_{90}$, and ΔE_R(Pt) [where $\Delta E_R(Pt) = E_R(Pt) - E_R(Pt)_{90}$] and the deviation of the B/PtN_4 dihedral angle from the perpendicular in the optimized lowest energy conformations, Δ(B/PtN_4), were investigated. Figure 7 presents these relationships for the Pt(NH_3)$_3$(nucleobase) adducts, which are almost identical to those of the Pt(dien)(nucleobase) adducts. From Figure 7, it may be seen that although plots of E_R versus Δ-(B/PtN_4) present scatters, the plots for the perpendicular approach display a more linear relationship between the steric and conformational parameters. A clustering of coordination sites of the kind discussed previously also becomes apparent; this is not unexpected. When ΔE_R(Pt) is plotted against Δ(B/PtN_4), the correlation is even stronger. In fact, ΔE_R(Pt) is effectively proportional to the deviation of the B/PtN_4 dihedral angle from the perpendicular which emphasizes the importance of steric effects for adduct geometry. Therefore, it is not inappropriate to suggest that rotation of the nucleobase away from the perpendicular operates as a *compensatory* mechanism to relieve the overall steric strain and that the increase in the steric repulsion between a carrier ligand and exocyclic functional

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groups upon rotation, ΔE_R(Pt), limits the extent to which such rotation can occur.

Conclusions

This work presents a detailed analysis of steric effects for the interaction of monofunctional platinum(II) complexes with endocyclic nitrogen sites on nucleobases. It has been demonstrated that the extent and distribution of steric bulk on either or both sides of the coordination plane (metal complex flatness) together with the steric demands of the binding site are important in defining the conformation of the final adduct and may be determinative of site selectivity.

With respect to the attribute of metal complex flatness, three categories of complex have been identified which, upon monodentate coordination, sterically discriminate in different ways between the various endocyclic nitrogen sites on nucleobases. In particular, it has been demonstrated that whereas for spherically symmetrical, encompassing species, such as $Cr(CO)_5$, steric effects for coordination to nucleobases are determined by the individual nature of neighboring exocyclic substituents,[4] those for flatter metal species are determined more by the number and distribution of such substituents.

In terms of their degrees of flatness, complexes classed as type iii, represented here by $Pt(NH_3)_3$ and Pt(dien), model a monofunctional attack of cisplatin on DNA. It is evident that the N7 positions of adenine and guanine, which are considered to be of most biological relevance,[22] are essentially sterically equivalent with respect to an initial monofunctional attack by such species. Therefore, steric considerations do not suggest that such an attack on the N7 position of guanine is preferred to an attack on the N7 position of adenine.[23] However, upon coordination, rotation about the Pt−N7 bond of adenine has been demonstrated to have a different steric character than rotation about the Pt−N7 bond of guanine, with the former being better able to absorb the resulting steric repulsion over a wide rotational range. This might be expected to influence the formation and the geometry of a consolidated bis adduct. This, in turn, would impinge upon the finer details of DNA motifs[24] resulting from GG and AG cross-links.[22] Work is in progress to accumulate experimental data on the binding of the three platinum species described here to sites on nucleobases, whereby some of the suggestions of the present study may be tested.

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Supporting Information Available: CSD Refcodes of the crystal structures used for derivation of force field parameters and coordinates for all energy minimized structures, including the 90°-constrained systems (130 pages). Ordering information is given on any current masthead page.

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