

An algorithm for predicting the NMR shielding of protons over substituted benzene rings

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In a strong magnetic field, hydrogen nuclei located over an aromatic ring experience a reduced magnetic field as a result of the induced magnetic field associated with circulating π electrons. We used GIAO-SCF, an ab initio subroutine in Gaussian 94 to calculate isotropic shielding values and to determine the proton nuclear magnetic resonance (NMR) shielding increment for a simple model system: methane held at various positions over a substituted benzene ring. The NMR shielding increments experienced by the proximal protons of methane have been mapped as a function of their position X, Y, and Z relative to the center of aniline and, separately, nitrobenzene. A mathematical function of the same form has been fit to the three-dimensional shielding increment surface at each of five distances from the face of each aromatic ring. In addition, a single mathematical equation has been developed for predicting the shielding caused by either substituted aromatic ring. The chemical shifts predicted by using the results of this equation in conjunction with additive substituent increments are compared to observed values.

Keywords: diamagnetic anisotropy, nuclear magnetic resonance, isotropic shielding value, GIAO-SCF, aniline, nitrobenzene

INTRODUCTION

The chemical shift of a proton can be estimated empirically as the sum of the contributions of nearby groups. These substituent increment values have been calculated and tabulated and are commonly used for structural determination.¹ However, several organic functional groups have associated with them

magnetic shielding properties that extend through space; these remote effects are generally not considered in the tabulated substituent constants. Limited aspects of the through-space shielding effects have been described, for example, in shielding diagrams,² but the net shielding effect has not been well quantified. This research was undertaken to provide a quantitative measure of the net nuclear magnetic resonance (NMR) shielding effect of substituted phenyl groups. Incorporation of the results of this research into molecular modeling programs that predict chemical shifts using a database additive substituent effect approach could offer a valuable addition to chemists' tools for structural determination.

There are many molecules that contain protons held in position directly over an aromatic ring (e.g., the cyclophanes). The NMR chemical shift of these protons is moved upfield because of their location with respect to the aromatic ring. This upfield shift is caused by diamagnetic anisotropy. Pauling³ first reported the effects of diamagnetic anisotropy, explaining the phenomenon in terms of abnormally large magnetic susceptibilities arising from the Larmor precession of the six π electrons in delocalized orbitals. The shielding effect of benzene was quantified by Pople⁴ and Bernstein et al.⁵ in 1956 using a point dipole approximation. Waugh and Fessenden⁶ and subsequently Johnson and Bovey⁷ developed an empirical model of shielding for benzene using a current loop model. Quantum mechanical approaches utilizing the Hückel method and the London approximation were developed separately by Pople⁸ and McWeeny.⁹ Amos and Roberts^{10–12} developed a theory based on uncoupled Hartree-Fock calculations, and Roberts¹³ extended it by evaluating some integrals numerically. Memory¹⁴ used a London approximation to predict the π electron effect on the chemical shift. Haigh and Mallion¹⁵ calculated shielding based on a variation of the McWeeny method. Recently, Martin et al.¹⁶ developed a simple equation for predicting the shielding of a proton held above the surface of benzene based on *ab initio* Hartree-Fock calculations of a simple model system.

However, structures that have a proton over an aromatic ring cannot contain benzene itself, but rather a substituted aromatic

Color Plates for this article are on pages 300–301.

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ring. Therefore, the extent to which substituents on an aromatic ring perturb the diamagnetic anisotropy and alter the shielding surface is of considerable interest. In this article, we report an extension of the calculations performed on benzene to include two monosubstituted aromatic rings having substituents with very different electronic effects: aniline and nitrobenzene. The result is an improvement in the accuracy of prediction relative to that obtained using the equation based solely on benzene. Furthermore, the algorithm reported herein is more generally applicable to predicting shielding effects on protons over variously (even multiply) substituted aromatic rings than the previous model.

COMPUTATIONAL METHODS

Input geometries of methane, aniline, and nitrobenzene were generated in *Spartan*¹⁷ molecular modeling software on an SGI Indigo2 R4000 computer and optimized at an *ab initio* level using Hartree-Fock theory, with a basis set of 6-31G(d,p).¹⁸ Files of the optimized structures were converted to a protein databank (.pdb) file format, at which point two files (methane and one of the substituted aromatic compounds) were textually merged to place the carbon of the methane molecule directly over the center of the aromatic ring with three protons oriented in a plane parallel to the aromatic ring at a distance of 2.5 Å. The coordinates of the methane portion of this file were manipulated in separate copies of the file to allow the aromatic compound to remain stationary while the methane molecule was "moved" over the face of the aromatic molecule in the X and Y directions, keeping the Z distance from the plane of the aromatic ring fixed. The twofold symmetry of aniline and nitrobenzene was employed to limit the number of geometries to be calculated. The X and Y coordinates of methane were changed in increments of 0.4 Å. At least 64 different geometries were calculated for each aromatic compound. Similar series of calculations were performed in which methane was positioned over the plane of the substituted aromatic compound at distances (Z axis) of 3.0, 3.5, 4.0, and 4.5 Å.

Using the same theory and basis set as employed in the geometry optimization calculations of the individual structures of methane and the substituted aromatic compound, single point calculations were done using *Gaussian 94*¹⁹ on a Cray T90. The NMR shielding data were calculated using the GIAO-SCF (gauge-including atomic orbital) method, developed by Ditchfield²⁰ and modified by Chesnut²¹ and subsequently by Wolinski et al.²² Calculations were performed on input geometries with methane coordinates covering one half of the aromatic compound (positive values of X, positive and negative values of Y; Figure 1). The isotropic shielding values calculated from these were manipulated mathematically (taking into account the symmetry of each aromatic compound) so that the entire surface over each of the aromatic molecules was covered. The isotropic shielding values for each proton on the methane molecule over the aromatic rings were recorded and transformed into the shielding increment $\Delta\sigma$ by subtracting from each data point the isotropic shielding value calculated for methane alone.

RESULTS AND DISCUSSION

The shielding increment ($\Delta\sigma$) values were plotted against the lateral distance (X and Y) from the center of the aromatic ring

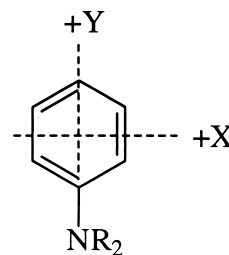


Figure 1. Schematic of Cartesian coordinates of substituted aromatic compounds; R=H or O.

at five distances (2.5, 3.0, 3.5, 4.0, or 4.5 Å) of separation (Z) from the plane of each aromatic ring (Color Plates 1 and 2). A three-dimensional shielding surface was generated for each set of data. Curve fitting of the resultant three-dimensional surfaces using the statistical modeling software *TableCurve3D*²³ yielded the same simple equation type (Equation 1) as the best fit function in common for each distance Z for each substituted aromatic ring (Table 1).

$$1/\Delta\sigma = \mathbf{a} + \mathbf{b}X^2 + \mathbf{c}Y^2 \quad (1)$$

This suggests that the perturbation due to the presence of a substituent has a relatively minor effect on the shielding surface and that the major effect is due to the aromatic ring. In an effort to develop a generally applicable shielding algorithm for aromatic rings, the values of **a**, **b**, and **c** in the specific Equation 1 for aniline, nitrobenzene, and benzene¹⁶ at each distance Z were averaged and the mean values were plotted vs the five distances Z from the plane of the aromatic ring. This allowed the relationship between the distance Z above the plane of the aromatic ring and the mean values of **a**, **b**, and **c** to be determined in terms of simple quadratic equations (Table 2) using *MSEExcel*.²⁴ Substituting these equations into Equation 1 gives a single equation (Equation 2) predicting the shielding increment $\Delta\sigma$:

$$\begin{aligned} 1/\Delta\sigma = & (0.2246 Z^2 - 0.9634 Z + 1.5011) \\ & + (0.0406 Z^2 - 0.2907 Z + 0.7022) X^2 \\ & + (0.0091 Z^2 - 0.0287 Z + 0.1668) Y^2 \quad (2) \end{aligned}$$

Table 1. Correlation coefficient **r** of the fit of an equation of the form of Equation 1 to the GIAO-SCF-calculated shielding increments for methane over aniline and nitrobenzene

Distance above ring (Å)	r (aniline)	r (nitrobenzene)
2.5	0.64	0.87
3.0	0.96	0.98
3.5	0.98	0.96
4.0	0.97	0.96
4.5	0.96	0.89

Table 2. Quadratic equations relating the constant *a* and the coefficients *b* and *c* in the overall Equation 1 to the distance *Z* from the plane of the aromatic ring and their correlation coefficients *r*

Equation	<i>r</i>
a = 0.2246 <i>Z</i> ² - 0.9635 <i>Z</i> + 1.5011	0.99
b = 0.0406 <i>Z</i> ² - 0.2907 <i>Z</i> + 0.7022	0.99
c = 0.0091 <i>Z</i> ² - 0.0287 <i>Z</i> + 0.1668	0.99

The applicability of this function was tested by calculating the shielding increments for several known systems having protons over a substituted aromatic ring. The shielding increment value was applied as an adjustment to the chemical shift predicted by the

use of additive substituent increments.¹ The results are compared to experimentally observed chemical shifts in Figure 2.

The shielding increment for each proton in each input file also was calculated using the overall shielding function developed. These function-calculated values were compared to the shielding increments calculated by GIAO-SCF. The root mean square (RMS) deviation between the chemical shift increment calculated by our equation and that calculated by GIAO-SCF is reported in Table 3. This is a measure of the fit of the shielding function to the GIAO-SCF calculated shielding values and provides an indication of the accuracy of the predictions made using this new algorithm.

A graphical comparison of the shielding values calculated by Equation 2 is made to those calculated by several other methods in Figure 3. The shielding increments predicted by the model based on calculations of the methane-aromatic ring

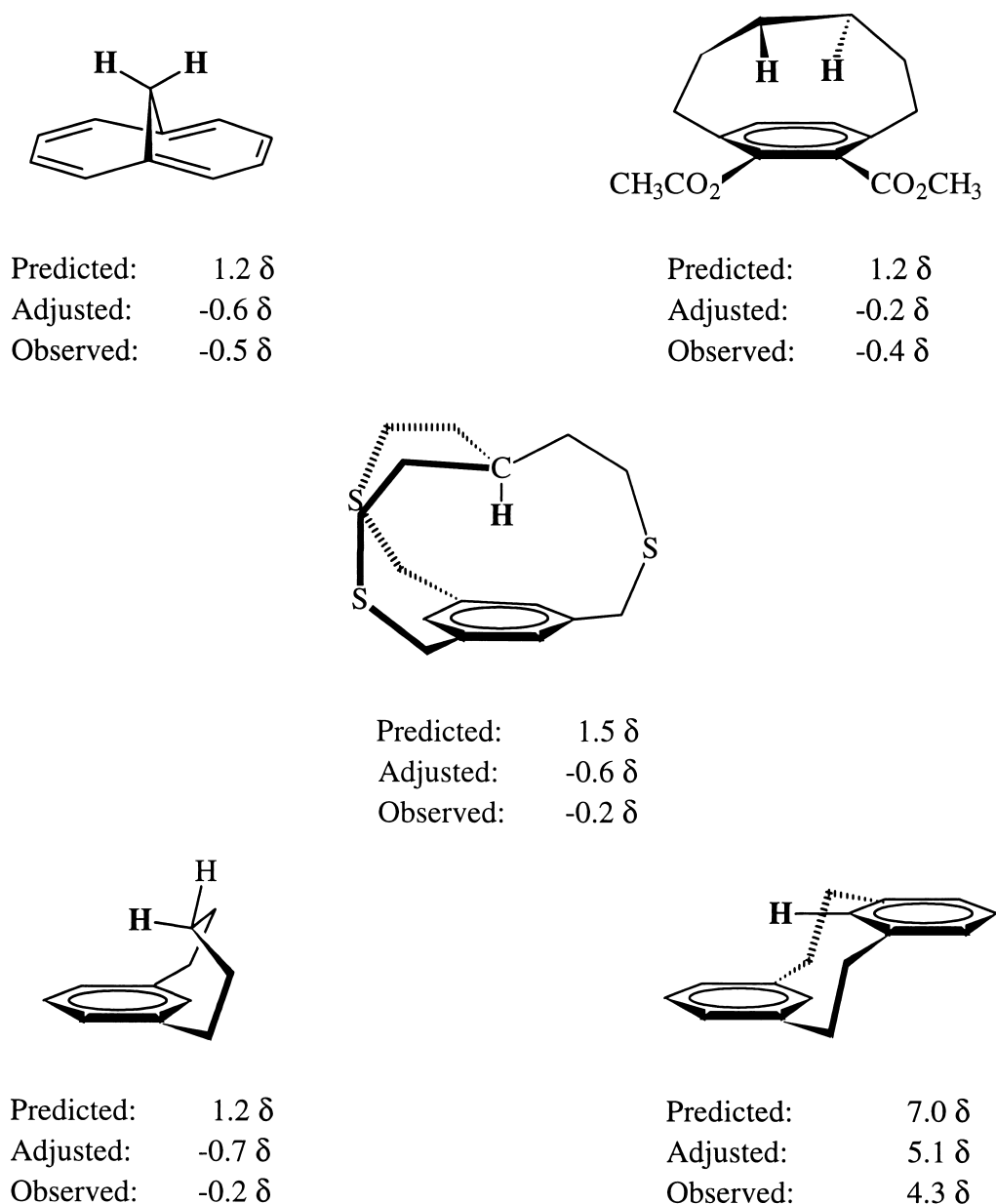


Figure 2. Chemical shifts of selected protons (in bold) predicted by substituent increments (Predicted),⁵ predicted chemical shift values adjusted by the shielding increment calculated by Equation 2 (Adjusted), and experimental values (Observed).

Table 3. Root mean square (RMS) deviation of the $\Delta\sigma$ values calculated by the overall shielding equation (Equation 2) from the values calculated by GIAO-SCF as a function of the distance above each aromatic ring

Distance above aromatic ring (Å)	RMS deviation (ppm) above		
	Aniline	Nitrobenzene	Benzene
2.5	0.34	0.19	0.23
3.0	0.14	0.18	0.08
3.5	0.09	0.10	0.06
4.0	0.06	0.06	0.06
4.5	0.04	0.04	0.07

model system resemble those predicted by the Johnson-Bovey model for protons 3.5 Å and farther from the aromatic ring. However, for protons closer to the ring, the GIAO-SCF model (Equation 2) shows less shielding, more in line with the values calculated by the methods of Roberts¹³ and Memory.¹⁴ Indeed, the curvature of the shielding plot (Fig. 3) for the GIAO-SCF model (Equation 2) becomes less steep as the distance from the aromatic ring diminishes, unlike all of the other models. This may be reflective of an increasing contribution of the same kind of deshielding at close proximity to the π electron system as we reported in alkenes.^{25–28} The other theoretical models treat only the magnetic anisotropy effect of the π electron system at a point in space relative to the center of the ring. Our model treats magnetic anisotropy of the π system as well as other important contributions to the observed chemical shift, such as the magnetic anisotropy of other nearby bonds, electric field effects, orbital interactions, and dispersion to the extent

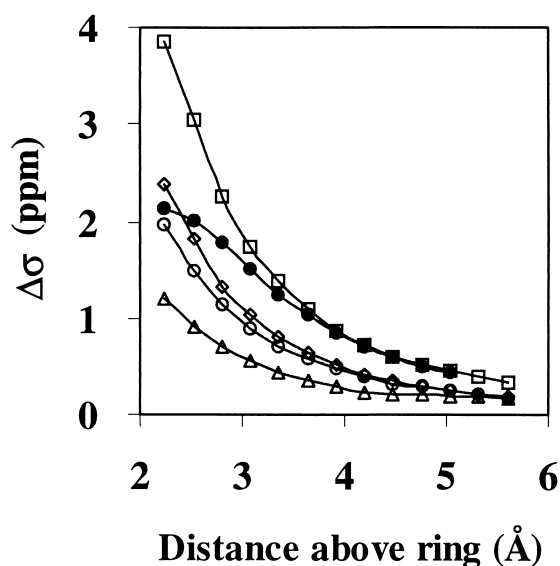


Figure 3. Shielding increment $\Delta\sigma$ (in ppm) as a function of distance (in Å) above the center of a benzene ring calculated by (a) the Johnson-Bovey method (open squares), (b) Equation 2 (solid circles), (c) the Roberts method (open diamonds), (d) the Memory method (open circles), and (e) the McWeeny method (open triangles).

that these effects are calculated by the GIAO-SCF method. Thus, it is not surprising that the shielding values estimated using Equation 2 agree well with the observed NMR shielding values in the diverse structures shown in Figure 2.

CONCLUSIONS

The shielding increment $\Delta\sigma$ has been calculated for protons of methane held at various positions over the planes of aniline and nitrobenzene using GIAO-SCF in *Gaussian 94*. A plot of the calculated $\Delta\sigma$ against X and Y displacement from the center of the aromatic ring gives a smooth curved surface for each of five distances above the ring. Each of these $\Delta\sigma$ surfaces could be fitted well by an equation (Equation 1) of the same general form. The constant and the coefficients in the specific equations at each distance above the aromatic ring found for aniline, nitrobenzene, and benzene were averaged, and the mean values were plotted against the distance Z above the aromatic ring. The quadratic equations fitting the resulting curves were substituted into Equation 1 to give one equation (Equation 2) for predicting the shielding increment experienced by protons held over the plane of a substituted benzene ring. Application of this equation to several examples demonstrates its predictive validity.

Deviation of the function-calculated shielding increment from the values calculated directly by GIAO-SCF is greatest for protons closest to the ring (Table 3). This may be explained by a greater perturbation effect caused by the substituent for protons closer to the substituent. It is known that ring current shielding effects project well above and below the plane of the ring.¹⁶ Mathematical functions fit the shielding increment surface at 2.5 Å much poorer than at distances farther from the ring (Table 1, and Color Plates 1 and 2). It should be noted that although the RMS deviation is greatest at 2.5 Å, the calculated shielding increments also are greater (up to 3 ppm) at that proximity to the ring, making the RMS deviation approximately 10% of the predicted shielding increment, comparable to its relative value at the other distances.

ACKNOWLEDGMENTS

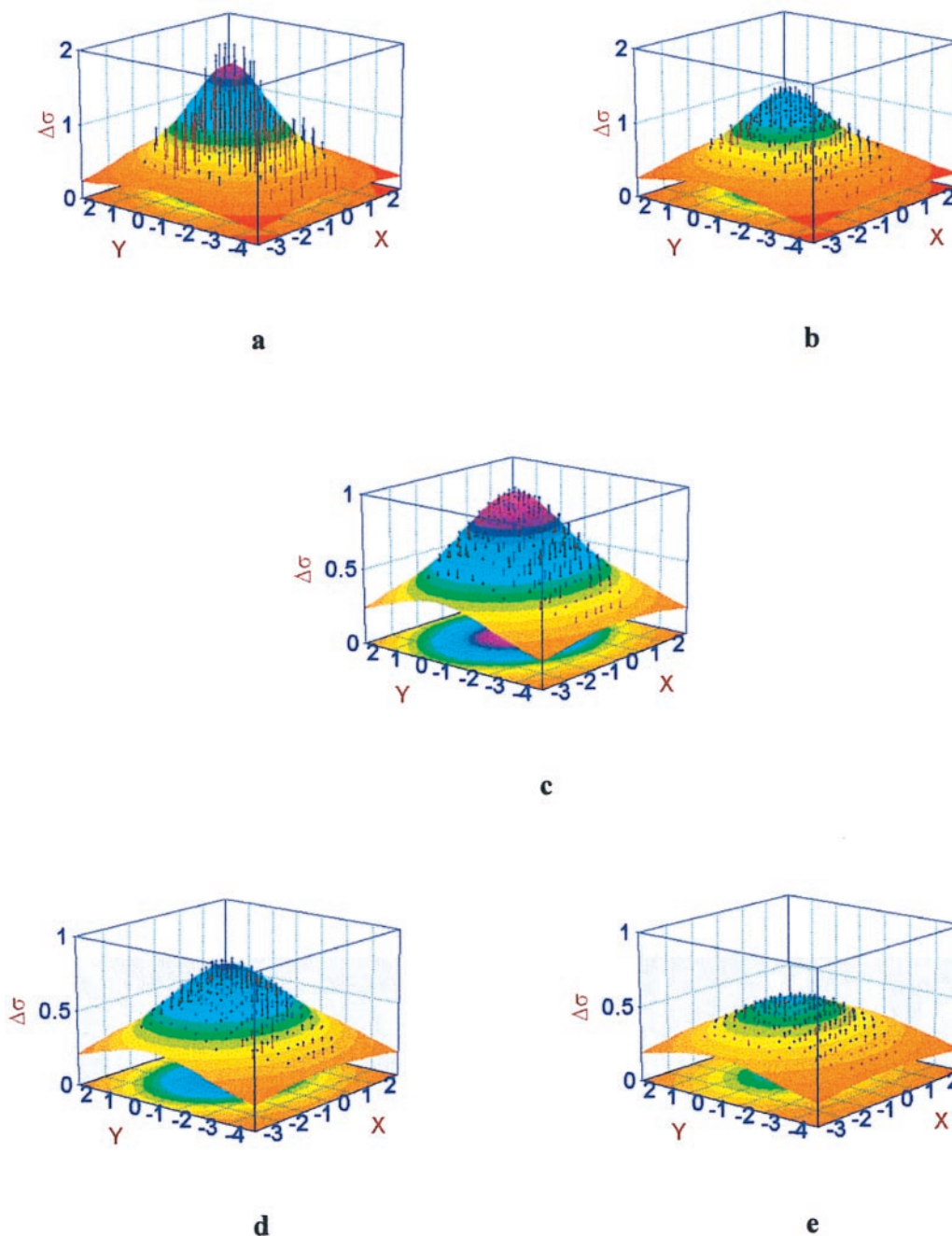
The authors gratefully acknowledge support of this work by the donors of The Petroleum Research Fund, administered by the American Chemical Society, Cray Research Incorporated, the North Carolina Supercomputing Center, and the College of Arts and Sciences of UNCW.

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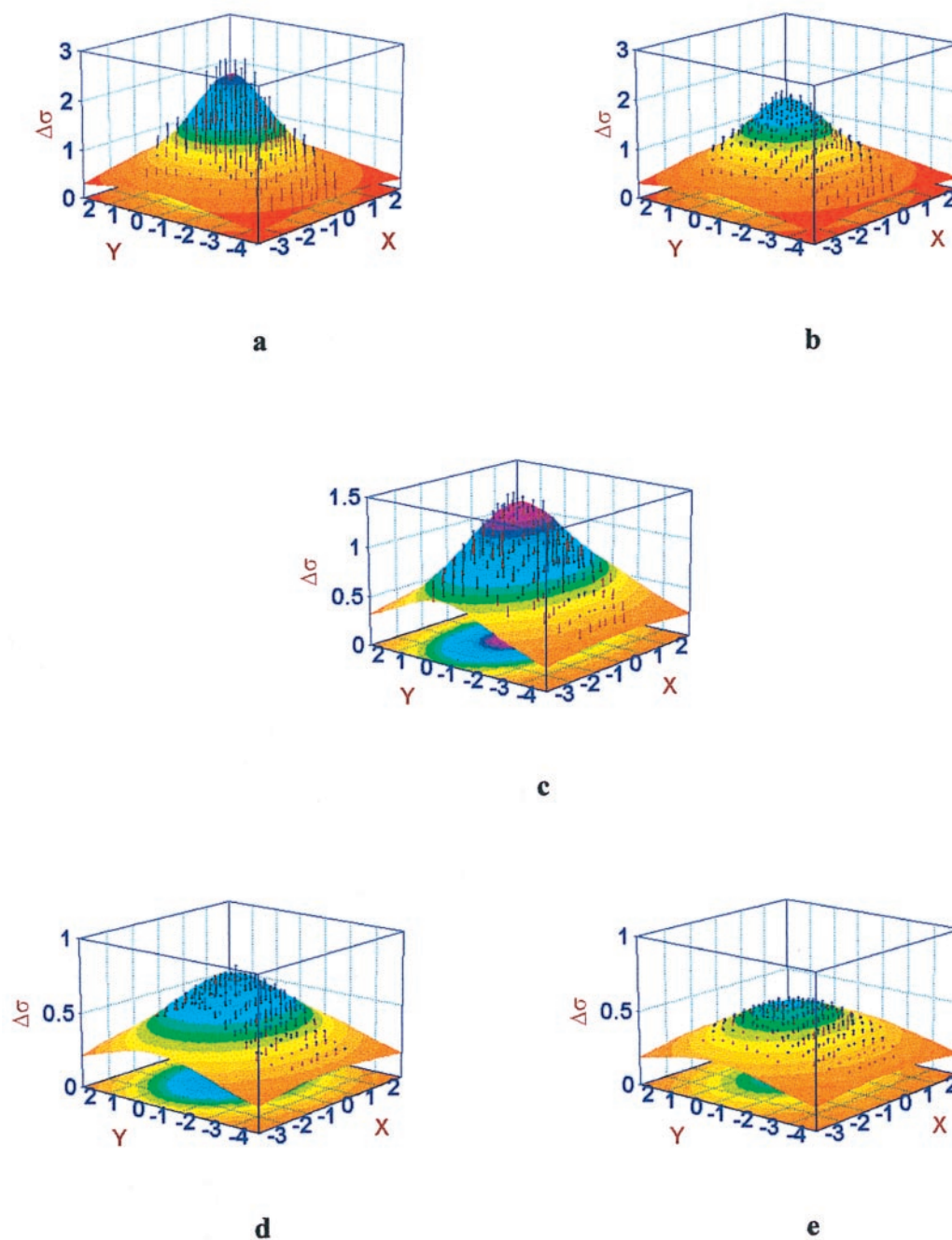
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Color Plate 1. Surfaces of the shielding increment ($\Delta\sigma$) above aniline at (a) 2.5 \AA , (b) 3.0 \AA , (c) 3.5 \AA , (d) 4.0 \AA , and (e) 4.5 \AA above the aromatic ring.



Color Plate 2. Surfaces of the shielding increment ($\Delta\sigma$) above nitrobenzene at (a) 2.5 Å, (b) 3.0 Å, (c) 3.5 Å, (d) 4.0 Å, and (e) 4.5 Å above the aromatic ring.