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MOLECULAR SURFACE ELECTROSTATIC POTENTIALS IN THE ANALYSIS OF NON-HYDROGEN-BONDING NONCOVALENT INTERACTIONS

by

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Electrostatic potentials computed on molecular surfaces are used to analyze some noncovalent interactions that are not in the category of hydrogen bonding, e.g. "halogen bonding". The systems examined include halogenated methanes, substituted benzenes, *s*-tetrazine and 1,3-bisphenylurea. The data were obtained by *ab initio* SCF calculations.

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1. Introduction

The electrostatic potential V(**r**) created in the space around a molecule by its nuclei and electrons is well established as a tool for the elucidation of molecular reactive behavior, including studies of electrophilic, nucleophilic and recognition interactions (Politzer and Daiker, 1981; Politzer and Murray, 1991; Scrocco and Tomasi, 1973). V(**r**) is defined rigorously by eq. (1):

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\,d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (1)$$

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$, and $\rho(\mathbf{r})$ is the electronic density function for the molecule. The electrostatic potential V(**r**) is a real physical property that can be determined experimentally by diffraction methods, as well as computationally (Politzer and Truhlar, 1981). Unlike $\rho(\mathbf{r})$ itself, which represents only the electronic density at the point **r**, V(**r**) gives the net result at a given point of the integrated effects of all of the nuclei and the electrons, thus giving a total electrostatic picture. The sign of V(**r**) at any point in space is dependent upon whether the nuclear or the electronic term is dominant there.

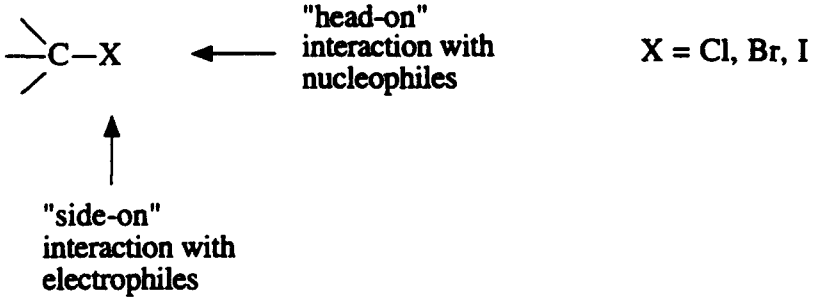
The electrostatic potential is particularly well-suited for the analysis of noncovalent interactions, which do not involve making or breaking covalent bonds and which occur without any extensive polarization or charge transfer between the interacting species. For example, V(**r**) has been shown to be useful in studies of hydrogen bonding, providing some useful guidelines concerning sites and directional preferences (e.g., Brinck, et al., 1993; Kollman, et al., 1975; Leroy, et al., 1976) as well as accepting and donating tendencies (Murray and Politzer, 1991; Murray and Politzer, 1992; Murray, et al., 1991a). However hydrogen bonding is just one specific type of weak electrostatic interaction. It is the use of V(**r**) in elucidating some of the other types, which do not fall in the category of hydrogen bonding, that will be our topic of discussion in this article.

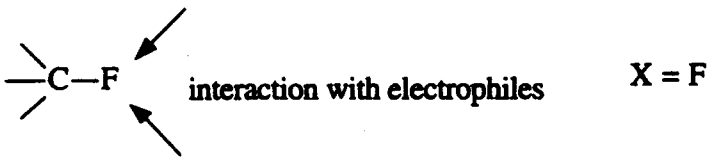
2. Methods and Procedure

This analysis of noncovalent interactions that do not involve hydrogen bonding will be based on our *ab initio* self-consistent field molecular orbital calculations, using the code GAUSSIAN 92 (Frisch, et al., 1992), for a variety of molecules: (a) halogenated methanes (Brinck, et al., 1992); (b) substituted aromatics, (c) *s*-tetrazine (Politzer, et al., 1992) and (d) 1,3-bisphenylurea (Murray, et al., 1991b) . The results for (a), (c) and (d) are taken from earlier work. Our general approach has been to compute optimized structures for the molecules of interest, at the HF/STO-3G* level for (a), (b) and (d) and HF/3-21G for (c). These have been used to compute V(**r**) on molecular surfaces defined, following Bader et al (1987), as the 0.001 au contour of the electronic density, at the HF/STO-5G* level for (b) - (d) and the HF/6-31G* for (a).

3. "Halogen" bonding

It has been observed that certain directional preferences exist in the orientations of halogen-containing organic molecules in the crystalline state (Murray-Rust, et al., 1983; Ramasubbu, et al., 1986). When the halogen X is Cl, Br, or I, electrophilic portions of neighboring molecules generally tend to interact with it in a "side-on" manner, nearly normal to the C-X bond, whereas for nucleophiles it is usually approximately "head-on", along the C-X axis. Interactions with





fluorine in a C–F bond tend to be only by electrophiles and somewhere intermediate between "side-on" and "head-on" approaches.

We have computed surface potentials for CF_4, CCl_4 and CBr_4, and have shown that the potentials associated with the chlorines and bromines are actually *positive* at the end regions (i.e. on the C–X axis, beyond X) despite the high electronegativities of Cl and Br. There is a negative ring around the sides of the Cl and Br, with surface minima ($V_{S,min}$) at angles of 102° and 96° with the C-Cl and C-Br bonds, respectively. These results indicate tendencies for intermolecular interactions with both nucleophiles and electrophiles, with directional preferences corresponding to what has been found experimentally in organic crystals. In contrast to CCl_4 and CBr_4, our surface potential for CF_4 is negative both at the ends and along the sides of the fluorines, with the $V_{S,min}$ forming angles of 132° with the C-F bonds. This is consistent with fluorine in organic crystals interacting only with electrophiles and in an intermediate-type approach.

The strongly positive potentials at the ends of the chlorines and bromines in CCl_4 and CBr_4 suggest that they should in general be able to interact with negative portions of other systems. This has indeed been observed, e.g. with the π electrons of aromatic rings such as benzene or *p*-xylene (Gotch, et al., 1991; Ham, 1953; Hooper, 1964) and with the lone pair regions of pyridine and tetrahydrofuran (Dumas, et al., 1978), and quinuclidine (**1**) and diazabicyclo[2.2.2]octane (**2**) (Blackstock, et al., 1987). Lorand *et al* (1993) have introduced the term "halogen-bonding" to

1

2

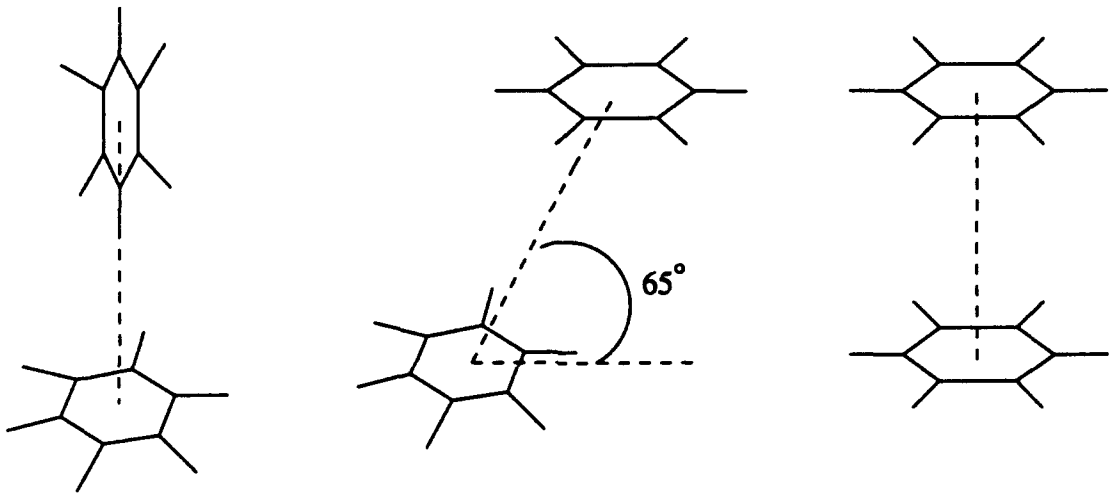
designate this type of electrostatic interaction between the ends of the larger halogens Cl, Br and I in carbon-halogen bonds and electron-donating portions of other molecules.

Our results for CCl_4 and CBr_4 are also relevant to spectroscopic studies showing that a variety of non-hydrogen-containing fluorocarbons (e.g., CF_3Cl, C_2F_5Cl, CF_3Br, C_2F_5Br) can act as hydrogen bond breakers (DiPaulo and Sandorfy, 1974). The latter capability has been linked to the anesthetic potencies of halocarbons; it has been suggested that molecules such as CF_3Cl and

CF_3Br act as electron acceptors and displace the donors in preexisting hydrogen bonds, thereby disrupting the latter and forming halogen bonds.

4. Benzene and Substituted Benzenes

The surface electrostatic potential of benzene has a symmetrical pattern with negative regions above and below the aromatic ring, due to the π electrons, and positive regions forming a ring around the molecule (Sjoberg, 1989). This pattern can explain the existence of both the T-shaped structure (3) and the parallel-displaced structure (4) that have been reported experimentally



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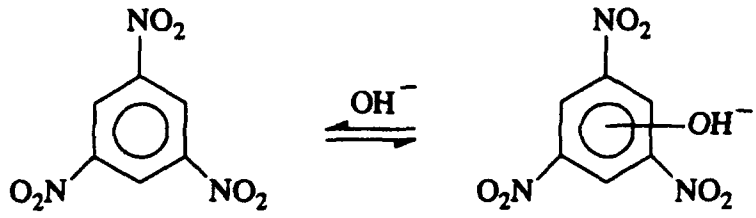
and theoretically for the benzene dimer (Hobza, et al., 1993), and argues against a sandwich-type structure (5), which has indeed been found computationally to be less stable than 3 and 4 (Hobza, et al., 1990). The surface V(r) of benzene is also consistent with the orientation of benzene molecules in the crystal, which is essentially a three-dimensional extension of the T-shaped dimer 3 (Cox, et al., 1958).

It is well known that a substituent X on a benzene ring can have a major or a minor effect on chemical reactivity, depending upon the degree of interaction between the substituent and the aromatic ring. This is quantified by the Hammett constants for the various substituents (Exner, 1988). However the question that we address in this section is how substituents modify the intermolecular interactions of the resulting derivatives relative to those of benzene.

We have accordingly computed the surface electrostatic potentials of a group of C_6H_5X molecules, where X = NH_2, OH, OCH_3, CH_3, F, Cl, Br, I, CHO, CN and NO_2. The surface V(**r**) of these molecules can be categorized into three main groups.

The relatively strongly resonance-donating substituents $-NH_2$, –OH and $-OCH_3$ produce very similar surface V(**r**) patterns (Figure 1). The negative regions above and below the rings are more negative than those of benzene, and even stronger negative potentials are found in the vicinities of the heteroatoms (N or O); the latter are attributed to the lone pair electrons of the heteroatom. These surface V(**r**) patterns suggest that these molecules could interact with electrophilic species both above and below the aromatic rings as well as through the lone pair region(s) of the heteroatoms. Berthelot (1992) has indeed found that $C_6H_5NH_2$, C_6H_5OH and $C_6H_5OCH_3$ act as bifunctional bases.

Looking next at the strongly electron-withdrawing substituents, –CN, $-NO_2$ and –CHO, we have found that the negative regions above and below the aromatic ring are totally eliminated in the cases of benzonitrile (X = CN, Figure 2) and nitrobenzene, and significantly weakened in benzaldehyde. In addition, these molecules have strong negative regions associated with the oxygens of $-NO_2$ and –CHO and the nitrogen of –CN. Electrophilic intermolecular interactions would be predicted to occur in the vicinities of these heteroatom negative regions, and indeed Berthelot (1992) has found benzonitrile, nitrobenzene and benzaldehyde to be monofunctional oxygen or nitrogen bases. The positive regions above the rings in C_6H_5CN and $C_6H_5NO_2$ could serve as sites for nucleophilic interactions. Our results for nitrobenzene and other nitroaromatics (Politzer, et al., 1984; Murray, et al., 1990) are consistent with the observed interactions of these molecules with hydroxide and alkoxide ions to form Meisenheimer complexes, e.g. as shown below for 1,3,5,-trinitrobenzene (**6**) [eq. (2)].



(2)

6 π-complex

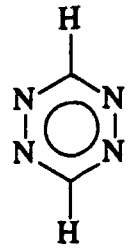
The monohalogenated benzenes form a third group (Figure 3). The surface potentials above and below their aromatic rings are negative but less so than that of benzene. There is also a weak negative region associated with each halogen atom. C_6H_5Cl, C_6H_5Br and C_6H_5I have an additional interesting feature; the surface V(**r**) at the end of the chlorine, bromine or iodine is positive, suggesting a tendency for interactions with nucleophiles at these sites. This feature was also found for CCl_4 and CBr_4, as we have discussed in the previous section. The overall pattern of the surface potentials of the halogenated benzenes suggests that they will undergo weak electrophilic interactions above and below their aromatic rings and through the halogen atoms.

The methyl substituent was not included in any of the above-mentioned groups. The surface V(**r**) of toluene is actually very similiar to that of benzene. The main differences are that the negative regions above and below the ring in toluene are very slightly strengthened, and that the $-CH_3$ group introduces asymmetry into the pattern.

The surface electrostatic potentials of the substituted benzenes demonstrate the significant differences in pattern that can occur by varying the substitutent. These modifications should be taken into account in trying to understand and predict the types of noncovalent interactions in which these molecules become involved.

5. *s*-Tetrazine

The surface potential of *s*-tetrazine (**7**) is strongly positive above and below the aromatic ring (Politzer, et al., 1992), with the most positive values ($V_{S,max}$) being 47 kcal/mole, in striking contrast to benzene, which is negative in this region. The hydrogens also have relatively strong



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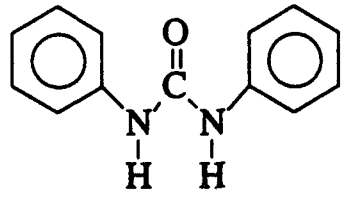
positive potentials; their $V_{S,max}$ values are 23 kcal/mole, compared to the hydrogen $V_{S,max}$ of benzene, 9 kcal/mole. Negative potentials are associated only with the ring nitrogens in 7.

The pattern of positive and negative electrostatic potential regions on the molecular surface of *s*-tetrazine helps to explain its formation of a dimer as well as complexes with other molecules, e.g. HCl, H_2O and C_2H_2, and its crystal structure (Politzer, et al., 1992). For example, in one of its complexes with acetylene (C_2H_2), the latter is above the plane of 7 and bisecting its N–N bonds (Morter, et al., 1991); the π electrons of C_2H_2 can interact with the positive V(r) above the center of 7 and the acetylenic protons with the negative nitrogens. In the *s*-tetrazine crystal, the planes of adjacent molecules are perpendicular to one another (Bertinotti, et al., 1956), consistent with the negative N–N portions of each being located above the positive ring centers of its neighbors.

On the other hand, the *s*-tetrazine-HCl system is believed to have a nearly linear N···H–Cl bond (Haynam, et al., 1987). Thus some of the noncovalent interactions of 7 clearly fit into the category of traditional hydrogen bonding, while others - - even though they may involve hydrogens - - appear to be less localized in nature. Admittedly, the distinction can become blurred.

6. <u>1,3-bisphenylurea</u>

1,3-bisphenylurea (8) is the parent compound of a large family of derivatives, most of which do *not* cocrystallize with guest molecules (Etter, et al., 1990). Even when put into solution



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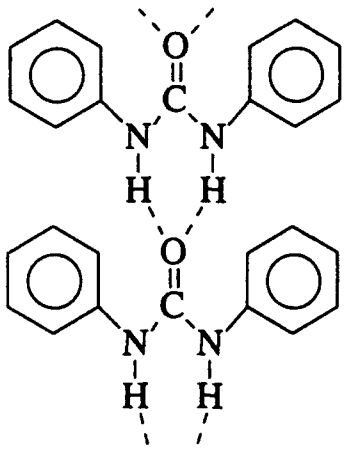
with strong hydrogen bond acceptors, e.g. dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and triphenylphosphine oxide (TPPO), most diphenyl ureas crystallize with other molecules of the same kind in a connectivity pattern shown below (**9**) instead of forming cocrystals (e.g. **10**).



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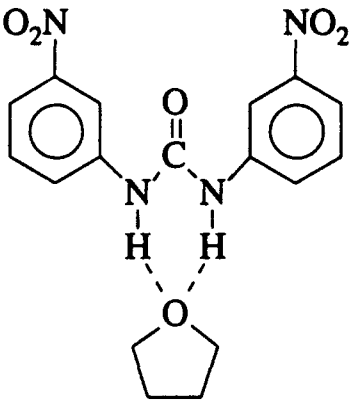

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We have proposed that the tendency for **8** to form homomeric rather than guest-host crystals is due largely to a relatively strong and nonlocalized electrostatic attraction between diphenylurea molecules (Murray, et al., 1991b). Our surface electrostatic potential for **8** shows an extended negative region along the top edge of the molecule and a long positive one along the bottom edge. The suggested nonlocalized electrostatic interaction between the top and bottom edges of neighboring molecules, which is more extensive than typical hydrogen bonding, apparently provides sufficient stability that homomeric cyrstal formation is not disrupted even by the presence of very strong hydrogen bond accceptors in solution when crystallization is occuring.

Conclusion

The great importance and widespread occurrence of hydrogen bonding may sometimes obsure the fact that there are other types of weak electrostatic interactions that can also have quite significant consequences. Our objective in this essentially qualitative discussion has been to draw attention to some of these, such as halogen bonding. Recognition of the roles that can be played by non-hydrogen-bonding noncovalent interactions can help to explain some interesting, perhaps

surprising, observations. We have tried to show that the analysis of electrostatic potentials calculated on molecular surfaces is an effective approach for this purpose; it encompasses a wide array of interactions, including traditional hydrogen bonding, and avoids what may sometimes be rather artificial distinctions.

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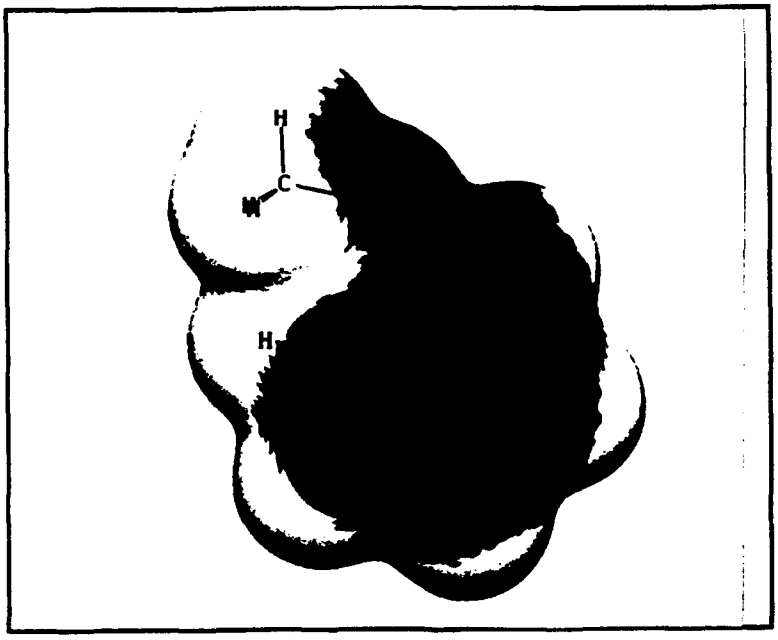
Figure Captions

Figure 1. Calculated electrostatic potential on the molecular surface of anisole ($C_6H_5OCH_3$). Color code, in kcal/mole: white, $V(r) > 0$; gray, $-15 < V(r) < 0$; black, $V(r) < -15$.

Figure 2. Calculated electrostatic potential on the molecular surface of benzonitrile (C_6H_5CN). Color code, in kcal/mole: white, $V(r) > 0$; gray, $-15 < V(r) < 0$; black, $V(r) < -15$.

Figure 3. Calculated electrostatic potential on the molecular surface of bromobenzene (C_6H_5Br). Color code, in kcal/mole: white, $V(r) > 0$; gray, $-15 < V(r) < 0$. Note that there is a small white region at the top of the bromine.



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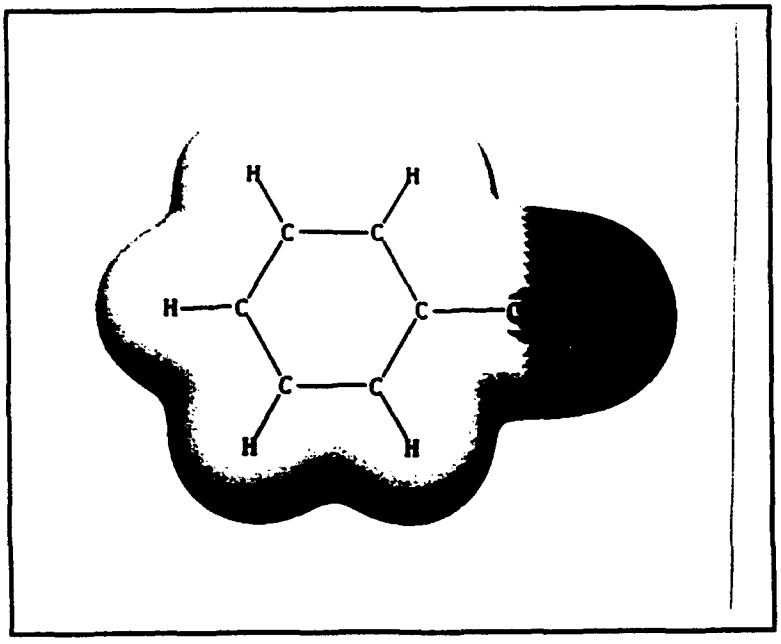

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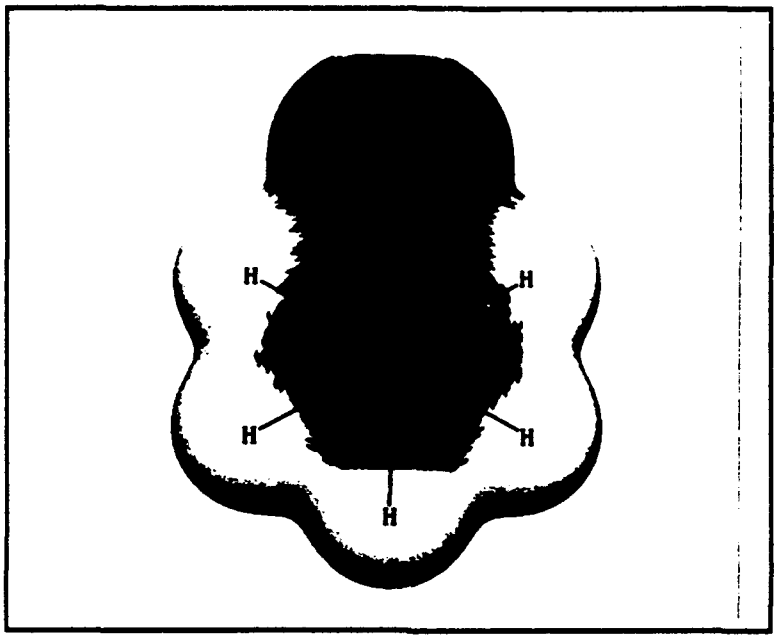

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