J. Am. Chem. Soc. 1992, 114, 8263–8268

Ab Initio Study of σ- and π-Effects in Benzenes Fused to Four-Membered Rings: Rehybridization, Delocalization, and Antiaromaticity

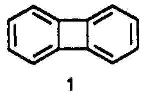
Rüdiger Faust, Eric D. Glendening, Andrew Streitwieser,* and K. Peter C. Vollhardt*

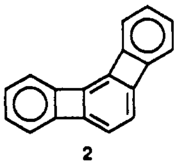
Contribution from the Department of Chemistry, University of California at Berkeley, and the Chemical Sciences Division, Lawrence Berkeley Laboratory, Berkeley, California 94720.
Received February 20, 1992

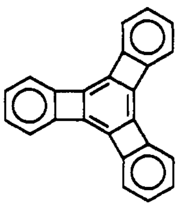
Abstract: The geometries of benzene incrementally fused to cyclobutenes, 3,4-dimethylenecyclobutenes, and cyclobutadienes are investigated with ab initio SCF-MO methods and by natural bond orbital (NBO)/natural resonance theory (NRT) analysis. These systems show various degrees of bond alternation in the six-membered ring with fused bonds elongated and bonds adjacent to the site of annelation contracted compared to those of benzene. NBO analysis reveals significant strain in the σ-frame as evidenced by strong rehybridization at the annelated carbon centers. This effect accounts, in part, for the bond alternation in the cyclobutadieno-fused benzenes, but has negligible influence on that of the cyclobuteno- and 3,4-dimethylenecyclobuteno-fused analogs. The relative contributions of the two Kekulé resonance forms are assessed by NRT analysis and are found to be in accord with the postulate originally presented by Mills and Nixon. Our results suggest that the principal source of bond alternation is either hyperconjugation (in cyclobuteno-fused benzenes) or conjugation (in benzenes annelated to 3,4-dimethylenecyclobutene or cyclobutadiene). In all cases, deletion of these delocalizing interactions from the wave function leads to a more symmetrical benzene geometry.

The concept of aromaticity,[1] usually associated with Hückel's $4n + 2$ rule, has proven to be extremely fruitful in organic chemistry. The exploration of structural and hence electronic limitations of aromatic behavior in the benzene nucleus has been the focus of enormous efforts, exemplified by the extensive experimental studies of *p*-cyclophanes[2] and small-ring-annelated benzenes.[3] In the latter case, it has been argued[4] that imposing sufficient strain on the central six-membered ring could induce a bond-alternating carbon framework with double bonds directed away from the sites of annelation, but experimental evidence for this so-called Mills–Nixon effect remains scarce.[5]

Bond-alternating 1,3,5-cyclohexatriene moieties have been observed in the benzocyclobutadieno-fused benzenes biphenylene (**1**),[6] angular [3]phenylene (**2**),[7a] and triangular [4]phenylene (**3**),[7b] the degree of alternation increasing along the series.[8] In these systems, the benzene nucleus is incorporated into extensively delocalized π-networks via four-membered rings, raising the possibility of enhanced bond alternation to minimize antiaromatic cyclobutadienoid interactions.


1


2


3

Strain is certainly one of several contributors to the observed bond alternation in annelated benzenes. Depending on the nature of the fused carbocycle, conjugative or hyperconjugative interactions between the substituents and the benzenoid π-system may simultaneously enforce structural variations in the σ-frame. The notion that σ-strain alone would suffice to reduce the D_{6h} symmetry of benzene to bond alternating D_{3h} has been supported by model studies[9] of benzene with pairwise distortions of HCC angles from an optimal value of 120° to highly strained 90°, thereby mimicking fusion to four-membered rings. These models have been further scrutinized in a computational study[10] in which the formation of a cyclohexatrienoid topology is attributed mainly to σ-rehybridization effects induced by the strained carbon framework. The degree of π-delocalization remains substantial, even in benzenes severely distorted to D_{3h}. Rehybridization has been invoked previously to explain the reactivity of fused benzenes[11] and recently was the subject of a computational investigation aimed at understanding the origin of the Mills–Nixon effect in benzocyclobutenes.[12] These interpretations, however, are based either on empirical reasoning or on the application of maximum overlap methodology[13] and do not take into account π-resonance effects

---

[1] (a) Garratt, P. J. *Aromaticity*; Wiley: New York, 1986. (b) Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds*; Wiley: New York, 1989.

[2] (a) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic: New York, 1978. (b) Keehn, P. M.; Rosenfeld, S. M., Eds. *Cyclophanes*; Academic: New York, 1983; Vols. 1 and 2. (c) Rossa, L.; Vögtle, F.; Boekelheide, V.; Tabushi, I.; Yamamura, K. *Topics in Current Chemistry*; Springer: New York, 1983; Vol. 113. (d) Vögtle, F., Ed. *Topics in Current Chemistry*; Springer: New York, 1983; Vol. 115. (e) Vögtle, F. *Cyclophan-Chemie*; Teuben: Stuttgart, 1990. (f) Diederich, F. *Cyclophanes*; Royal Society of Chemistry: Cambridge, 1991.

[3] (a) Thummel, R. P. *Isr. J. Chem.* **1982**, *22*, 11. (b) Vollhardt, K. P. C. *Pure Appl. Chem.* **1980**, *52*, 1645.

[4] (a) Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* **1930**, 2510. (b) Longuet-Higgins, H. C.; Coulson, C. A. *Trans. Faraday Soc.* **1946**, *42*, 756. (c) Badger, G. M. *Q. Rev. Chem. Soc.* **1951**, *5*, 147. (d) Hiberty, P. C.; Ohanessian, G.; Delbecq, F. *J. Am. Chem. Soc.* **1985**, *107*, 3095. (e) Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* **1986**, *108*, 3241.

[5] (a) Mitchell, R. H.; Slowey, P. D.; Kamada, T.; Williams, R. V.; Garratt, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 2431 and references therein. (b) Collins, M. J.; Gready, J. E.; Sternhell, S.; Tansey, C. W. *Aust. J. Chem.* **1990**, *43*, 1547.

[6] (a) Fawcett, J. K.; Trotter, J. *Acta Crystallogr.* **1966**, *20*, 87. (b) Eckert-Maksić, M.; Hodošček, M.; Kovaček, D.; Maksić, Z. B.; Poljanek, K. *Chem. Phys. Lett.* **1990**, *171*, 49.

[7] (a) Diercks, R.; Vollhardt, K. P. C. *Angew. Chem.* **1986**, *98*, 268; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 266. (b) Diercks, R.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 3150.

[8] The heats of hydrogenation of **2** and **3** have been determined and will be the subject of a forthcoming publication: Faust, R.; Mohler, D. L.; Rogers, D. W.; Sawhney, A. J.; Vollhardt, K. P. C.; Wolff, S. Manuscript in preparation.

[9] (a) Stanger, A.; Vollhardt, K. P. C. *J. Org. Chem.* **1988**, *53*, 4879. (b) Stanger, A. *J. Am. Chem. Soc.* **1991**, *113*, 8277. We thank Professor Stanger for providing the manuscript prior to publication.

[10] Glendening, E. D.; Faust, R.; Streitwieser, A.; Vollhardt, K. P. C. Manuscript in preparation.

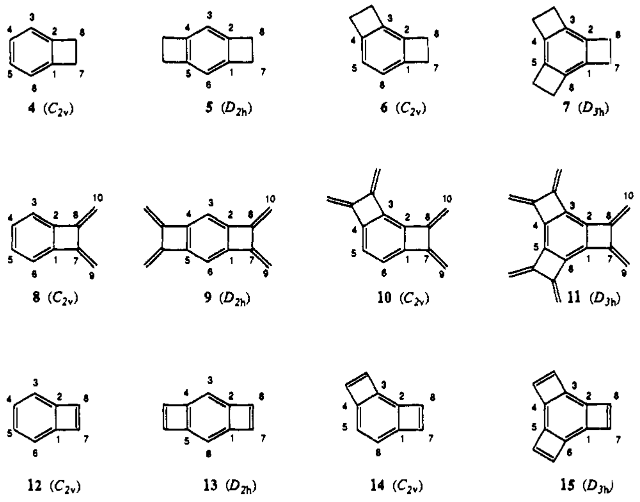
[11] (a) Finnegan, R. A. *J. Org. Chem.* **1965**, *30*, 1333. (b) Streitwieser, A.; Ziegler, G. R.; Mowery, P. C.; Lewis, A.; Lawler, R. G. *J. Am. Chem. Soc.* **1968**, *90*, 1357.

[12] Eckert-Maksić, M.; Kovaček, D.; Hodošček, M.; Mitić, D.; Poljanek, K.; Maksić, Z. B. *J. Mol. Struct.* (*THEOCHEM*) **1990**, *206*, 89.

[13] (a) Randić, M.; Maksić, Z. B. *Chem. Rev.* **1972**, *72*, 43. (b) Kovačević, K.; Maksić, Z. B. *J. Org. Chem.* **1974**, *39*, 539. (c) Maksić, Z. B.; Rubčić, A. *J. Am. Chem. Soc.* **1977**, *99*, 4233.

0002-7863/92/1514-8263$03.00/0 © 1992 American Chemical Society

Chart I



4 (C_{2v}) 5 (D_{2h}) 6 (C_{2v}) 7 (D_{3h})

8 (C_{2v}) 9 (D_{2h}) 10 (C_{2v}) 11 (D_{3h})

12 (C_{2v}) 13 (D_{2h}) 14 (C_{2v}) 15 (D_{3h})

or hyperconjugative interactions. It was further suggested[9b] that the "flexibility" of the electron distribution at the benzene substituents is responsible for the bond alternation, and that the formation of bent bonds prevents certain systems from adopting a cyclohexatrienoid geometry.

We now report a comprehensive ab initio investigation regarding the effect of incremental four-membered ring fusion on the structural and electronic characteristics of the benzene nucleus. Special attention focuses on the annelation of appropriately functionalized cyclobutenes, whose geometries reflect the salient structural features of **1**–**3** (Chart I). Comparison of the electronic properties of benzenes fused to cyclobutene, 3,4-dimethylenecyclobutene, and cyclobutadiene provides insight into the effect of various degrees of strain and π-conjugation (or hyperconjugation) on the geometry of the benzene frame. Applying natural bond orbital (NBO)[14] analysis to the computed wave functions allows discrimination between the σ- and π-electronic contributions to the bond alternation in these molecules.

Computational Methods

Ab initio SCF wave functions for each of the compounds under consideration were calculated at the 3-21G[15] level by either GAMESS[16] or GAUSSIAN 90,[17] and geometries were fully optimized within the designated symmetry constraints (cf. Chart I. Input files are available from the authors upon request). Total energies and selected geometrical parameters are listed in Table I. Wave function analysis was performed by the natural bond orbital (NBO)[14] method, which generates a set of localized, one- and two-center orbitals (the NBOs) that are subsequently decomposed into atomic contributions, the natural hybrid orbitals (NHOs). Electron delocalization is revealed in the non-negligible occupancies of, for example, the antibonding NBOs. The structural effect of delocalization can be assessed by removing selected delocalizing interactions from the wave function followed by geometry reoptimization. The NBO program deletes the Fock matrix elements describing these interactions and diagonalizes the resulting matrix to form a set of "localized" molecular orbitals. Geometry reoptimization is then performed with respect to the energy of the wave function formed from these orbitals. Unfortunately, analytic gradients are not available, necessitating the use of numerical optimization techniques. Due to this limitation, we examine the geometrical consequences of delocalization in **7**, **11**, and **15** only, structures that have a limited number of symmetry-unique internal coordinates.

Table I. Energies and C–C Bond Lengths of Annelated Benzenes[a]

	4	**5**	**6**	**7**
energy	−305.846455	−382.276199	−382.2732244	−458.699833
d(1–2)	1.386 (1.391)	1.390 (1.399)	1.397	1.408
d(1–6)	1.370 (1.385)	1.382 (1.394)	1.372	1.361
d(1–7)	1.538 (1.518)	1.538 (1.521)	1.540	1.538
d(2–3)	1.370 (1.385)	1.382 (1.394)	1.361	1.361
d(2–8)	1.538 (1.518)	1.538 (1.521)	1.536	1.538
d(3–4)	1.396 (1.400)	1.382 (1.394)	1.397	1.408
d(4–5)	1.386 (1.399)	1.390 (1.399)	1.372	1.361
d(5–6)	1.396 (1.400)	1.382 (1.394)	1.408	1.408
d(7–8)	1.600 (1.576)	1.597 (1.575)	1.599	1.598
	8	**9**	**10**	**11**
energy	−381.111513	−532.807635	−532.803494	−684.495982
d(1–2)	1.398	1.405	1.410	1.424
d(1–6)	1.370	1.381	1.372	1.359
d(1–7)	1.504	1.502	1.504	1.498
d(2–3)	1.370	1.381	1.359	1.359
d(2–8)	1.504	1.504	1.501	1.498
d(3–4)	1.396	1.381	1.410	1.424
d(4–5)	1.389	1.405	1.372	1.359
d(5–6)	1.396	1.381	1.408	1.424
d(7–8)	1.530	1.528	1.530	1.531
d(7–9)	1.312	1.312	1.312	1.309
d(8–10)	1.312	1.312	1.312	1.309
	12	**13**	**14**	**15**
energy	−304.611533	−379.7915462	−379.819669	−455.039433
d(1–2)	1.426	1.392	1.484	1.524
d(1–6)	1.339	1.381	1.326	1.309
d(1–7)	1.546	1.568	1.519	1.503
d(2–3)	1.339	1.381	1.313	1.309
d(2–8)	1.546	1.568	1.519	1.503
d(3–4)	1.438	1.381	1.484	1.533
d(4–5)	1.358	1.392	1.326	1.309
d(5–6)	1.438	1.381	1.487	1.524
d(7–8)	1.337	1.331	1.343	1.341

[a] SCF/3-21G values. Energies are given in hartrees and bond lengths in angstroms. Cf. C–C bond length of benzene (3-21G): 1.385 Å. For numbering scheme, see Chart I. Experimental values (in parentheses) are taken from ref 26a.

Resonance contributions to the ab initio wave functions were determined by natural resonance theory (NRT).[18] This method is based on the formation of a resonance-weighted density operator $\hat{\Gamma}$.

$$\hat{\Gamma} \approx \sum_{\alpha} \omega_{\alpha} \hat{\Gamma}_{\alpha} \qquad (1)$$

The idealized density operator for the αth resonance structure, $\hat{\Gamma}_{\alpha}$, is constructed from quantities obtained by NBO analysis of the full wave function. Resonance weights $\{\omega_{\alpha}\}$ are variationally optimized to best describe the NBO occupancies (i.e., diagonal elements of the full density operator $\hat{\Gamma}$) within the constraints

$$\sum_{\alpha} \omega_{\alpha} = 1,\ \omega_{\alpha} \geq 0 \text{ (for all } \alpha) \qquad (2)$$

Previous applications[18] have demonstrated that the NRT method accurately reproduces delocalization patterns for a variety of molecules and that the NRT resonance weights are largely basis set independent.[19] We have restricted the analysis presented here to strong (primarily π-) delocalization effects.

Results and Discussion

Geometries and Rehybridization Effects. In light of the great interest the Mills–Nixon effect has received over the years, the amount of experimental data for molecules pertaining to this work

---

(14) (a) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (c) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *QCPE Bull.* **1990**, *10*, 58. The NBO program is incorporated into the GAUSSIAN 9X series of programs (Link 607).

(15) Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039.

(16) GAMESS: Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Jensen, J. H.; Koseki, S.; Gordon, M. S.; Nguyen, K. A.; Windus, T. L.; Elbert, S. T. *QCPE Bull.* **1990**, *10*, 52.

(17) GAUSSIAN 90, Revision F.: Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzales, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1990.

(18) (a) Glendening, E. D. Ph.D. Thesis, University of Wisconsin at Madison, 1991. (b) Glendening, E. D.; Weinhold, F. Manuscript in preparation.

(19) For example, resonance weights for the systems **4**, **8**, and **12** based on SCF/6-31G* wavefunctions differ by less than 3.3% from the corresponding SCF/3-21G values reported in Table III.

Table II. NHO Character of Selected Carbon Centers[a]

	4	**5**	**6**	**7**
h(1–2)	2.21 (2.28)	2.16 (2.19)	2.21	2.28 (2.19)
h(1–6)	1.58 (1.61)	1.60 (1.61)	1.56	1.55 (1.66)
h(1–7)	2.34 (2.21)	2.36 (2.28)	2.37	2.31 (2.22)
h(2–1)	2.21 (2.28)	2.16 (2.19)	2.27	2.28 (2.19)
h(2–3)	1.58 (1.61)	1.60 (1.61)	1.57	1.55 (1.66)
h(2–8)	2.34 (2.21)	2.36 (2.28)	2.28	2.31 (2.22)
h(6–1)	1.88 (1.80)	1.91 (1.94)	1.85	1.55 (1.66)
h(6–5)	1.91 (2.00)	1.91 (1.94)	1.92	2.28 (2.19)

	8	**9**	**10**	**11**
h(1–2)	2.33	2.30	2.35	2.45
h(1–6)	1.55	1.51	1.54	1.54
h(1–7)	2.26	2.25	2.27	2.17
h(2–1)	2.33	2.30	2.42	2.45
h(2–3)	1.55	1.51	1.56	1.54
h(2–8)	2.26	2.25	2.17	2.17
h(6–1)	1.91	1.94	1.87	1.54
h(6–5)	1.91	1.94	1.92	2.45

	12	**13**	**14**	**15**
h(1–2)	2.44	2.15	2.35	3.01
h(1–6)	1.40	1.51	1.54	1.33
h(1–7)	2.43	2.53	2.27	2.12
h(2–1)	2.44	2.15	2.82	3.01
h(2–3)	1.40	1.51	1.37	1.33
h(2–8)	2.43	2.53	2.19	2.12
h(6–1)	1.80	1.93	1.69	1.33
h(6–5)	2.04	1.93	2.17	2.12

[a] Values listed (SCF/3-21G) are the exponents λ of the sp^{λ} hybrids. Hybrid *h*(A–B) is centered on A, directed toward B. For comparison, $\lambda = 1.88$ in benzene. Values in parentheses are taken from ref 12 and converted from %s-character to sp^{λ} hybridization using $\lambda = (\%s)^{-1} - 1$. For numbering scheme, see Chart I.

(Chart I) is surprisingly small. Several of the unsubstituted parent compounds are known,[20–25] but crystallogrphic data are available only for **4** and **5**.[26] Comparison of these data with the ab initio optimized structures of **4** and **5** (Table I) reveals good agreement. In the 3-21G calculated geometries, C–C bond lengths within the six-membered rings are slightly shorter by an average of 0.009 and 0.011 Å for **4** and **5**, respectively. The discrepancy is somewhat larger in the cyclobutene substructures (C–C bond lengths longer by an average of 0.021 Å in **4** and 0.020 Å in **5**), a region where highly extended basis sets are necessary to account for the "strained" electron distribution.[27,28]

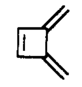
The effect of fusion to four-membered rings is apparent in the structural variation of the benzene frame (Table I). Generally, the common bond (C1–C2) is elongated, whereas the adjacent benzenoid bond (C1–C6) is contracted with respect to unsubstituted benzene. Hence, the quantity ΔR,

$$\Delta R = d(1-2) - d(1-6) \qquad (3)$$

defined as the difference between these two bond lengths, is a useful measure of the degree of bond alternation and is considered throughout the following discussion.

The geometry of the benzene nucleus along the series **4**–**7** is only weakly perturbed by four-membered ring fusion. Thus, ΔR increases from 0.004 Å in **4** to only 0.047 Å in **7**, a finding that implies a weak, but non-negligible Mills–Nixon effect, consistent with previous analyses.[5b,9b,12,26a] This interpretation is further corroborated in the hybridizations of the benzenoid carbons (Table II). It is evident from the hybrids at the center of annelation in **4**–**7** that small ring fusion leads to some redistribution of p-character along the carbon–carbon bonds, the longer bonds showing higher percentage p-character than the shorter ones [cf. $h(1\text{–}2) = sp^{2.21}$ with $h(1\text{–}6) = sp^{1.58}$ in **4**]. However, the unsubstituted carbons in **4**–**6** use hybrids [*h*(6–1) and *h*(6–5) ranging from $sp^{1.85}$ to $sp^{1.92}$] essentially identical to those of benzene ($sp^{1.88}$), suggesting that the amount of ring strain transmitted along the σ-framework is negligible. The usefulness of the hybridization concept in explaining the geometrical changes associated with fusion of cyclobutene to the benzene nucleus has recently been demonstrated by Maksič et al.[12] Comparison of the carbon hybrids derived from the maximum overlap method[12] with those obtained from NBO analysis reveals excellent agreement between these two inherently different approaches and allows correlation of molecular properties with computed hybridizations with a reasonable degree of certainty.[29]

The benzene isomer 3,4-dimethylenecyclobutene (**16**)[30] has attracted a great deal of attention due to its intriguing electronic properties that have been borne out by both theory and experiment.[31] Based on HMO resonance energies, this compound was classified to be antiaromatic,[31a] opening the opportunity to juxtapose aromatic and antiaromatic substructures within one molecular framework by fusing **16** to benzene. This design found its realization in the synthesis of **8** by Cava and Mitchell,[24] but high reactivity prevented rigorous structural characterization and presumably discouraged attempts to synthesize the higher homologs **9**, **10**, and **11**. Comparison of the calculated geometries of **8**–**11** with those of **4**–**7** (Table I) reveals that the effect of annelating dimethylenecyclobutene is similarly small. Thus, ΔR increases from 0.028 Å in **8** to only 0.065 Å in **11**, a trend not significantly different from that found in the benzocyclobutene series. One possible explanation for the slightly higher degree of bond alternation along the series **8**–**11** relies on the greater extent of rehybridization at the centers of annelation than found in **4**–**7**. The bond connecting the two ortho substituents [*d*(7–8)] is somewhat shorter in the dimethylenecyclobuteno-fused series [cf. $d(7\text{–}8) = 1.600$ Å in **4** and $d(7\text{–}8) = 1.530$ Å in **8**], resulting in increased ring strain imposed on the benzene frame. This strain in turn manifests itself in greater rehybridization at the carbon centers, as is evident from inspection of Table II. Hence, to



16

---

(20) **4**: Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2225.

(21) **5**: (a) Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1960**, *82*, 2524. (b) Thummel, R. P.; Nutakul, W. *J. Org. Chem.* **1977**, *42*, 300. (c) Gray, R.; Harruf, L. G.; Krymowski, J.; Peterson, J.; Boekelheide, V. *J. Am. Chem. Soc.* **1978**, *100*, 2892. (d) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 4608.

(22) **6**: (a) Thummel, R. P. *J. Am. Chem. Soc.* **1976**, *98*, 628. (b) Giovannini, E.; Vuilleumier, H. *Helv. Chim. Acta* **1978**, *60*, 1452.

(23) **7**: (a) Nutakul, W.; Thummel, R. P.; Taggart, A. D. *J. Am. Chem. Soc.* **1979**, *101*, 770. (b) Doecke, C. W.; Garratt, P. J.; Shahriari-Zavereh, H.; Zahler, R. *J. Org. Chem.* **1984**, *49*, 1412.

(24) **8**: Cava, M. P.; Mitchell, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 2080.

(25) **12**: (a) Chapman, O. L.; Chang, C. C.; Rosenquist, N. R. *J. Am. Chem. Soc.* **1976**, *98*, 261. (b) Koenig, T.; Imre, D.; Hoobler, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 6446. (c) Trahanovsky, W. S.; Fischer, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 4971.

(26) (a) Boese, R.; Bläser, D. *Angew. Chem.* **1988**, *100*, 293; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 304. The X-ray structures of some derivatives are known. **7**: (b) Cobbledick, R. E.; Einstein, F. W. B. *Acta Crystallogr., Sect. B* **1976**, *32*, 1908. (c) Thummel, R. P.; Korp, J. D.; Bernal, I.; Harlow, R. L.; Soulen, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 6916. **12**: (d) Winter, W.; Straub, H. *Angew. Chem.* **1978**, *90*, 142; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 127. (e) Tsukada, H.; Shimanouchi, H.; Sasada, Y. *Acta Crystallogr., Sect. B* **1977**, *33*, 2951. (f) Tsukada, H.; Shimanouchi, H.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 985.

(27) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(28) Geometry optimizations of **4** and **5** employing the 6-31G* basis set show that *d*-type polarization functions on the second-row elements alone do not suffice to improve on the congruity between experimental and theoretical data. We note, however, that Maksič et al.[12] found good agreement using the smaller 6-31G basis set without polarization functions.

(29) For recent applications of the hybridization model, see: Maksič, Z. B.; Orville-Thomas, W. J. *J. Mol. Struct.* (*THEOCHEM*) **1988**, *169*, 1–568.

(30) (a) Huntsman, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1963**, *85*, 3308. (b) Huntsman, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 342.

(31) (a) Hess, B. A., Jr.; Schaad, L. J. *Aust. J. Chem.* **1972**, *25*, 2213 and references therein. (b) Leibovici, C. *J. Mol. Struct.* **1972**, *12*, 343. (c) Kent, J. E.; Harman, P. J.; O'Dwyer, M. F. *J. Phys. Chem.* **1981**, *85*, 2726. (d) Brown, R. D.; Godfrey, P. D.; Hart, B. T.; Ottrey, A. L.; Onda, M.; Woodruff, M. *Aust. J. Chem.* **1983**, *36*, 639.

maximize overlap with neighboring carbons, the annelated centers of dimethylenecyclobuteno-fused benzenes consistently use hybrids of higher percentage p-character along C1–C2 and of higher percentage s-character along C1–C6 relative to the hybrids of **4**–**7**. An alternative explanation for the enhanced bond alternation in **8**–**11** is based on antiaromatic interactions across the four-membered rings, a possibility that will be further explored below. However, analysis of the geometries of **8**–**11** suggests that the dimethylenecyclobutene moiety **16** possesses only weak antiaromatic character.

The small incremental increase of ring strain resulting from stepwise dimethylenecyclobutene fusion along the series **8**–**11** is reflected in the changes of hybridization. Thus, the hybrid of center 1 directed along the site of annelation [$h(1-2)$] ranges from $sp^{2.33}$ in **8** to $sp^{2.45}$ in **11**, whereas a hybrid of nearly fixed $sp^{1.54}$ character is used to form the shorter benzenoid bond C1–C6. Again, the unsubstituted carbons in **8**–**10** remain largely unaffected by annelation [cf. $h(6-1)$ and $h(6-5)$], indicating that fusion of up to two dimethylenecyclobutene units does not cause serious distortions of the σ-skeleton.

A completely different picture arises when benzene is fused to cyclobutadiene, the antiaromatic species par excellence. Here, bond alternation is already evident with annelation of the first ring (ΔR = 0.087 Å in **12**) and reaches a maximum in tris(cyclobutadieno)benene (ΔR = 0.215 Å in **15**) with benzenoid bond lengths of 1.524 and 1.309 Å, respectively. Although it is tempting to attribute the cyclohexatrienoid geometry entirely to interactions between the ethylenic part of the molecule and the π-system of the six-membered ring, one should also recognize that the dramatically short cyclobutadiene bond C7–C8 [$d(7-8)$ = 1.337 Å in **12**] severely perturbs the σ-framework. Shortening of $d(7-8)$ induces a compression of bond angle C2–C1–C7 (88.4° in **12** as opposed to 94.0° in **4**) resulting in increased rehybridization at the centers of annelation. Accordingly, fusion of one cyclobutadiene moiety causes redistribution of p-character from $sp^{1.88}$ in unsubstituted benzene to $sp^{2.44}$ [$h(1-2)$] and $sp^{1.40}$ [$h(1-6)$] in **12**. The extent of rehybridization is even greater in angularly fused **14** ($sp^{2.82}$ and $sp^{1.37}$ at center 2) and reaches extreme values of $sp^{3.01}$ and $sp^{1.23}$ in trisannelated **15**. In contrast to the cyclobuteno- and dimethylenecyclobuteno-fused series, the effect of ring strain is also apparent in the hybrids of unsubstituted carbon centers. Thus, $h(6-1)$ and $h(6-5)$ in **12** ($sp^{1.80}$ and $sp^{2.04}$, respectively) show an appreciable deviation from the carbon hybrids in benzene, the strain-induced rehybridization being even more pronounced in **14** [$h(6-1) = sp^{1.69}$, $h(6-5) = sp^{2.17}$]. In linearly fused **13**, on the other hand, the symmetry equivalent bonds C1–C6 and C5–C6 are equally strained, leading to hybrids ($sp^{1.93}$) at center 6 that are only marginally different from those of benzene. Note that NBO analysis of rehybridization effects in annelated benzenes is in full accord with, and thereby provides, a quantum mechanical basis for earlier hybridization models.[11]

Comparison of the calculated geometries of **12**, **14**, and **15** with those of **1**,[6a] **2**,[7a] and **3**[7b] clearly shows less pronounced bond alternation in the latter series of molecules as one might anticipate in light of the different extents to which σ- and π-effects are operational. In the cyclobutadieno-fused systems, bonds between carbons 7 and 8 (Table I) are significantly shorter than the analogous bonds in **1**–**3** (cf. 1.426 Å in **1**, 1.413 Å in **2**, and ca. 1.405 Å in **3**), resulting in reduced strain imposed on the central ring of the phenylenes. In addition, antiaromatic interactions are largely attenuated by strong delocalization in the terminal benzene rings (vide infra). It is clear on the other hand that dimethylenecyclobuteno-fused benzenes (**8**, **10**, and **11**) do not serve as good model compounds for **1**–**3**, the former systems showing nearly unperturbed benzene nuclei.

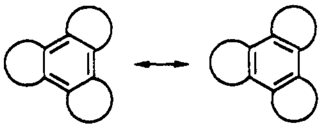
In a recent contribution to this journal,[9b] Stanger attributed the remarkable difference of bond alternation in **7** and **15** in part to the increased "flexibility" of sp^3-hybridized substituent carbons of the former, which enables the system to effectively evade angular strain inherent in the four-membered rings by forming bent bonds to the benzene nucleus. This conclusion, intuitively appealing because of the more diffuse electronic distribution around sp^3-carbons, cannot be substantiated by the present quantum mechanical calculations. Inspection of the bonding properties of the trisannelated benzenes reveals nearly identical degrees of bond bending [compare, for example, the deviation of $h(1-7)$ from the internuclear axis: **7**, 19.4°; **11**, 19.4°; **15**, 21.5°],[32] clearly independent of the extent of bond alternation. Furthermore, Stanger tacitly implies that all benzenes annelated by sp^2-carbons should exhibit pronounced bond alternation, a conclusion obviously at odds with the calculated geometry of **11**. Instead, our analysis suggests that the C–C bond length of the four-membered ring [$d(7-8)$] is largely responsible for rehybridization at the center of annelation and thereby may contribute importantly to the degree of bond alternation in the benzene nucleus, particularly in cyclobutadieno-fused **15**. In addition to these strain arguments, **15** has to accommodate π-electronic effects that should reinforce the cyclohexatrienoid structure in accord with the original Mills–Nixon postulate. Both of these contributions are significantly diminished in **7**, leading to nearly equal C–C bond lengths in the six-membered ring. The importance of π-delocalization for the benzene geometry of **15** will be addressed below.

Table III. NRT Analysis of Annelated Benzenes[a]

	4	**6**	**7**
w_A	51.1	53.5	56.5
w_B	46.2	44.3	43.3
w_A/w_B	1.1	1.2	1.3
	8	**10**	**11**
w_A	47.3	44.4	43.2
w_B	42.4	35.1	29.0
w_A/w_B	1.1	1.3	1.5
	12	**14**	**15**
w_A	59.5	71.3	64.5
w_B	22.3	11.6	4.4
w_A/w_B	2.7	6.1	14.7

[a] Values given are percentage weights w_A and w_B for the dominant resonance forms A and B (see text). Dipolar structures account for the residual resonance weights.

Natural Resonance Theory (NRT). In order to evaluate resonance contributions to the wave functions of the various benzocyclobutenes, we employed the natural resonance theory (NRT)[18] formalism, which is based on the NBO method. In this discussion we restrict our attention to the two dominant Kekulé forms A and B in the annelated benzenes with C_{2v} and D_{3h} symmetries (Table III). Compounds **5**, **9**, and **13** are of D_{2h} symmetry for which the two resonance structures are identical.



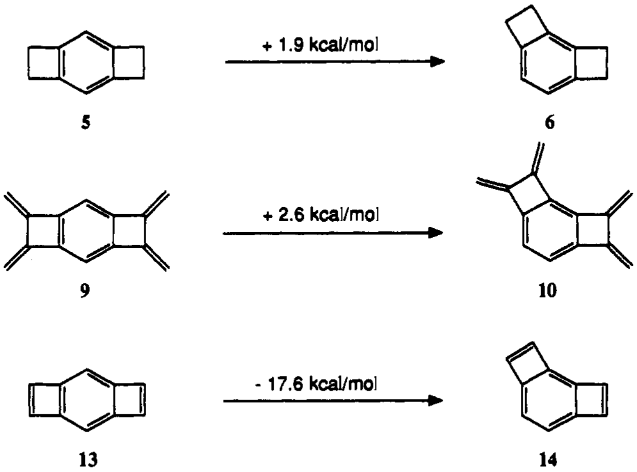
From the data presented, it is apparent that the π-electronic distribution generally favors structure A with double bonds adjacent to the sites of annelation, thus supporting the original prediction made by Mills and Nixon. This preference, however, is rather small in **4**, **6**–**8**, **10**, and **11** with the ratio of the weights of resonance forms A and B barely exceeding unity. Introducing antiaromatic cyclobutadienoid substructures into the atomic assembly, such as in **12**, **14**, and **15**, suppresses the resonance contribution of B, the ratios ranging from 2.7 in the monoannelated case to a dramatic 14.7 in trisannelated **15**. Obviously, the relative resonance weights of the two Kekulé forms reflect the degree of

---

[32] Similarly, the computed electronic centroids of the C1–C7 NBOs show deviations from the internuclear axis of 9.4° (**7**), 10.6° (**11**), and 11.6° (**15**). This analysis finds further support from an evaluation of the location of bond critical points[33] in the electron density distribution. The values obtained are 2.5° (**7**), 2.7° (**11**), and 3.1° (**15**).

[33] (a) Bader, R. F. W. *Acc. Chem. Res.* **1985**, *18*, 9. (b) Bader, R. F. W. *Atoms in Molecules – A Quantum Theory*; Clarendon: Oxford, 1990.

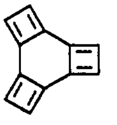
Scheme I. Energy Difference between Linear and Angular Isomers of Bisannelated Benzenes[a]



[a] Energies are calculated from data given in Table I (1 hartree = 627.5 kcal/mol).

alternation in these molecules, although it has been noted that the relationship between bond length and order can be misleading if strained ring systems are involved.[4e,34] Further support for the predominance of A in cyclobutadieno-fused benzenes is obtained by comparing the energies of linear and angular isomers of bisannelated benzenes (Scheme I). Whereas angular **6** and **10** are destabilized with respect to their corresponding linear analogs by 1.9 kcal/mol and 2.6 kcal/mol respectively, cyclobutadieno-fused **14** is stabilized by 17.6 kcal/mol relative to its linear isomer.[35] The stabilization of **14** clearly arises from its ability to avoid cyclobutadienoid resonance forms, the slightly higher energy content of **6** and **10** presumably arising from increased ring strain caused by angular fusion.

It is noteworthy that NRT analysis of the cyclobutadieno-fused benzenes shows no evidence for contribution of resonance forms with a radialenic arrangement of double bonds as depicted in **17**,



17

lending support to conclusions derived from X-ray data of derivatives of **12**.[26d-f] The ease with which metal fragments such as CpCo and $Fe(CO)_3$ coordinate in an η^4-fashion to the cyclobutadiene moiety of **12** and **13**[36] therefore seems to derive from a π-electronic distribution in accord with resonance structure B.

Delocalization and Hyperconjugation in Trisannelated Benzenes. The above discussion of geometries and hybridizations developed the concept that the σ-skeleton of the benzene frame responds to imposed strain in a bond-alternating fashion. In addition to such σ-effects, four-membered ring fusion to the benzene nucleus also gives rise to hyperconjugative (**4–7**) and conjugative (**8–15**) interactions. The presence of hyperconjugation between the benzenoid π-system and methylene group orbitals[37] of appropriate symmetry (π_{CH}, π^*_{CH}) has been established by photoelectron spectroscopy.[38] Similarly, in dimethylenecyclobuteno- and cyclobutadieno-fused benzenes, resonance form B is susceptible to antiaromatic interactions within the four-membered ring, thereby favoring the double bond arrangement of A. It thus appears that hyperconjugation, π-delocalization, and σ-effects do have an important influence on bond alternation in the benzene nucleus, but quantification of each of these contributions remains speculative. The NBO method lends itself to an assessment of such conjugative effects by geometry reoptimization with suppression of selected interactions. Because we are mainly concerned with the perturbation of the benzene nucleus by external groups, we delete all π-type interactions between these groups and the benzenoid substructure, while maintaining "aromatic" π-delocalization in the latter. For reasons of computational economy and because bond alternation is most pronounced in trisannelated benzenes, we focus our attention on **7**, **11**, and **15** (Table IV).

Table IV. Bond Lengths of Trisannelated Benzenes Reoptimized with Selected NBO Deletions[a]

	7	**11**	**15**
NBO deletion[b]	π_{CH}–π^*; π–π^*_{CH}	π–π^*	π–π^*
d(1–2)	1.381 (–0.027)	1.377 (–0.047)	1.448 (–0.076)
d(1–6)	1.380 (+0.019)	1.385 (+0.026)	1.329 (+0.020)
d(1–7)	1.590 (+0.052)	1.570 (+0.072)	1.627 (+0.124)
d(7–8)	1.595 (–0.003)	1.514 (–0.017)	1.319 (–0.022)
d(7–9)		1.309 (0.0)	
d(7–H)	1.077 (–0.004)		1.066 (0.0)
ΔR	0.001 (–0.046)	0.007 (–0.058)	0.119 (–0.096)

[a] SCF/3-21G values in angstroms. Bond length changes (with respect to the fully optimized structures of Table I) are listed in parentheses. For numbering scheme, see Chart I. [b] For details regarding the type of deletion, see text.

Geometry reoptimization with deletion of pertinent π-type interactions between the cyclobutene and the benzene moieties generally results in significantly reduced bond alternation in the six-membered ring. In the absence of π_{CH}–π^*_{CC} and π_{CC}–π^*_{CH} interactions between the methylene groups and the benzene frame, **7** reoptimizes to a structure with essentially equal benzenoid carbon bond lengths, indicating that bond alternation in delocalized **7** is caused by hyperconjugation rather than angular strain. Likewise, when **11** is reoptimized with deletion of π-delocalization between the exocyclic double bonds (i.e., C7–C9) and those of the benzene frame, ΔR diminishes from 0.065 Å in the fully delocalized system to only 0.007 Å, demonstrating that π–π^* interaction is responsible for bond alternation in **11**. The residual ΔR (after reoptimization) is only marginally larger than that of **7**, suggesting that the increase of ring strain, going from cyclobuteno-fused benzenes to the dimethylene annelated series, is minimal.

The importance of antiaromatic interactions in cyclobutadieno-fused **15** becomes apparent when π–π^* conjugation between the ethylenic double bonds and the central ring is deleted. In this case, reoptimization leads to a ΔR of 0.119 Å that is greatly diminished from that of the fully delocalized system (ΔR = 0.215 Å). Therefore, the π-delocalization of **15** (or its propensity to minimize antiaromaticity) contributes roughly half (56%) of the calculated bond alternation, the remainder being attributable to strain (rehybridization) effects.

In conclusion, NBO analysis of annelated benzenes reveals that perturbations of the σ-frame (i.e., strain effects) are less severe than usually anticipated. The main sources of benzenoid bond

---

(34) (a) Carstensen-Oeser, E.; Müller, B.; Dürr, H. *Angew. Chem.* **1972**, *84*, 434; *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 422. (b) Billups, W. E.; Char, W. Y.; Leavell, K. H.; Lewis, E. S.; Margrave, J. L.; Sass, R. L.; Shieh, J. J.; Werress, P. G.; Wood, J. L. *J. Am. Chem. Soc.* **1973**, *95*, 7878.

(35) Surprisingly, the most simple derivative of benzodicyclobutadiene known is linearly fused: (a) Toda, F.; Ohi, M. *J. Chem. Soc., Chem. Commun.* **1975**, 506. (b) Toda, F.; Takahma, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2515.

(36) (a) Davis, R. E.; Pettit, R. *J. Am. Chem. Soc.* **1970**, *92*, 716. (b) Duclos, R. I.; Vollhardt, K. P. C.; Yee, L. S. *J. Organomet. Chem.* **1979**, *174*, 109. (c) Straub, H.; Doering, G.; Winter, W. *Z. Naturforsch., B* **1979**, *34*, 125. (d) Winter, W.; Butters, T. *Acta Crystallogr., Sect. B* **1981**, *37*, 1528. (e) Butters, T.; Winter, W.; Toda, F. *Acta Crystallogr., Sect. B* **1981**, *37*, 1532. (f) Moreto, J.; Maruya, K.; Bailey, P. M.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1982**, 1341.

(37) For the construction of group orbitals see: (a) Jorgensen, W. L.; Salem, L. *The Organic Chemist's Book of Orbitals*; Academic: New York, 1973. (b) Clark, T. *A Handbook of Computational Chemistry*; Wiley: New York, 1985; pp 121–139.

(38) (a) Brogli, F.; Giovannini, E.; Heilbronner, E.; Schurter, R. *Chem. Ber.* **1973**, *106*, 961. (b) Santiago, C.; Gandour, R. W.; Houk, K. N.; Nutakul, W.; Cravey, W. E.; Thummel, R. P. *J. Am. Chem. Soc.* **1978**, *100*, 3730. (c) Heilbronner, E.; Kovač, B.; Nutakul, W.; Taggart, A. D.; Thummel, R. P. *J. Org. Chem.* **1981**, *46*, 5279.

alternation appear to be hyperconjugation and π-delocalization within the fused ring systems, although strain-induced changes in the hybridization are important in determining the geometry of highly strained **15**.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. 87-21134) and the Director, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy (Contract DE-AC 03-76SF00098). Portions of this investigation were completed at the San Diego Supercomputer Center and at the College of Chemistry Graphics Facility at the University of California at Berkeley (funded in part by the National Institutes of Health, Grant No. 8S0RR05651A). R.F. is a recipient of a Kekulé fellowship provided by the Fonds der chemischen Industrie, Germany (1989–1992).

Registry No. 4, 694-87-1; **5**, 1610-51-1; **6**, 58436-35-4; **7**, 60323-52-6; **8**, 20265-84-3; **9**, 93716-74-6; **10**, 93716-73-5; **11**, 143330-04-5; **12**, 4026-23-7; **13**, 24447-42-5; **14**, 61960-82-5; **15**, 69038-28-4.

The Effect of Basis Set and Electron Correlation on the Predicted Electrostatic Interactions of Peptides

Sarah L. Price,*[†] Jamie S. Andrews,[‡] Christopher W. Murray,[‡] and Roger D. Amos[‡]

Contribution from the Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK, and University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. *Received April 6, 1992*

Abstract: The realism of molecular modelling studies of peptides depends on the model of the electrostatic forces, and thus on the quality of the wave function used to derive the atomic charges or multipoles. To establish this dependence, we have studied the electrostatic properties of *N*-acetylalanine *N'*-methylamide ($CH_3CONHCHCH_3CONHCH_3$) calculated from a distributed multipole representation of both SCF and correlated wave functions with a range of respectable basis sets. The electron correlation is included in the wave function at second-order Møller–Plesset theory using a "direct" method which calculates the relaxed electron density. To predict the electrostatic potential on the water-accessible surface of the peptide to within a few kJ mol^{-1} requires a correlated wave function and a large basis set of double-zeta plus polarization quality or better. For a given basis set, the SCF wave function overestimates the electrostatic potential by around 15%, the inclusion of electron correlation producing a consistent change in the electron density. Changing the basis set, within a given ab initio method, also produces significant differences in the electrostatic potential around the peptide and in its electrostatic interaction with water. However, it is observed that the electrostatic potential for this peptide correlates strongly with the total dipole moment of the charge density, as the direction of the dipole moment is almost independent of basis set within each ab initio method. Upon correlating the wave function there is a small, almost constant, change in the direction of the dipole moment of 3.5° ± 0.1°. Thus, the electrostatic potential calculated from smaller (split valence) basis sets can be scaled to give good agreement with more accurate calculations.

I. Introduction

The model for the intermolecular forces is the fundamental input to any computer simulation study of the behavior of molecules, and so it is important that the model potentials used are sufficiently accurate for the simulation to be realistic. The search for more reliable model potentials for biologically important molecules, such as polypeptides, has recently focused on the model for the electrostatic interactions, as the contribution which appears to control "molecular recognition", including hydrogen bonding, provided steric constraints are satisfied. Early force fields represented the electrostatic interaction by empirically fitted atomic point charges;[1] however, since this requires Draconian assumptions about the nature of the charge distribution, such charge models have widely been superseded by models derived from the ab initio charge densities of the molecules.

The electrostatic interaction energy in terms of the charge distribution, $\rho^A(\mathbf{r}_i)$, of molecule A and, $\rho^B(\mathbf{r}_j)$, of molecule B is given by:

$$U_{el}^{AB} = \int \frac{\rho^A(\mathbf{r}_i)\rho^B(\mathbf{r}_j)\,d^3\mathbf{r}_i\,d^3\mathbf{r}_j}{4\pi\epsilon_0|\mathbf{R} + \mathbf{r}_j - \mathbf{r}_i|} \qquad (1)$$

where **A** and **B** are arbitrary chosen origins in the molecules and $\mathbf{R} = \mathbf{B} - \mathbf{A}$. This is costly to evaluate so a simplified representation of the charge density is usually defined which is suitable for use in computer simulations. The Mulliken atomic charges[2] were used widely and, indeed, are still used in some commercial modelling packages, but it has often been reported that these give a poor approximation to the electrostatic potential.[3-6] Many alternatives have been proposed. There is considerable interest in the method of potential derived charges,[3,7] where the atomic charges are fitted directly to the electrostatic potential, as evaluated by integration, at a large grid of points in the region of interest outside the molecule. This will clearly give the most accurate representation of the potential in the grid region which is possible with the atomic charges. However, the residual errors in this fitting process emphasize that an atomic point charge model cannot exactly represent the electrostatic forces between molecules, because it explicitly assumes that the charge distribution around each atomic site is spherical. However, the valence electrons of a molecule are often far from spherically distributed, with features such as lone pair and π electron density being invoked to describe chemical bonding and the orientation dependence of hydrogen bonding. Thus another approach to representing the molecular charge distribution is to represent it in terms of sets of multipoles (charge, dipole,

---

[†] University College London.

[‡] University Chemical Laboratory.

(1) Hagler, A. T.; Huler, E.; Lifson, S. *J. Am. Chem. Soc.* **1974**, *96*, 5319.

(2) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

(3) Momany, F. A. *J. Phys. Chem.* **1978**, *82*, 592.

(4) Cox, S. R.; Williams, D. E. *J. Comput. Chem.* **1981**, *2*, 304.

(5) Price, S. L.; Harrison, R. J.; Guest, M. F. *J. Comput. Chem.* **1989**, *10*, 552.

(6) Price, S. L., Richards, N. G. J. *J. Comp. Aid. Molec. Design.* **1991**, *5*, 41.

(7) Singh, U. C.; Kollman, P. A. *J. Comput. Chem.* **1984**, *5*, 129.

0002-7863/92/1514-8268$03.00/0 © 1992 American Chemical Society