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Halogen bonding: the σ-hole

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Abstract Halogen bonding refers to the non-covalent interactions of halogen atoms X in some molecules, RX, with negative sites on others. It can be explained by the presence of a region of positive electrostatic potential, the σ-hole, on the outermost portion of the halogen's surface, centered on the R–X axis. We have carried out a natural bond order B3LYP analysis of the molecules CF_3X, with X = F, Cl, Br and I. It shows that the Cl, Br and I atoms in these molecules closely approximate the $s^2 p_x^2 p_y^2 p_z^1$ configuration, where the z-axis is along the R–X bond. The three unshared pairs of electrons produce a belt of negative electrostatic potential around the central part of X, leaving the outermost region positive, the σ-hole. This is not found in the case of fluorine, for which the combination of its high electronegativity plus significant sp-hybridization causes an influx of electronic charge that neutralizes the σ-hole. These factors become progressively less important in proceeding to Cl, Br and I, and their effects are also counteracted by the presence of electron-withdrawing substituents in the remainder of the molecule. Thus a σ-hole is observed for the Cl in CF_3Cl, but not in CH_3Cl.

Keywords Halogen bonding · Sigma-hole ·
Electrostatic potential · DFT

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Introduction

The term "halogen bonding" is usually taken to mean the non-covalent interaction of a halogen atom X in one molecule with a negative site, such as the lone pair electrons of a Lewis base, in another. X can be chlorine, bromine or iodine, but not (to our knowledge) fluorine, and halogen bonding does not necessarily always occur for the other halogens, particularly chlorine. X can be part of a dihalogen, e.g. Br_2, or it may be a substituent on some other molecule, often organic. Thus, halogen bonding can be depicted as

$$R - X - - - : B$$
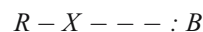
where :B is the Lewis base. The R–X–B angle is typically close to 180°. The strength of the interaction increases in going from chlorine to bromine to iodine.

The preceding description summarizes the findings of considerable experimental work, including solution studies [1–3] and analyses of crystallographic structural data [4–6]. Analogies between halogen and hydrogen bonding have long been recognized, [7, 8] and Sandorfy et al. have shown via infrared spectra that the former can compete and interfere with the latter [9–12].

It is increasingly recognized that halogen bonding occurs in various biological systems and processes [13, 14], and can be utilized effectively in drug design. Another area of application is crystal engineering; [14] co-crystals can be produced that have specific desired features of structure and composition, leading to, for example, non-linear optical activity and enhanced conducting properties.

Electrostatic potentials and halogen bonding

A seemingly puzzling aspect of halogen bonding is that halogen atoms are themselves usually viewed as having partial negative charges. Why then would they interact non-covalently with a negative portion of another molecule?

It was demonstrated some time ago [15, 16], and again more recently [13, 17], that this can be explained in terms of the electrostatic potentials $V_S(r)$ on the halogens' surfaces. The electrostatic potential at any point in the space of a molecule is given by

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|} \quad (1)$$

In Eq. 1, Z_A is the charge on nucleus A, located at R_A, and $\rho(r)$ is the molecule's electronic density. $V(r)$ is a physical observable, which can be determined experimentally by diffraction techniques [18, 19], as well as computationally. In analyzing non-covalent interactions, we have found it effective to calculate $V(r)$ on the molecular surface, which we take to be the 0.001 electrons Bohr^{-3} contour of $\rho(r)$, as proposed by Bader et al. [20]; this surface potential is designated $V_S(r)$.

The electrostatic potential of any ground-state spherically symmetric atom is positive everywhere [21, 22]; the effect of the nucleus dominates over that of the dispersed electrons. It is when atoms combine to form a molecule that the accompanying rearrangements of electronic charge normally produce one or more regions of negative $V(r)$. These are often associated with the more electronegative atoms, and with the π regions of unsaturated hydrocarbons [22].

Figure 1 shows $V_S(r)$ for CF$_4$. As anticipated, the fluorine hemispheres are negative. However when a chlorine is substituted, Fig. 2, a positive potential develops on the outermost portion of its surface, around its intersection with the C–Cl axis. We shall refer to this positive region, which is centered on the C–X axis, as the "σ-hole" in the belt of negative potential that encompasses the chlorine. Analogous results are obtained for CF$_3$Br and CF$_3$I, but the σ-holes on the bromine and the iodine are progressively larger and more positive (Figs. 3 and 4). Note that the color scale is the same throughout this paper. The figures were created with the Molekel program [23, 24].

It is these positive regions that are responsible for the halogen-bonding capabilities of CF$_3$Cl, CF$_3$Br and CF$_3$I, as well as other halogen-bearing molecules. However, the features and even the existence of σ-holes depend very much on the environments of the respective halogen atoms in the molecules. Thus, halogen bonding by CF$_3$Cl, CF$_3$Br and CF$_3$I is greatly enhanced by the three electron-withdrawing fluorines. In their absence, CH$_3$Cl does not even have a σ-hole [13, 15–17], and those on the bromine

Fig. 1 The molecular electrostatic potential, in Hartrees, at the 0.001 electrons Bohr^{-3} isodensity surface of CF$_4$
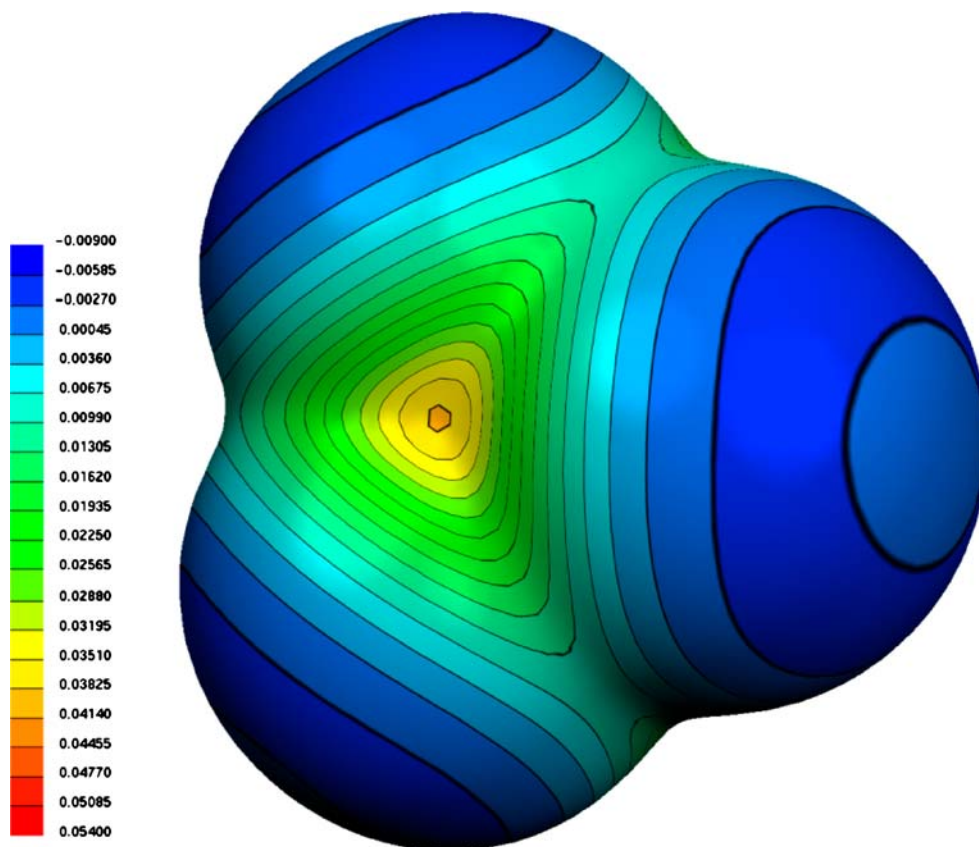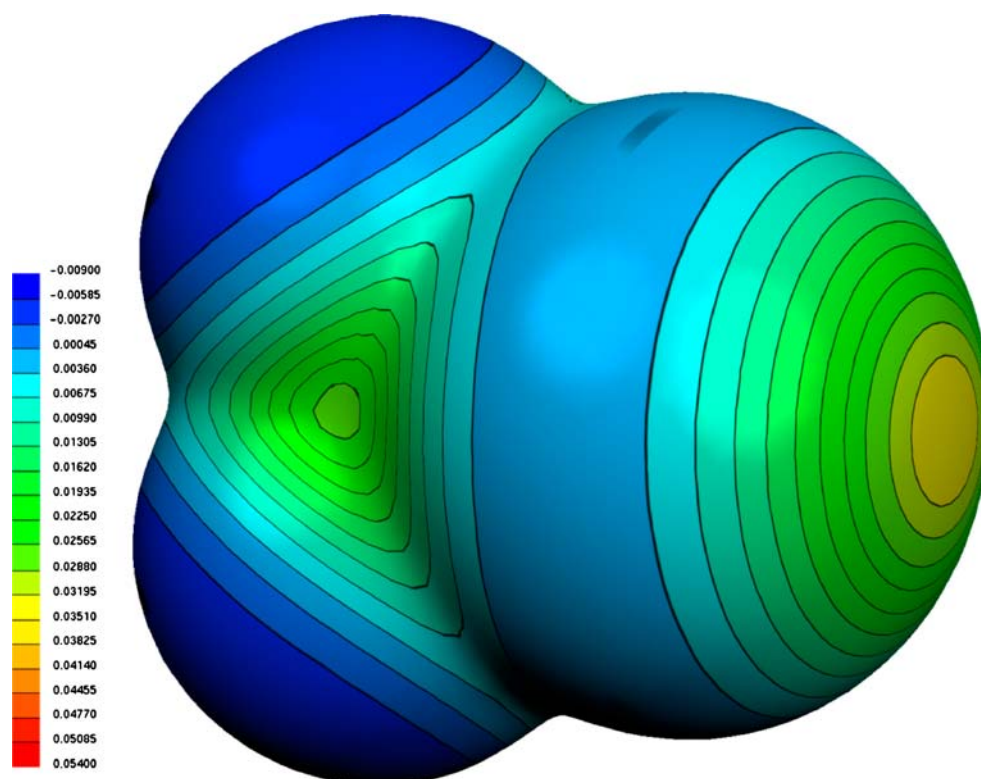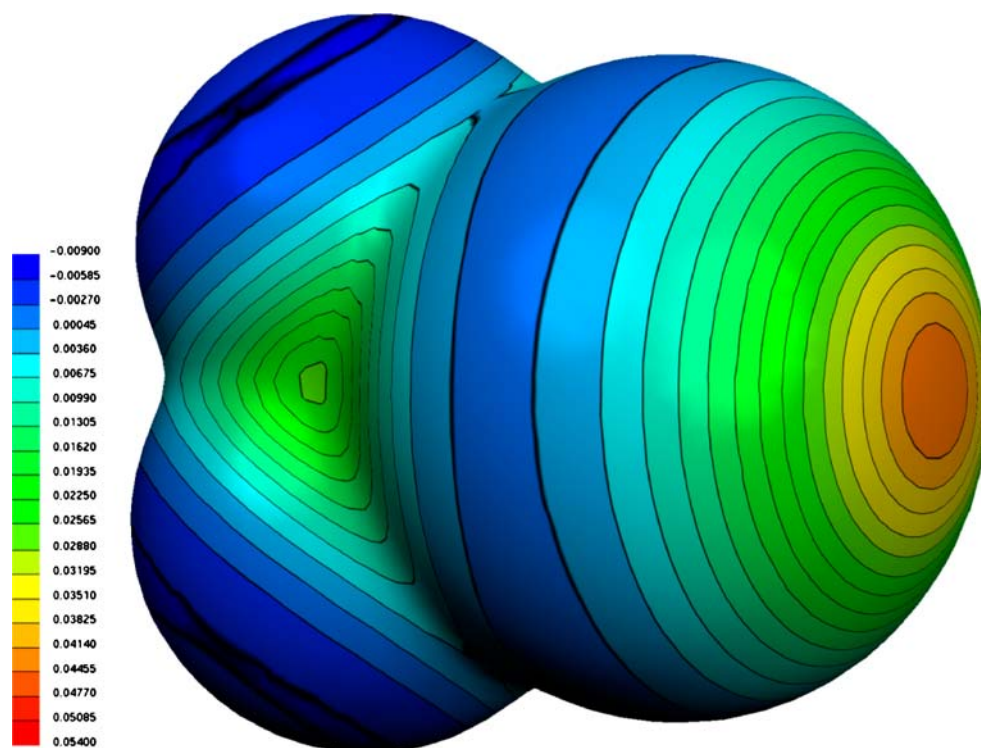
Fig. 2 The molecular electrostatic potential, in Hartrees, at the 0.001 electrons Bohr^{-3} isodensity surface of CF_3Cl

and iodine in CH_3Br and CH_3I are much weaker. For more extensive discussions of these features in various halogenated systems, see Auffinger et al. [13] and Politzer et al. [17] There have also been a number of calculations of the strengths of halogen bonds in various systems, [17, 25–27] which predict interaction energies as high as 8 kcal mol^{-1}.

The σ-Hole

Our objective in this paper is to provide some insight into the origins of the positive σ-holes manifested by some halogen substituents. To this end, we present in Table 1 the results of a natural bond order (NBO) population analysis

Fig. 3 The molecular electrostatic potential, in Hartrees, at the 0.001 electrons Bohr^{-3} isodensity surface of CF_3Br

Fig. 4 The molecular electrostatic potential, in Hartrees, at the 0.001 electrons Bohr^{-3} isodensity surface of CF$_3$I
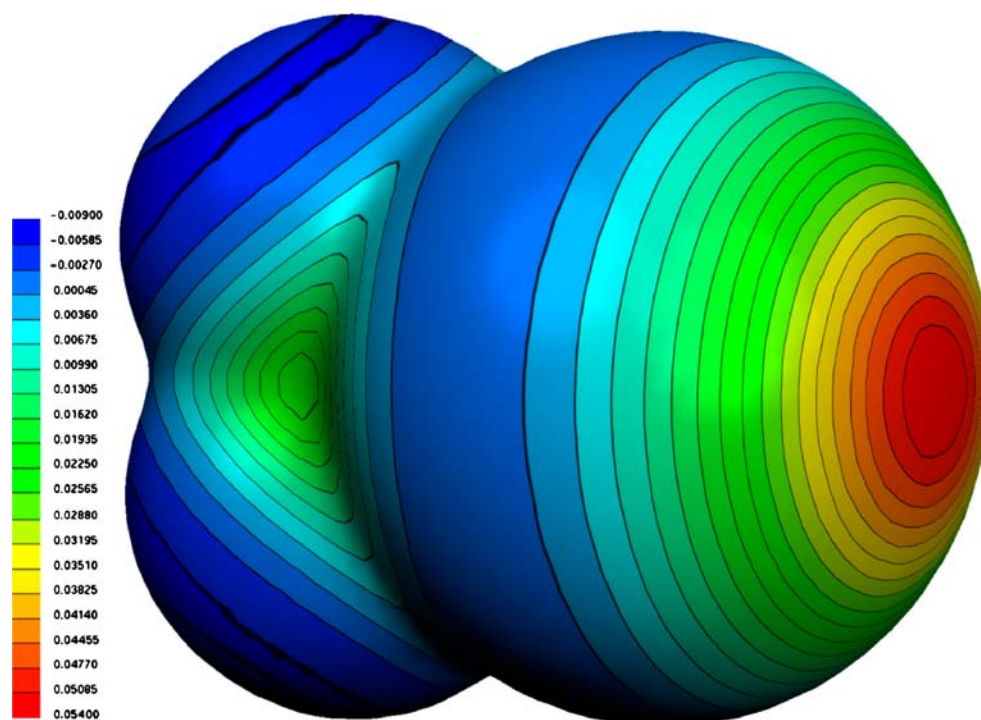
[28] of the electronic configuration of the halogen atom X in each of the molecules CF$_3$X, where X = F, Cl, Br and I. The hybrid B3LYP density functional procedure was used [29, 30], with the 6–311+G(d) basis set [31–41] for CF$_4$, CF$_3$Cl and CF$_3$Br, and DGDZVP [42, 43] for CF$_3$I.

In the molecules CF$_3$X, each atom X is involved in a C–X bonding orbital, σ_{CX}, and also has three unshared pairs of electrons, two of which are in p-orbitals perpendicular to the C–X axis. The third unshared pair is in what is largely an s-orbital, but with some degree of p-hybridization along the C–X axis; Table 1 shows that the extent of this is much greater when X = F (24.9%) than when X is Cl, Br or I (12.0 to 8.4%). The lower level of sp-hybridization for the latter three means that their unshared electron pairs approximate the $s^2 p_x^2 p_y^2$ distribution of a Cl$^+$ ion constrained to have an empty p-orbital. The contribution of each X to the bonding σ_{CX} is primarily a p-orbital, although the situation is again somewhat different when X = F, for which there is 25% s-character (more than double what is found for Cl, Br and I). Also notable is that only for X = F (by far the most electronegative atom) is there a considerable

shifting of the bonding electrons toward X; its share is 71.4%, compared to approximately 50% for Cl, Br and I.

The σ-holes seen in Figs. 2, 3 and 4, and in other molecules [13, 15, 17], simply reflect the fact that the positive $V_S(\mathbf{r})$ that totally encompasses the free, ground-state spherically symmetric atom X has not been countered in that region by an influx of electronic charge. The atom X in these molecules is similar to a single atom X with an $s^2 p_x^2 p_y^2 p_z^1$ electronic configuration (where the C–X bond lies along the z-axis), in which two p-orbitals are filled and one is half-filled. An example is shown in Fig. 5; a σ-hole is clearly visible, surrounded by a belt of negative potential (This is not present in the neutral, spherically symmetric X atom because each of the three p-orbitals then contains, on average, only 5/3 electrons.).

Why is a σ-hole not found when X = F, as well as in some other instances, e.g. CH$_3$Cl [15, 17]? Firstly, the higher electronegativity of fluorine gives it a disproportionately large share of the σ_{CX} bonding electrons, which helps to neutralize the σ-hole. This also applies as chlorine in CH$_3$Cl, which does not have a σ-hole and does not halogen

Table 1 NBO population analyses for CF$_3$X (X = F, Cl, Br, I)

X	NBO charge on X	Halogen population in the σ_{CX}-NBO (%)	Valence populations		σ_{CX} (NBO)		Unshared s-electron pair (NBO)	
			s	p	%s	%p	%s	%p
F	−0.332	71.4	1.86	5.47	25.00	74.57	75.12	24.88
Cl	−0.004	53.1	1.89	5.10	12.06	87.30	88.00	12.00
Br	0.041	49.4	1.91	5.03	8.54	90.88	91.53	8.47
I	0.107	45.7	1.91	4.97	8.56	90.50	91.61	8.38

Fig. 5 The molecular electro-static potential, in Hartrees, at the 0.001 electrons Bohr^{-3} iso-density surface of the Cl atom. The electronic configuration is $s^2 p_x^2 p_y^2 p_z^1$, where a σ-bond could be made in the z-direction
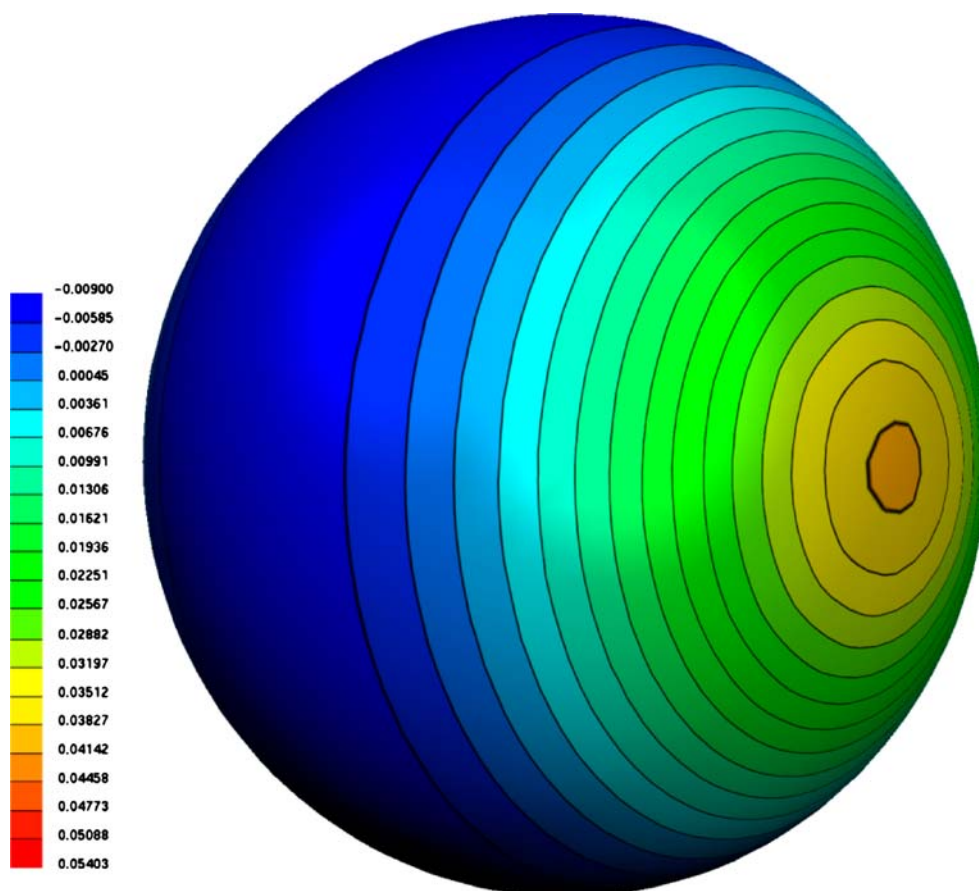

bond [15, 17]. In CF$_3$Cl, on the other hand, the electron-attracting power of the chlorine is overwhelmed by that of the three fluorines. Secondly, a factor that applies only when X = F is the greater degree of sp-hybridization along the C–X axis [44, 45], mentioned above and seen in Table 1. This is further confirmed by Fig. 6, which shows how much less spherical is the s unshared pair in CF$_4$ than in CF$_3$Br. This sp hybridization moves additional, electronic charge into the σ-hole.

Summary

Halogen bonding involves iodine, bromine and sometimes chlorine, typically substituted in molecular environments that are electron-withdrawing. The three pairs of unshared electrons on the halogen atom X form a belt of negative electrostatic potential around its central region, leaving a positive "σ-hole" on the outermost portion of its surface, centered around the R–X axis. This σ-hole can interact favorably with negative sites on other molecules, giving rise to halogen bonding.

If the electron-attracting power of X is greater than that of the remainder of its molecule (R), then the halogen atom may gain enough electronic charge to neutralize the σ-hole.

Fig. 6 The unshared s-electron pair in CF$_4$ (*left*) and CF$_3$Br (*right*). The former has nearly three times as much p-character as the latter (Table 1)
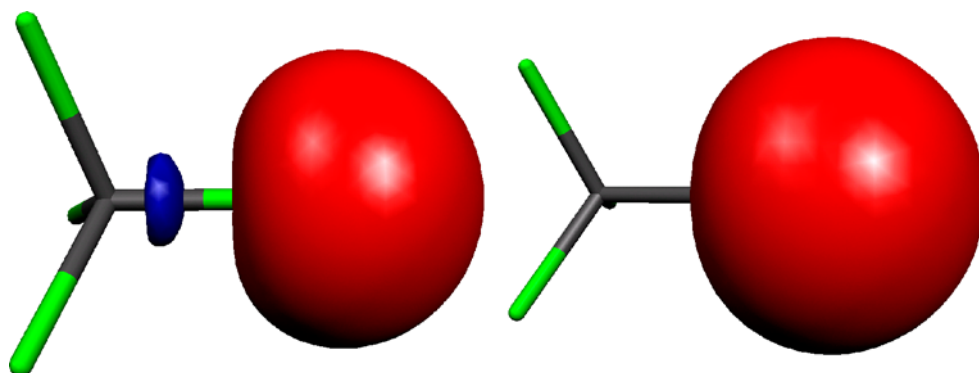
This result is also promoted by *sp*-hybridization of the unshared *s*-valence electrons of X. Both factors are operative when X = F, which explains why fluorine does not participate in halogen bonding.

References

1. Dumas J-M, Peurichard H, Gomel M (1978) J Chem Res Synop 54–55
2. Dumas J-M, Geron C, Peurichard H, Gomel M (1976) Bull Soc Chim France 720–728
3. Dumas J-M, Kern M, Janier-Dubry JL (1976) Bull Soc Chim France 1785–1790
4. Murray-Rust P, Motherwell WDS (1979) J Am Chem Soc 101:4374–4376
5. Murray-Rust P, Stallings WC, Monti CT, Preston RK, Glusker JP (1983) J Am Chem Soc 105:3206–3214
6. Ramasubbu N, Parthasarathy R, Murray-Rust P (1986) J Am Chem Soc 108:4308–4314
7. Bent HA (1968) Chem Rev 68:587–648
8. Hassel O (1970) Science 170:497–502
9. Bernard-Houplain M-C, Sandorfy C (1973) Can J Chem 51: 1075–1082
10. Bernard-Houplain M-C, Sandorfy C (1973) Can J Chem 51: 3640–3646
11. Di Paolo T, Sandorfy (1974) Chem Phys Lett 26:466–469
12. Di Paolo T, Sandorfy C (1974) Can J Chem 52:3612–3622
13. Auffinger P, Hays FA, Westhof E, Shing Ho P (2004) Proc Nat Acad Sci 101:16789–16794
14. Metrangolo P, Neukirch H, Pilati T, Resnati G (2005) Acc Chem Res 38:386–395
15. Brinck T, Murray JS, Politzer P (1992) Int J Quantum Chem, Quantum Biol Symp 19:57–64
16. Murray JS, Paulsen K, Politzer P (1994) Proc Indian Acad Sci (Chem Sci) 106:267–275
17. Politzer P, Lane P, Concha MC, Ma Y, Murray JS (2006) J Mol Model DOI 10.1007/s00894-006-0154-7 (this issue)
18. Stewart RF (1972) J Chem Phys 57:1664–1668
19. Naray-Szabo G, Ferenczy GG (1995) Chem Rev 95:829–847
20. Bader RFW, Carroll MT, Cheeseman JR, Chang C (1987) J Am Chem Soc 109:7968–7979
21. Weinstein H, Politzer P, Srebrenik S (1975) Theor Chim Acta 38:159–163
22. Politzer P, Murray JS (2002) Theor Chem Accts 108:134–142
23. Flükiger PF (1992) Development of the molecular graphics package MOLEKEL and its application to selected problems in organic and organometallic chemistry. Thèse No. 2561. Département de chimie physique, Université de Genève, Genève
24. Portmann S, Lüthi HP (2000) CHIMIA 54:766–770; http://www.cscs.ch/molekel/index.html
25. Lommerse JPM, Stone AJ, Taylor R, Allen FH (1996) J Am Chem Soc 118:3108–3116
26. Valerio G, Raos G, Meille SV, Metrangolo P, Resnati G (2000) J Phys Chem A 104:1617–1620
27. Romaniello P, Lelj F (2002) J Phys Chem A 106:9114–9119
28. Reed AE, Curtiss LA, Weinhold F (1988) Chem Rev 88:899–926
29. Becke AD (1993) J Chem Phys 98:5648–5652
30. Lee C, Yang W, Parr RG (1988) Phys Rev B 37:785–789
31. Ditchfield R, Hehre WJ, Pople JA (1971) J Chem Phys 54:724–728
32. Hehre WJ, Ditchfield R, Pople JA (1972) J Chem Phys 56:2257–2261
33. Hariharan PC, Pople JA (1974) Mol Phys 27:209–214
34. Gordon MS (1980) Chem Phys Lett 76:163–168
35. Hariharan PC, Pople JA (1973) Theo Chim Acta 28:213–222
36. Blaudeau J-P, McGrath MP, Curtiss LA, Radom L (1997) J Chem Phys 107:5016–5021
37. Francl MM, Pietro WJ, Hehre WJ, Binkley JS, DeFrees DJ, Pople JA, Gordon MS (1982) J Chem Phys 77:3654–3665
38. Binning RC Jr, Curtiss LA (1990) J Comp Chem 11:1206–1216
39. Rassolov VA, Pople JA, Ratner MA, Windus TL (1998) J Chem Phys 109:1223–1229
40. Rassolov A, Ratner MA, Pople JA, Redfern PC, Curtiss LA (2001) J Comp Chem 22:976–984
41. Clark T, Chandrasekhar J, Spitznagel GW, Schleyer PvR (1983) J Comp Chem 4:294–301
42. Godbout N, Salahub DR, Andzelm J, Wimmer E (1992) Can J Chem 70:560–571
43. Sosa C, Andzelm J, Elkin BC, Wimmer E, Dobbs KD, Dixon DA (1992) J Phys Chem 96:6630–6636
44. Kutzelnigg W (1984) Angew Chem 96:262–286
45. Kutzelnigg W (1984) Angew Chem Int Ed Engl 23:272–295