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The cytotoxicity of ortho alkyl substituted 4-X-phenols: A QSAR based on theoretical bond lengths and electron densities

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Abstract—A new method called quantum topological molecular similarity (QTMS) was recently proposed [O'Brien, S. E.; Popelier, P. L. A. *J. Chem. Inf. Comp. Sci.* **2001**, *41*, 764] and has been shown to be successful in a variety of medicinal, ecological and physical organic QSAR/QSPRs. QTMS method uses electronic descriptors drawn from ab initio wavefunctions of geometry-optimized molecules. We investigated a remarkable and unusual set of ortho alkyl-substituted phenols [Selassie, C. D.; Verma, R. P.; Kapur, S.; Shusterman, A. J.; Hansch, C. *J. Chem. Soc., Perkin* **2002**, *II*, 1112], recently studied by the Hansch group. Our results do not support their proposal that a steric factor is important in the determination of the cytotoxicity of this set of substituted phenols. Thus, we conclude that the cytotoxicity of these sterically encumbered phenols is dependent primarily on electronic and radical effects, and that steric issues do not appear to be a critical distinguishing factor.

In recent years, many research groups have focused on the phenolic hydroxyl group due to its wide radius of activity.[1,2] On the one hand, it appears to act as an antioxidant or radical scavenger[3] whilst on the other hand, it demonstrates significant toxicity.[4,5] This dichotomy[6] in activity is believed to be associated with its hydrogen abstraction and subsequent formation of aryloxyl free radicals.

In a recent series of studies[7–10], the Hansch group examined the cytotoxicity of a set of simple and complex mono-substituted phenols towards a fast-growing murine leukaemia cell line. For electron-rich phenols a QSAR was obtained[9] comprising log *P* and the homolytic O–H bond dissociation enthalpy (BDE). The significant presence of the latter quantity implied a radical mechanism of toxicity. That study also reported that ortho mono-substituted phenols showed no significant dependence on either hydrophobic or steric parameters, since an excellent QSAR was obtained with a single BDE parameter.

In their most recent study[10], they investigated a set of poly-substituted electron-rich phenols, comprising analogues of the well-known and widely used antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). Although regarded as safe food additives by the USA Food and Drug Administration, studies have shown that these molecules exhibit toxic (be it in very large doses) and carcinogenic properties in animals.[11] In an effort to gain insight into the mechanism of action of poly-substituted phenols like BHA and BHT, they studied the cytotoxicity towards the same leukaemia cell line (L1210). Remarkably, the best QSAR obtained (Eq. 6 in their paper) showed a considerable dependence on Taft's steric parameter E_{S-2} (for the larger of the two ortho substituents.) This strong dependence of cytotoxicity on E_{S-2} led them to examine the role of hydrophobicity. The resulting QSARs, all involving C log *P* and no steric parameters, gave rise to much poorer correlations. The authors concluded[12] that their ortho alkyl substituted phenol series 'deviates from most other phenols'. This conclusion was reinforced by three more QSARs of a series of 2,6-di-*tert*-butylphenols with substituents in the 4-position, linking the hydrogen abstraction reaction rate to their structure.

In this article, we re-examine the role of the steric effect by means of a new method developed in our laboratory, called quantum topological molecular similarity (QTMS). This method adopts the viewpoint of the quantum chemical electron density being the source of molecular properties. Originally it was designed as a

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practical implementation of the molecular similarity idea put forward by Carbó et al.,[13] in a similarity index depended as a 3D superposition of the electron densities of molecules *A* and *B*. We showed[14,15] that it suffices to compare the two densities by means of special points in space, as described by the topology of the electron density.[16,17] After successfully demonstrating this proof-of-principle, QSAR models[18] were constructed using partial least squares (PLS)[19] for the estimation of pK_a of carboxylic acids, anilines and phenols,[20] the prediction of σ_p, σ_m, σ_I and σ_p^0 parameters of mono-[14] and polysubstituted benzoic acids, phenylacetic acids and bicyclo carboxylic acids.[21] Most recent work[22] delivered a successful model for the prediction of σ^- Hammett constant of a set of para-substituted phenols and σ^+ of substituted toluenes and of bromophenethylamines. The action radius of QTMS did also extend into QSARs of medicinal[23–25] and ecological[21,26–28] nature. The QTMS approach inspired work in other groups (e.g., Ref. 29,30).

It should be stressed that QTMS (in its current stage of development) offers a reliable alternative to electronic parameters only.[22] In other words, we have accumulated substantial evidence that the two other types of parameters, hydrophobic and steric, are *not* modelled by QTMS. Of course, the QTMS descriptors can be combined with externally provided steric and/or lipophilicity parameters, but QTMS does not generate them independently. The important point is that because of this clear discriminatory capacity, QTMS can determine, based on quantum chemical electron densities, whether a given activity is due to steric effects or electronic effects. Here, we use QTMS to re-examine the remarkable and unusual set of ortho alkyl substituted phenols investigated by the Hansch group.[10] We wish to determine if the cytotoxic activity is captured by a QSAR model built from electronic effects or instead from steric effects, as claimed before by Selassie et al.[10]

The full details of the QTMS can be found in O'Brien et al.[15] but here we reiterate salient features. QTMS consists of three stages. First, geometry optimisation is performed on the dataset to obtain bond lengths and wavefunctions at a number of levels of theory. The lowest level is the semi-empirical AM1 method,[31] the next level is HF/6-31G(d),[32] and the third is B3LYP/6-31+G(d,p).[32] For convenience these levels are referred to as I, II and III. The ab initio calculations are performed with the GAUSSIAN03 suite of programs.[33]

Second, the so-called bond critical points (BCPs) are localised by a local version of the program MORPHY.[34] In short, BCPs are points where the gradient of the electron density vanishes. One BCP is found for every bond in the common skeleton, shown in Figure 1. Four topological descriptors (ρ, $\nabla^2\rho$, ε, and K(r)) are evaluated at each BCP, and together with the computed bond lengths (r_e), these five descriptors comprise the variable inputs. The topological descriptors are defined and extensively discussed elsewhere.[17] Loosely speaking, the first three descriptors can be interpreted as a measure of bond order, covalency and π character, respectively. We note here that optimised bond lengths on their own (not in conjunction with topological descriptors) can also provide a successful model, as discussed below (Table 2). Because of the lack of core electron densities in the AM1 method, level I does not yield BCPs, and a pure bond length model is the only type of model it generates.

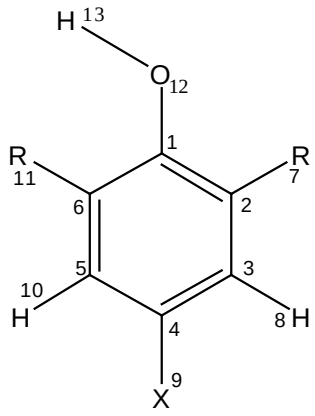

Figure 1. Labelling scheme for the series of 2-alkyl and 2,6-dialkyl-4-X-phenols.

Third and finally, a chemometric analysis employs PLS to construct the models from the descriptor set (''X-variables'') and experimentally obtained activity data (''Y-variables''). As a supervised method PLS combines linear least-squares with principal component analysis and constructs linear combinations of the X-variables, called latent variables (LV). The quality of QTMS-generated models is assessed by the correlation coefficient, r^2 and the cross-validated correlation coefficient, q^2. The 'leave one out' (LOO) q^2 coefficient is now thought to be a less trustworthy measure of internal predictivity and may contribute to optimistic q^2 values quoted in QSAR work.[35] Instead, the QTMS methodology uses the 'leave one seventh out' q^2 coefficient, which is more reliable and is the default used by the program SIMCA-P[36] software performing the PLS analysis. Further validation of the constructed models is measured by the randomisation validation statistics r^2(int) and q^2(int). These measures safeguard against correlations determined by chance by estimating the probability that a good fit can be obtained after random reorganisation of the dependent variables. That is, the activities become deliberately associated with the wrong descriptors, which should give rise to a deterioration of models fitted to permuted data. Each r^2 and q^2, generated for each 'scrambled' dataset, is then plotted against the absolute value of the correlation coefficient between the original set of activities and its permutation. Lines are drawn through the r^2 and q^2 values and the intercepts are examined. A model is deemed valid if $r^2(\text{int}) < 0.4$ and $q^2(\text{int}) < 0.05$. The randomisation test must be performed at least 10 times to ensure that a good model is not merely the result of pure chance. Together these four statistical measures provide a robust framework to assess the quality of the models constructed. The significance of the independent variables to the model

is assessed by the variable importance to projection (VIP)[37] plots. The VIPs give the relative importance of each descriptor contributing to the model, and can be conveniently plotted in a histogram.

Ref. 10 provided all cytotoxicity data, in the shape of log(1/C), where C constitutes the molar concentration of X-phenol that induces 50% inhibition of growth in the cell line. It also provided the Taft parameter E_{S-2}, the Otsu E_R parameter,[38] specifically designed for radical reactions (based on hydrogen abstraction from substituted cumenes by a polystyryl radical) and the lipophilicity parameter C log *P*. Table 1 contains the list of 21 compounds with all data.

The PLS statistics for the bond length and BCP models, respectively, are reported in Table 2. It is clear that the QTMS descriptors (which are purely electronic in nature) can be combined with the Taft, Otsu and C log *P* parameters. For all models reported, the following three phenols were excluded as outliers: 2,6-di-OMe-, 2-Me-4-NO_2- and 2-Me-4-COMe-phenols, consistent with the work of Selassie et al.[10]

All bond length models passed the randomisation validation check described above. Bond lengths alone produce good models. Level I and Level II bond lengths produce equally good statistics, while Level III calculations produce slightly improved models in terms of r^2. The addition of the Taft steric parameter or the hydrophobic parameter to the bond length descriptors does not improve the models constructed at any level of calculation. The addition of Otsu's parameter improves the models at all levels of calculation. Level I and Level II again produce very similar quality models and Level III again produces a slightly better model.

Table 2. PLS statistics for bond length and BCP models with and without the inclusion of physicochemical parameters

Model[a]	Level of calculation	With additional descriptor	LVs	r^2	q^2
1	Level I	None	2	0.91	0.73
2	Level I	Taft	2	0.92	0.73
3	Level I	Otsu	2	0.93	0.80
4	Level I	C Log *P*	2	0.91	0.72
5	Level II	None	2	0.91	0.73
				0.91[b]	**0.65**
6	Level II	Taft	2	0.91	0.73
				0.91	**0.66**
7	Level II	Otsu	2	0.94	0.81
				0.92	**0.69**
8	Level II	C Log *P*	2	0.91	0.72
				0.91	**0.66**
9	Level III	None	2	0.92	0.71
				0.91	**0.65**
10	Level III	Taft	2	0.92	0.70
				0.91	**0.65**
11	Level III	Otsu	2	0.95	0.80
				0.92	**0.68**
12	Level III	C Log *P*	2	0.92	0.70
				0.91	**0.65**

[a] The outliers: 2,6-di-OMe-, 2-Me-4-NO_2- and 2-Me-4-COMe-phenols were excluded from all models obtained here.
[b] The bold font corresponds to the statistics of BCP properties.

All BCP models are poorer than bond length models, particularly in terms of the q^2 values. BCP descriptors alone produce reasonable models. The addition of the Taft steric parameter or the hydrophobic parameter to the BCP descriptors does not improve the models constructed at either Level II or III. As with the bond length models the addition of Otsu's parameter improves the models at both levels. This improvement is less noticeable compared to the bond length models.

Table 1. Observed and predicted cytotoxicity data and physicochemical parameters for the series of 2-alkyl and 2,6-dialkyl, 4-X-phenols

Compound	Substituent	Observed toxicity (Log1/C)	Predicted toxicity (Log1/C)	Taft parameter (E_{s-2})	C Log *P*[a]	Otsu parameter (E_R)
1	2,6-di-Me	3.02	3.02	−1.24	2.37	0.06
2	2,6-di-OMe	3.86	—	−0.55	1.11	0.22
3	2,4,6-tri-Me	3.2	3.09	−1.24	2.87	0.09
4	2,6-di-CMe_3	3.85	3.84	−2.78	4.93	0.06
5	2,6-di-CMe_3-4-Me	4.04	3.92	−2.78	5.43	0.09
6	2,6-di-Et	3.26	3.07	−1.31	3.43	0.06
7	2,6-di-$CHMe_2$	3.25	3.31	−1.71	3.93	0.06
8	2,4,6-tri-CMe_3	3.9	4.09	−2.78	6.75	0.09
9	2-CMe_3-6-Me	3.73	3.68	−2.78	3.65	0.06
10	2,6-di-CMe_3,4-NO_2	4.9	4.82	−2.78	5.31	0.47
11	2,6-di-CMe_3-4-Et	3.91	3.93	−2.78	5.96	0.09
12	2,6-di-CMe_3-4-Br	4.11	4.18	−2.78	6.09	0.18
13	2,4-di-CMe_3	4.24	4.03	−2.78	5.03	0.06
14	2-CMe_3-4-Me	3.8	3.87	−2.78	3.7	0.06
15	2,4-di-Me	3.04	3.22	−1.24	2.42	0.06
16	2-Me-4-F	3.09	3.21	−1.24	2.36	−0.04
17	2-Me-4-NO_2	3.49	—	−1.24	2.3	0.44
18	2-Me-4-Br	3.46	3.5	−1.24	3.08	0.15
19	2-Me-4-OMe	3.39	3.31	−1.24	2.02	0.14
20	2-Me-4-COMe	3.14	—	−1.24	1.9	0.27
21	2-CMe_3-4-Et	3.8	3.90	−2.78	4.23	0.06

[a] Calculated using the program C log *P* version 4.0.

The most striking feature of the regression statistics reported above is the total failure of Taft's steric parameter to improve the models constructed from either bond lengths or BCP descriptors alone. This observation is very much at odds with the work of Selassie et al.,[10] who reported 'the strong dependence of cytotoxicity on E'_{s-2} (Taft's parameter). Selassie et al. also reported 'a much poorer correlation' when using CLogP in place of E_{s-2}. Our results show neither an improvement nor reduction in model quality when adding the hydrophobicity parameter to either the bond length or BCP models.

It is interesting that both bond lengths and BCP descriptors alone successfully produce predictive models for the cytotoxicity of the series of substituted phenols used here. In some cases, local linear relationships exist between bond lengths and BCP properties[39] and it is usually the case that BCP properties calculated at ab initio levels are superior to bond lengths obtained semi-empirically. Recent work[40] concluded that AM1 bond length calculations could provide a swift mechanism for screening large datasets for the importance of electronic effects. A decision on proceeding with more costly ab initio calculations could subsequently be made.

The results presented here provide evidence that electronic effects characterised by bond lengths or BCP descriptors are important to the cytotoxicity displayed by this series of substituted phenols. Indeed, the QTMS procedure successfully models this electronic part of the activity. However, the inclusion of Otsu's radical reaction parameter improves both sets of models—most notably for the bond length models. This parameter was designed by Otsu et al. specifically to correlate radical reactions and its use in correlating radical reactions is extensive.[41] In essence, the overall toxicity of these sterically encumbered phenols involves a critical balance between the electronic effects described by changes in the bond lengths and the radical effects as described by Otsu's parameter. The VIP plot shown in Figure 2 indicates that, in order of decreasing importance, bond lengths C_1–C_2, C_3–H_8, C_2–H_7, O_{12}–H_{13}, C_5–H_{10} and Otsu's parameter are the most important to the model with a VIP > 1. To put this in context, in a recent QTMS study[42] on predicting the BDEs of a completely different set[43] of phenols, the phenolic bonds C–O and O–H featured prominently in the VIP plot, well above the other bonds. This was a gratifying result since the activity (i.e., dependent variable) in that case was embodied in and confined to the breaking of the O–H bond. Here we do not find such clear evidence for a radical mechanism in terms of the localisation of the phenol's active centre. The reliability of QTMS in the designation of active sites has been verified[15,22,23,25] before. In the framework of phenols, it is reinforced by an early study[27] on a set of para-substituted phenols.[44] When the pK_a is taken as the dependent variable, then the O–H bond shows the highest VIP value, consistent with the released proton disrupting this bond most, closely followed by the C–O bond. When biodegradability (2nd order rate constant of oxidation) is taken as the dependent variable, the $C_{ortho} = C_{meta}$ bond has the highest VIP value, hinting at an attack by oxygenase at this location, affecting this bond most.

We investigated a remarkable and unusual set of ortho alkyl substituted phenols, recently studied by the Hansch group. We applied a method called quantum topological molecular similarity (QTMS), which uses modern quantum chemical descriptors, associated with the wavefunctions of geometry optimised molecules. Our results do not support their proposal that a steric factor is important in the determination of the cytotoxicity of this set of substituted phenols. In fact, the results suggest no steric contribution whatso-

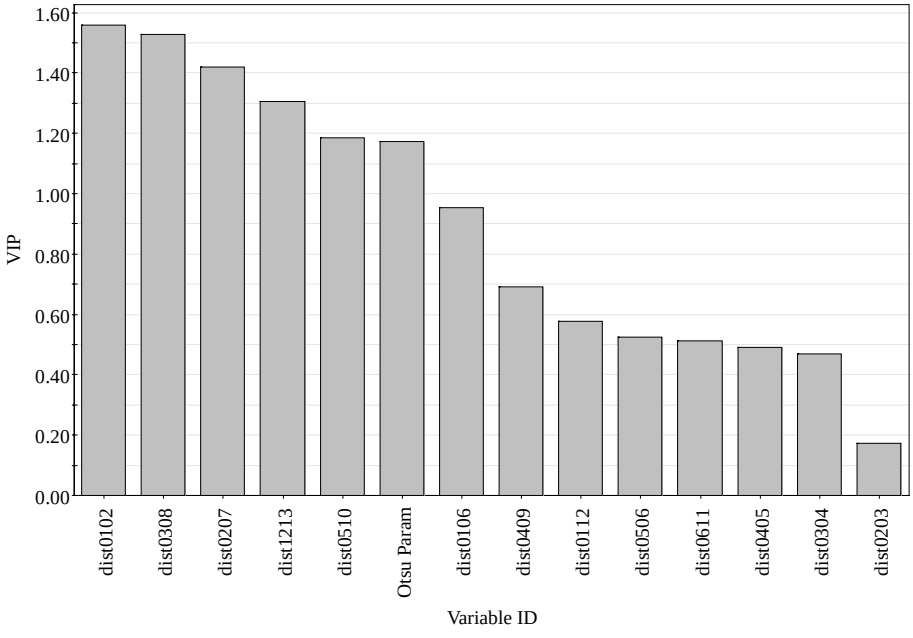

Figure 2. Variable importance plot (VIP) computed at level III.

ever. QTMS descriptors capture electronic effects only but can be combined with externally provided descriptors of any nature. A slight improvement is observed with the addition of the Otsu radical reaction parameter. AM1 bond length models combined with the Otsu radical reaction parameter offer quite good predictive models which, surprisingly, are not improved upon when calculated at ab initio levels or when BCP descriptors are used for ab initio models. It is not clear why the B3LYP functional, which includes electron correlation, does not improve the quality of the bond length and BCP models constructed. However, if this were the case then similar and larger series of phenols can be analysed at a fraction of the computational cost of ab initio levels. It is also worth pointing out that the hydrophobic parameter does not improve the model either. Thus, we conclude that the cytotoxicity of these sterically encumbered phenols is dependent only on electronic and radical effects.

Supplementary material

The descriptors ('X-variables') can be obtained as spreadsheets (Microsoft Office Excel 2003) from the corresponding author, upon request, by contacting pla@manchester.ac.uk.

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References and notes

1. Stich, H. F. *Mut. Res.* **1991**, *259*, 307.
2. Selassie, C. D.; Garg, R.; Kapur, S.; Kurup, A.; Verma, R. P., et al. *Chem. Rev.* **2002**, *102*, 2585.
3. Rice-Evans, C. A.; Diplock, A. T. *Free Radic. Biol. Med.* **1993**, *15*, 77.
4. Ren, S.; Kim, H. *J. Chem. Inf. Comp. Sci.* **2003**, *43*, 2106.
5. Schultz, T. W.; Cronin, M. T. D.; Walker, J. D.; Aptulad, A. O. *J. Mol. Struct.-Theochem.* **2003**, *622*, 1.
6. Garg, R.; Kapur, S.; Hansch, C. *Med. Res. Rev.* **2001**, *21*, 73.
7. Selassie, C. D.; DeSoyza, T. V.; Rosario, M.; Gao, H.; Hansch, C. *Chem. Biol. Interact.* **1998**, *113*, 175.
8. Zhang, L.; Gao, H.; Hansch, C.; Selassie, C. D. *J. Chem. Soc., Perkin Trans.* **1998**, *2*, 2553.
9. Selassie, C. D.; Shusterman, A. J.; Kapur, S.; Verma, R. P.; Zhang, L. T., et al. *J. Chem. Soc., Perkin* **1999**, *2*, 2729.
10. Selassie, C. D.; Verma, R. P.; Kapur, S.; Shusterman, A. J.; Hansch, C. *J. Chem. Soc., Perkin* **2002**, *2*, 1112.
11. Witschi, H.; Lock, S. *Toxicol. Appl. Pharmacol.* **1979**, *50*, 391.
12. Selassie, C. D.; Verma, R. P.; Kapur, S.; Shusterman, A. J.; Hansch, C. *J. Chem. Soc., Perkin II* **2002**, 1112.
13. Carbo, R.; Leyda, L.; Arnau, M. *Int. J. Quant. Chem.* **1980**, *17*, 1185.
14. Popelier, P. L. A. *J. Phys. Chem. A* **1999**, *103*, 2883.
15. O'Brien, S. E.; Popelier, P. L. A. *J. Chem. Inf. Comp. Sci.* **2001**, *41*, 764.
16. Bader, R. F. W. *Atoms in Molecules. A Quantum Theory*; Oxford University Press: Oxford, GB, 1990.
17. Popelier, P. L. A. *Atoms in Molecules. An Introduction*; Pearson: London, Great Britain, 2000.
18. Popelier, P. L. A. Quantum Topological Molecular Similarity—Past, Present and Future. In *EuroQSAR2002: Designing Drugs and Crop Protectants: Processes, Problems and Solutions*, Ford, M., Livingstone, D. J., Dearden, J., van de Waterbeemd, H. Eds.; Blackwell: Blackwell, Oxford, GB, 2003; pp 130.
19. Wold, S.; Sjostrom, M.; Eriksson, L. Partial Least Squares Projections to Latent Structures (PLS) in Chemistry. *Encycl. Comp. Chem.*: Wiley, Chichester, GB, 1998; pp 2006.
20. Chaudry, U. A.; Popelier, P. L. A. *J. Org. Chem.* **2004**, *69*, 233.
21. Popelier, P. L. A.; Chaudry, U. A.; Smith, P. J. *J. Chem. Soc., Perkin II* **2002**, 1231.
22. Smith, P. J.; Popelier, P. L. A. *Org. Biol. Chem.* **2005**, *3*, 3399.
23. O'Brien, S. E.; Popelier, P. L. A. *J. Chem. Soc., Perkin Trans.* **2002**, *2*, 478.
24. Popelier, P. L. A.; Chaudry, U. A.; Smith, P. J. *J. Comp.-Aided Mol. Design* **2004**, *18*, 709.
25. Smith, P. J.; Popelier, P. L. A. *J. Comp.-Aided Mol. Design* **2004**, *18*, 135.
26. Chaudry, U. A.; Popelier, P. L. A. *J. Phys. Chem. A* **2003**, *107*, 4578.
27. O'Brien, S. E.; Popelier, P. L. A. Quantum Molecular Similarity: Use of Atoms in Molecules Derived Quantities as QSAR Variables. In *ECCOMAS Proceedings*, Barcelona, Spain, 2000.
28. O'Brien, S. E. Quantum Molecular Similarity, An Atoms in Molecules Approach; PhD Thesis, Department of Chemistry, UMIST: Manchester, Great Britain, 2000.
29. Alsberg, B. K.; Marchand-Geneste, N.; King, R. D. *Chem. Intell. Lab. Syst.* **2000**, *54*, 75.
30. Alsberg, B. K.; Marchand-Geneste, N.; King, R. D. *Anal. Chim. Acta* **2001**, *446*, 3.
31. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
32. Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*; 2nd ed.; Gaussian Inc.: Pittsburgh, USA, 1996; p 302.
33. GAUSSIAN03. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. J.; Vreven, J., T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. In Gaussian, Inc., Pittsburgh PA, 2003.

34. MORPHY98. A Program Written by P.L.A. Popelier with a Contribution from R.G.A. Bone, UMIST, Manchester, England, EU; 1998.
35. Golbraikh, A.; Tropsha, A. *J. Mol. Graph Modell.* **2002**, *20*, 269.
36. UMETRICS SIMCA-P 10.0; info@umetrics.com: www.umetrics.com, Umeå, Sweden.
37. Wold, S. *Chemometric Methods in Molecular Design*; VCH: Weinheim, Germany, 1995, pp 195.
38. Otsu, T.; Ito, T.; Fujii, Y.; Imoto, M. *Bull. Chem. Soc. Japan* **1968**, *41*, 204.
39. O'Brien, S. E.; Popelier, P. L. A. *Can. J. Chem.* **1999**, *77*, 28.
40. Smith, P. J. Quantum Chemical Topological Properties as Electronic Descriptors in Quantitative Structure-Activity/Property Relationships; PhD Thesis, Department of Chemistry, UMIST: Manchester, Great Britain; 2003.
41. Hansch, C.; Gao, H. *Chem. Rev.* **1997**, *97*, 2995.
42. Singh, N.; Loader, R.; O'Malley, P. J.; Popelier, P. L. A. Submitted.
43. Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 1736.
44. Damborsky, J.; Schultz, T. W. *Chemosphere* **1997**, *34*, 429.