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The anomeric effect: the dominance of exchange effects in closed-shell systems†

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The origin of the anomeric effect has remained an open question. After Mo demonstrated that hyperconjugation is not responsible for the anomeric effect [Y. Mo, *Nature Chem.*, 2010, **2**, 666.], electrostatic interactions and Pauli repulsions have been at the center of this debate. In this work, the total energies of the most stable rotamers of the equatorial and axial anomers of fluoro, hydroxyl, cyano and amino groups in cyclohexane and 2-substituted tetrahydropyran rings are decomposed into their fundamental kinetic, electrostatic and exchange components. In this partitioning scheme, the differences in the total energies among the most stable rotamers of each anomer correlate very well with the differences in the exchange components, revealing that the anomeric effect has no electrostatic origin. Indeed, the anomeric effect is dominated by the exchange energy. This proposal for the origin of the anomeric effect brings new insights that, once incorporated, may improve qualitative chemical models. Implications of this new proposal for the origin of the anomeric effect on geometric parameters and solvation are also discussed.

Introduction

Carbohydrates that differ from each other in just a few structural aspects can be found in all realms of nature and can have extremely distinct biological roles. One of the most impressive examples of this is illustrated by the disaccharides cellobiose and maltose, both composed only of glucose molecules. They differ from each other in the anomerisation of the glycosidic linkage β,1-4 (cellobiose) and α,1-4 (maltose)[1] and are found in cellulose and glycogen polysaccharides, respectively. The strikingly different properties of these two polysaccharides strongly imply that the glycosidic linkage configuration (α or β) determines their function. Moreover, the conformation of the glycosidic linkage, the values of the dihedral angles ϕ and ψ, which define the relative orientation of the monosaccharide units, is of importance as well, because it also contributes to the spatial arrangement of the polymeric main chain.[2,3] Therefore, the structure of a carbohydrate together with knowledge of its conformation is a starting point for understanding its biological role. The conformational versatility of carbohydrates, which is undoubtedly related to the various roles they play, is a big challenge in both theory and experiment. Only recently we have identified a property that is sufficient for distinguishing between conformers that differ from each other exclusively by the orientation of the hydrogen atom in the hydroxyl groups for simpler systems, like monosaccharides. Using this property, we are able to validate the most abundant conformation of monosaccharides.[4] The validation procedure, *i.e.*, the test of the ability of any set of proposed conformers to reproduce experimental data, is mandatory in studies involving carbohydrate samplings because very often, the energy difference between many conformers is smaller than the accuracy of the theoretical method used to describe them.

It is important to understand the nature of carbohydrate stabilising effects to guarantee that these stabilising effects are properly quantified by the theoretical method chosen to describe them. Certainly, the first stabilising effect that needs to be well understood is the anomeric effect, which is the unusual preference that an electronegative X substituent in a heterocyclic structure containing the sequence of atoms C–Y–C–X (where Y = N, O or S, and X = Br, Cl, F, O or S) shows for the axial (A) orientation, over the equatorial (E) orientation.[5–8]

Two different explanations for the anomeric effect can be found in the literature. The first one, the "rabbit-ear effect", is stereoelectronic in nature and states that there is an electrostatic repulsion between the lone electron pairs of the Y and X atoms in the E configuration that destabilise the E anomer relative to the A anomer. This hypothesis is reinforced when a preference for the E anomer is observed in polar solvents. This is explained by the ability of a polar solvent to reduce the Y–X

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† Electronic supplementary information (ESI) available: Total energy values and their components (in hartree) and geometrical parameters are reported for all compounds studied. See DOI: 10.1039/c2ob26818c

lone pair repulsion.[7] However, this electrostatic model does not provide any explanation for the characteristic shortening of the Y–C bond in the A anomer in comparison to the length of the same bond in the E anomer. Additionally, it is seldom mentioned that the dipole moment values for the different conformers of the A anomer of glucose are generally higher than the values for the conformers of the E anomer in aqueous solution.[9] This points to a more intense electrostatic interaction between the A anomer and the solvent than between the E anomer and the solvent. Nevertheless, this is not reflected by the experimental value of 38 : 62[10] found for the α : β anomeric abundance.

The second hypothesis for explaining the anomeric effect is that there is an interaction between an electron lone pair of the Y atom and the C–X antibonding molecular orbital, which is referred to as hyperconjugation. This would stabilise the A anomer relative to the E anomer. This hypothesis is consistent with the available geometric data, which show that the Y–C bond length is shorter in the A anomer than in the E anomer. The shortening of the bond distance is sometimes assumed to be a consequence of hyperconjugation. However, the hyperconjugation model does not provide any explanation for the preference of E over A anomers in solvents with high dielectric constants, such as water.

Very recently, by adopting a naturally local valence bond description, Mo has shown that the origin of the anomeric effect is not related to hyperconjugation.[11] Few possibilities remain to explain the anomeric effect in addition to some type of steric effect. Although qualitative descriptions of the steric effect are common in chemistry textbooks, its physicochemical foundation, which might furnish a quantitative model, is not yet well established. For instance, while Mo describes steric effects as being composed of both electrostatic interactions and Pauli repulsions,[11] Badenhoop and Weinhold state that steric repulsions are generally considered to arise only from the "electronic permutational antisymmetry imposed by the Pauli exclusion principle".[12]

Surely, a clear and quantitative definition for the steric effect would be instrumental not only for the analysis of the anomeric effect but also to assess several other chemical concepts within a physicochemical framework. Nevertheless, this definition and its application to the analysis of the anomeric effect may, perhaps, be preceded by an analysis based on completely well established and simple quantities, *i.e.*, the energy terms that emerge directly from the application of the molecular Hamiltonian on the appropriate wavefunction. Such a decomposition scheme is proposed in this work, aiming to provide a clear separation between electrostatic and exchange effects, hopefully leading to separation of the contributions of each component to the anomeric effect.

Methodology

In this work, the wavefunction used was the simplest antisymmetrised wavefunction, expressed as a Slater determinant, as used in the Hartree–Fock method. This type of description has been shown to properly describe the correct ordering of all six 2-OH tetrahydropyran conformers.[13] The energy terms that constitute the total energy (E_{tot}) can be identified as the kinetic (T), electrostatic (V_{el}) and exchange (K) components. The electrostatic potential term comprises: the repulsion among all nuclei (V_{NN}); the repulsion among all electrons (V_{ee}), which is obtained from the summation of Coulomb integrals (J_{ij}); and the attraction among all nuclei and electrons (V_{Ne}) of the molecule, which are also quantified independently. These quantities are identified in the well-known Hartree–Fock energy expression for a closed shell as shown below, where N is the total number of spatial orbitals, and i and j refer to orbitals.

$$E_{\text{tot}} = 2\sum_{i=1}^{N/2}(T_i + V_{\text{Ne}_i}) + \sum_{i=1}^{N/2}\sum_{j=1}^{N/2}(2J_{ij} - K_{ij}) + V_{\text{NN}} \qquad (1)$$

This expression circumvents the energy partitioning scheme[14] that is most commonly used to handle the anomeric effect analysis, based on the unclear definitions of steric effects[12,15] and Pauli repulsions.[14,16] Such an energy partitioning scheme is formulated from an interpretation of Weisskopf's work[17] regarding the implications of the Pauli Exclusion Principle on the maximum possible kinetic energy value for a confined particle. This work also has been a source of inspiration for similar energy decompositions previously performed in the framework of density functional theory.[18]

This simple and physically intuitive analysis based on the terms of the energy expression sheds new light onto the origin of the anomeric effect. Such understanding is important because it may allow for its proper quantification, and may also guide choices of descriptors to be used in parameterisations of carbohydrate force fields. This information may improve the transferability of parameters, which is still very difficult even for "similar" compounds.[19]

Phenomenologically, the anomeric effect is quantitatively defined as the difference between the standard Gibbs free energy differences ($\Delta G°_{298.15\text{K}}$) for the axial (A) and equatorial (E) configurations of a carbohydrate (car), and of a cyclohexane (Cy) substituted with the same functional group, *i.e.*, $\Delta G°_{298.15\text{K}}$ (anomeric) = $[\Delta G°_{298.15\text{K}}(\text{carE}) - \Delta G°_{298.15\text{K}}(\text{carA})] - [\Delta G°_{298.15\text{K}}(\text{CyE}) - \Delta G°_{298.15\text{K}}(\text{CyA})]$.[20]

As the reference used to quantitatively measure the intensity of the anomeric effect is the corresponding cyclohexane, a quantitative analysis was first carried out for the effects promoted by substitutions of four groups with different electronegativities, F – fluoro, CN – cyano, OH – hydroxyl and NH_2 – amino, in a cyclohexane ring. The same substitutions were imposed on the corresponding oxane ring, generating the corresponding tetrahydropyran-2-yl (THP) compounds, which differ from the cyclohexane derivative compounds only by the substitution of a CH_2 group by an O atom in the ring, therefore incorporating the C–Y–C–X sequence and thus, the anomeric effect.

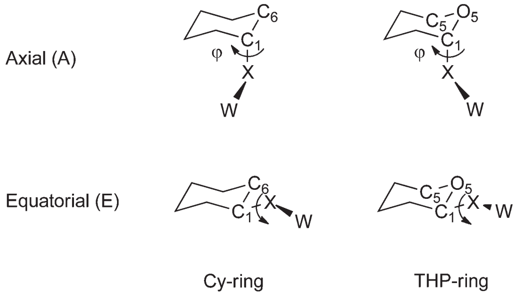

Fig. 1 The most common representations for A and E configurations in Cy and THP rings. XW=OH or NH_2. When X=F, there is no W atom, and when XW=CN, there are no different conformations generated by the C1–CN bond rotation because the cyano group is linear.

The calculations were first performed at the Hartree–Fock (HF)/6-31G(d,p) level. All local and global minima were properly characterised by frequency calculations. The Jaguar computational code[21] was used. The energy terms of the total energy were generated by the code and are reported in the ESI† section. Second order perturbative corrections on the geometry and energy were included for the most stable rotamers of each anomer by performing new calculations at the Møller–Plesset perturbation theory (MP2) level.[22] The 6-31G(d,p) and 6-31+G-(d,p) basis functions were adopted. Additionally, coupled cluster single point calculations on the MP2-optimised geometries were performed considering single and double excitations and non-iterative triple corrections (CCSD(T)).[23] The post-HF calculations were performed using the GAMESS computational code.[24]

Fig. 1 shows the most common representation of the corresponding A and E configurations of cyclohexane derivatives. The dihedral angle φ = C6–C1–X–W defines the relative orientation of the XW substituent. It is important to note that the cyclohexane derivatives do not undergo hemiacetal reactions, due to the absence of a keto or an enol group vicinal to a hydroxyl group. This is in contrast to the 2-substituted tetrahydropyran compounds, which can undergo hemiacetal reactions.[25] This reaction defines the A : E ratio when the equilibrium condition is reached and is completely governed by the anomeric effect.

Results and discussion

To quantify and investigate the origin of the anomeric effect, calculations were performed with the THP-ring compounds and the analogous Cy-ring compounds, which were chosen as the reference compounds. For each ring, the potential energy curves for the rotation of the OH and NH_2 substituent groups in both the A and E configurations were obtained, generating the four energetic profiles that are shown for each group in Fig. 2.

From Fig. 2 we can see that for both OH and NH_2 Cy derivatives (dashed lines), the equatorial configuration (solid square) is always energetically favoured for rotamers with φ approximately 180° or 300°, which are equivalent in energy due to symmetry, for both substituents. The global minima for 2-OH– and 2-NH_2–THP are the A rotamer with φ approximately 60° and the E rotamer with φ approximately 300°, respectively. Full geometry optimisation and frequency calculations were performed for the global and local minima of both configurations. The 2-NH_2–THP axial rotamer with φ = 180° is obtained only if the φ angle is kept frozen during the geometry optimisation calculation because it is not a minimum. The values for the total energy and its components for the global minimum and all local minima are found in the ESI.†

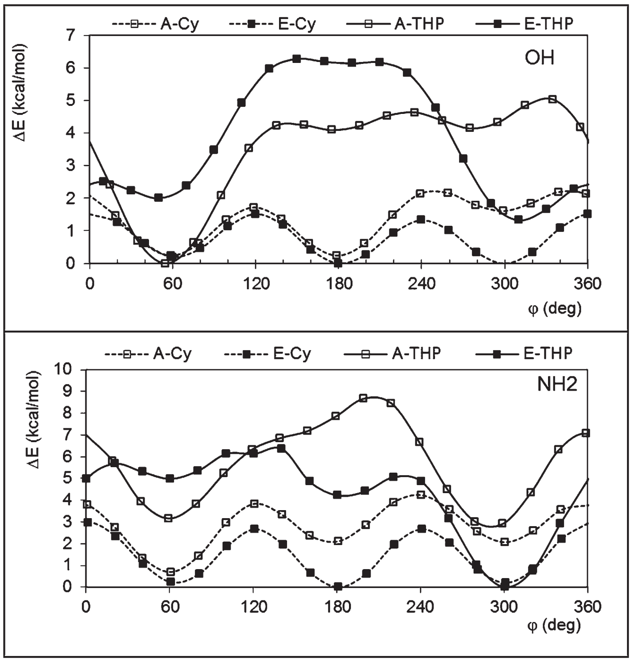

Fig. 2 Profiles for the relative energies calculated at the HF/6-31G(d,p) level, as a function of the φ angle for the OH and NH_2 substituents in Cy and THP rings.

Table 1 reports the values of the φ dihedral angle for these global and local minima, as well as their relative electronic energy values (ΔE_{tot}).

For Cy derivatives with F, CN, OH and NH_2 substituents, the $\Delta E_{tot} = [E_{tot}(E) - E_{tot}(A)]$ values for the most stable rotamers of each configuration are 0.20, −0.43, −0.27 and −0.70 kcal mol^{-1}, respectively. In comparison to the values found by Mo at the MP2/6-31+G(d) level,[11] which are 0.09 (F), −0.40 (OH) and −1.71 (NH_2) kcal mol^{-1}, the HF description used in this work was able to furnish acceptable energy values for the anomeric differences.

The geometric and energetic comparisons show very good agreement with previous studies of the 2-OH–THP compound, for which the inclusion of electron correlation with perturbative methods (MP2) does not improve the results,[26–28] as mentioned earlier. Additionally, the use of a more complete basis set (6-311++G(d,p)) or density functional methods does not seem to add any relevant information, and does not change the energetic ordering of the rotamers studied.[13] Among the results recently published by Mo,[11] the value of 1.32 kcal mol^{-1}

Table 1 Values of the φ angle (deg) and ΔE_{tot} (calculated at the HF/6-31G(d,p) level) for the global and local minima of OH, NH_2, F and CN substituents in Cy and THP rings. ΔE_{tot}, including zero point energy corrections, and standard Gibbs free energy differences are reported, respectively, in round and square brackets. All of the relative energy values are expressed in kcal mol^{-1}

Group			Cy			THP		
OH	(A)	φ	59.3	178.8	298.1	55.5	175.9	276.4
		ΔE_{tot}	0.27 (0.40)[0.45]	0.27 (0.40)[0.45]	1.68 (1.71)[1.69]	0.0^{e} (0.0)[0.0]	3.98 (3.58)[3.40]	4.08 (3.81)[3.69]
	(E)	φ	62.0	182.7	299.6	49.4	189.0	311.2
		ΔE_{tot}	0.20 (0.19)[0.19]	0.0^{a} (0.0)[0.0]	0.0 (0.0)[0.0]	1.90 (1.44)[1.30]	5.94 (5.17)[4.70]	1.24 (0.87)[0.78]
NH_2	(A)	φ	59.9	175.1	300.9	58.7	180.1	290.2
		ΔE_{tot}	0.70 (0.84)[0.90]	2.06 (2.16)[2.17]	2.06 (2.16)[2.17]	3.16 (3.26)[3.28]	7.80^{f} —	2.77 (2.90)[2.93]
	(E)	φ	65.1	181.2	300.9	59.2	186.3	301.7
		ΔE_{tot}	0.16 (0.12)[0.10]	0.0^{b} (0.0)[0.0]	0.16 (0.13)[0.11]	4.90 (4.55)[4.39]	4.12 (3.86)[3.76]	0.0^{g} (0.0)[0.0]
F	(A)	ΔE_{tot}		0.0^{c} (0.0)[0.0]			0.0^{h} (0.0)[0.0]	
	(E)	ΔE_{tot}		0.20 (0.13)[0.10]			2.95 (2.73)[2.70]	
CN	(A)	ΔE_{tot}		0.43 (0.53)[0.59]			0.0^{i} (0.0)[0.0]	
	(E)	ΔE_{tot}		0.0^{d}			0.68 (0.51)[0.47]	

Absolute values for E_{tot} are in a.u. [a] OH(E)–Cy = −309.08360. [b] NH_2(E)–Cy = −289.25439. [c] F(A)–Cy = −333.08114. [d] CN(E)–Cy = −325.96028. [e] OH(A)–THP = −344.90357. [f] NH_2(E)–THP = −325.07308. [g] F(A)–THP = −368.89900. [h] CN(A) = −361.76241. [i] Frequency calculations were not performed because φ had to be kept frozen in geometry optimisation calculations.

was found for the ΔE_{tot} = [E_{tot}(E) − E_{tot}(A)] difference with MP2/6-31+G(d) calculations, which was very close to the value we found (1.24 kcal mol^{-1}). Similar conclusions are extended to the NH_2 substituent, if the ΔE_{tot} difference found in this work (−2.77 kcal mol^{-1}) is compared to that reported by Mo (−2.73 kcal mol^{-1}) using perturbative methods.

For 2-CN–THP, the ΔE_{tot} = [E_{tot}(E) − E_{tot}(A)] found from the HF description (0.68 kcal mol^{-1}) is smaller than that found using MP2/6-311+G(2df,2p) and CCSD(T)/6-311G(2df,p)/MP2/6-311+G-(2df,2p), which are 1.51 and 1.07 kcal mol^{-1}, respectively.[29]

The comparison between the ΔE_{tot} = [E_{tot}(E) − E_{tot}(A)] from a HF description for the F substituent in THP (2.95 kcal mol^{-1}) with that obtained at the MP2/6-31+G(d) level[11] (3.41 kcal mol^{-1}) may be considered as acceptable. For this substituent and the CN substituent, the HF description underestimates the anomeric effect, introducing no artefact, which could magnify it in any of the cases studied. In all cases, corrections for zero point energy, room temperature and entropy have not brought any change to the ordering of the conformers of both anomers.

In Table 2 we report the difference in energy and its components, between the most stable rotamer of each configuration, for each substituent in cyclohexane and THP rings. In this table, kinetic energy (T) was summed with the electrostatic potential energy ($V_{el} = V_{NN} + V_{Ne} + V_{ee}$) to avoid the misleading interpretations that could arise from the individual evaluation of each component because the virial theorem is not exactly verified by non-scaled finite basis set Hartree–Fock solutions. Even for an exact wavefunction, an analysis of the total kinetic energy or the total potential energy is not able to furnish any new information regarding the system because both quantities are strictly related to the total energy and its derivatives at the geometry of interest.

Note that all energy deviations, in all cases, are approximately 0.5 kcal mol^{-1} (see ESI†), characterising a systematic error that in practice is cancelled out when relative quantities like those employed in this work are compared.

Even though the energy components present large values, the energy changes that govern the anomeric effect are small, but of chemical significance. Therefore, it is more preferable to look for a trend among the systems studied than to perform analysis on individual numerical values.

From Table 2, it can be observed that the E configuration is energetically favoured for the OH substituent in the Cy ring, and that approximately 85% of the energy difference among the configurations considered (ΔE_{tot}) is due to electrostatic and kinetic terms ($\Delta T + \Delta V_{el}$). The exchange energy (ΔK) plays no determinant role in this preference because its contribution to ΔE_{tot} is minor. When the same group is introduced into the THP ring, the A anomer becomes favoured over the E one (the anomeric effect). In this new system, while the difference of the quantity ($\Delta T + \Delta V_{el}$) between A and E anomers here has the same value in both rings, K is different in sign and magnitude. In fact, from Table 2, it can easily be observed that the axial preference for an OH substituent in a THP ring arises specifically due to exchange effects.

Table 2 Energy differences between the most stable rotamer of each anomer, in kcal mol^{-1}. The φ value is indicated for OH and NH_2 substituents

		ΔE_{tot} $(\Delta T + \Delta V_{el} + \Delta K)$	ΔT	ΔV_{el}	$\Delta T + \Delta V_{el}$	ΔK
Δ[F(A) − F(E)]	—Cy	−0.20	−6.47	6.10	−0.37	0.17
	—THP	−2.95	−3.38	3.21	−0.18	−2.77
Δ[CN(A) − CN(E)]	—Cy	0.43	0.19	0.73	0.92	−0.49
	—THP	−0.68	0.78	−0.55	0.23	−0.90
Δ[OH(A)59.3° − OH(E)299.6°]	—Cy	0.27	−6.40	6.63	0.23	0.04
Δ[OH(A)55.5° − OH(E)311.2°]	—THP	−1.24	−3.74	3.98	0.23	−1.47
Δ[NH_2(A)59.9° − NH_2(E)181.2°]	—Cy	0.70	−4.57	5.79	1.22	−0.52
Δ[NH_2(A)290.2° − NH_2(E)301.7°]	—THP	2.77	−7.00	10.57	3.57	−0.80

Table 3 Anomeric difference ($\Delta E_{anomeric}$) in kcal mol^{-1}

	6-31G(d,p)				6-31+G(d,p)			
	NH_2	CN	OH	F	NH_2	CN	OH	F
$\Delta E_{anomeric}$(HF)	−2.06	1.11	1.50	2.72	−1.81	1.15	1.55	2.96
$\Delta E_{anomeric}$(HF^0)^a	−2.15	1.07	1.43	2.69	−1.85	1.10	1.46	2.87
$\Delta E_{anomeric}$(MP2)	−2.08	0.96	1.57	2.76	−1.80	1.18	1.73	3.32
$\Delta E_{anomeric}$(CCSD(T))	−2.00	1.00	1.59	2.80	−1.74	1.22	1.73	3.32

[a] HF^0 = unperturbed HF wavefunction in the MP2 calculations.

Conversely, the energetic preference for the E configuration is present in both rings for the NH_2 substituent. In the THP ring, the preference for the E anomer is enhanced when compared to that in the Cy ring (the so-called reverse anomeric effect). Comparing the last two columns for this substituent shows that the exchange contributions, though larger in the most stable rotamer of the A configuration, are not sufficient to make the stability of the A anomer prevail over that of the E anomer when the CH_2 group of the Cy ring is replaced by the O atom in THP. Additionally, the electrostatic energy components, which are more destabilising in the A anomer than in the E anomer in all cases, are much larger in the THP ring than in the Cy ring. This could be related to the presence of two hydrogen atoms bonded to the N atom, and only one lone electron pair (see J and V_{NN} energy components in the ESI†).

For the fluoro group, Table 2 demonstrates that the axial configuration is energetically favoured in both the Cy and THP rings, as also shown, although not clearly discussed, by Mo.[11] It raises the question of whether both cases could be classified as manifestations of the anomeric effect, even in the absence of an electronegative atom Y in the Cy ring. This question is easily answered by examining the last columns of Table 2. When F is the substituent in a Cy ring, the total energy in the absence of the exchange (third column) is responsible for the larger stabilisation of the A configuration. However, in the THP ring, although the same energy terms contribute to stabilise the A anomer, the exchange effects dominate this stabilisation. Therefore, while the F-substituent is favoured in the axial position in both Cy and THP rings, the component of the total energy difference responsible for this stabilisation is different in each case.

The CN substituent is an interesting case because the anomeric effect is present and the characteristic C–Y–C–X moiety is not. In this case, the A anomer is more stable in the THP ring, while the E configuration is more stable in the Cy ring, as expected. Again, the larger value of the exchange component in the A anomer over the E anomer in the THP ring accounts for the higher stability of the A anomer. In fact, this particular result casts some doubt regarding the local character of this effect.

All of the preceding discussion is based on Hartree–Fock calculations. Additionally, MP2 and CCSD(T) calculations were performed for the most stable rotamer of each configuration, to take into account electronic correlations, and therefore achieve a more realistic physical model. The main energetic differences found are reported in Table 3, as the anomeric difference ($\Delta E_{anomeric}$), for the electronic energy (EE) values found from the expression $\Delta E_{anomeric} = \{[\mathrm{EE(THP\_E)} - \mathrm{EE(THP\_A)}] - [\mathrm{EE(Cy\_E)} - \mathrm{EE(Cy\_A)}]\}$.

In Table 3, the discrepancies among the $\Delta E_{anomeric}$ values found for different descriptions for the same chemical group are far below the accuracy of the calculation level employed. Therefore, the anomeric difference can be considered as independent of the theoretical method employed, *i.e.*, electronic correlation plays no determinant role in the anomeric difference, and the HF solutions are sufficient to properly and quantitatively account for this effect.

In Table 2 it is worth noting the change in the φ angle values inside the same rotameric family, when OH and NH_2 substituents are compared in Cy and THP rings. While the most stable rotamers for the OH substituent occur in the same φ region in both the Cy and THP rings, this is not observed when the substituent is an NH_2 group. In this case, the rotamer of the A configuration that corresponds to the global minimum for the Cy ring (φ = 59.9°) is different from the corresponding minimum for the THP ring (φ = 290.2°). A similar situation occurs with the E configuration: the φ angle is 181.2° and 301.7° for the global minimum in the Cy and THP ring, respectively.

Table 4 Energy differences (in kcal mol^{-1}) for an NH_2 group in Cy and THP rings. The most stable rotamers of both anomers are compared

X	E_{tot} $(T + V_{el} + K)$	T	V_{el}	$T + V_{el}$	K
Δ[(A)59.9° − (A)300.9°]-Cy	−1.36	−0.24	−0.11	−0.35	−1.01
Δ[(A)290.2° − (A)58.7°]-THP	−0.40	−1.35	0.59	−0.76	0.36
Δ[(E)181.2° − (E)300.9°]-Cy	−0.17	−0.04	1.10	1.05	−1.22
Δ[(E)301.7° − (E)186.3°]-THP	−4.12	3.59	−6.04	−2.45	−1.67

This particular behaviour prompted us to apply the same energy partitioning analysis to the group of rotamers for the NH_2 substituent. For this group, it is clear from Table 2 that the exchange effects are not responsible for the energetic preference of the E over the A configurations in both rings, but it is not clear whether they are responsible for the changes in the value of the dihedral φ angle for the most stable rotamer that arises from replacing the CH_2 group with an O atom in the ring. Table 4 reports the relative energy values found for the corresponding rotamers of each configuration.

From Table 4 we can see that, for A anomers in a Cy ring, both electrostatic and exchange effects contribute to the stabilisation of the φ = 59.9° rotamer. However, in the THP ring, the order of stability of the rotamers is different, as the system is stabilised only by the $T + V_{el}$ component at φ = 290.2°. For E anomers, the stabilisation that comes from φ = 301.7° in a THP ring is mainly due to electrostatic effects, *i.e.*, a considerable reduction of the nuclear (V_{NN}) and electronic (V_{ee}) repulsion terms. This means that the electrostatic and kinetic energy components are sufficient to explain the stabilisation of the E over the A configuration in NH_2–Cy and 2-NH_2–THP independently of the changes in the φ values, and that the anomeric effect (or the reverse anomeric effect), as proposed in this work, has nothing to do with this conformational preference.

Exchange energy and the anomeric effect

Fig. 3 reports the values of ΔK, $\Delta T + \Delta V_{el}$ and ΔE_{tot}, where $\Delta = X_{\text{most stable rotamer (A)}} - X_{\text{most stable rotamer (E)}}$, is ordered by the anomeric effect intensity as a function of the substituent considered. Therefore, when ΔE_{tot} is negative, the A configuration is more stable than the E configuration.

It can be observed from Fig. 3 that, for Cy rings, the relative total energy (ΔE_{tot}) curve follows the $\Delta T + \Delta V_{el}$ curve for all substituents, which means that the electrostatic and kinetic terms dominate the energy differences between the A and E configurations. In contrast, ΔE_{tot} follows $\Delta T + \Delta V_{el}$ only for 2-NH_2–THP, which does not experience an anomeric effect. Starting from the system with the 2-CN substituent, *i.e.*, the group with the least intense anomeric effect of all the compounds studied, ΔE_{tot} follows the exchange component (K) instead.

The exchange effects (K) for each compound and the summation of K_{ij} terms in eqn (1) spontaneously emerge from the action of the Hamiltonian operator over an antisymmetric wavefunction, a necessary condition because electrons are fermions. K is an eminently quantum-mechanical quantity, which receives contribution from all electrons of the system with the same spin, and has no classical analogue. It is a stabilising term that has its origin in the same two-electron operator from which the electronic repulsion (J) also appears. Although K is a global quantity, it may receive larger contributions from functional groups that are close to each other, but not necessarily bonded because it is proportional to $1/r_{ij}$, *i.e.*, the inverse of the distance between electrons with the same spin considered in each K_{ij} term.

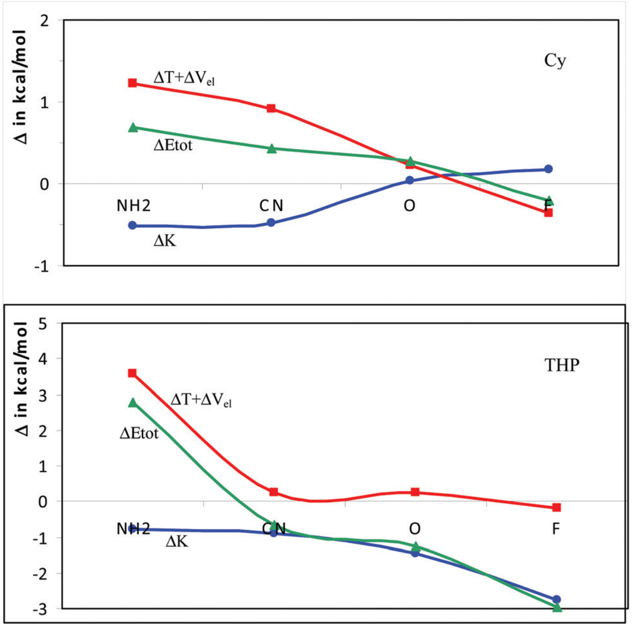

Fig. 3 ΔK, $\Delta T + \Delta V_{el}$ and ΔE_{tot} anomeric difference, as a function of the substituent in THP and Cy rings.

This analysis strongly suggests that the so-called anomeric effect is related to a stabilisation of the A anomer when a Y heteroatom with at least two electron lone pairs replaces a C atom in the ring and the XW group has a large electronic density. Such stabilisation comes from exchange effects and has absolutely no electrostatic origin, in contrast to what was supposed by Mo,[11] ourselves,[30] and all those in favour of the "rabbit-ear" effect, which relies on a purely electrostatic basis. Similar results for the ethane barrier between the staggered and eclipsed forms were found by Mo and co-workers,[15] and suggested by Karplus and co-workers,[31] a long time ago. In fact, the ΔK values linearly correlate with the ΔE values inside each A and E rotameric family of OH anomers (see ESI†).

A similar analysis performed for the MP2 energy values is reported in the ESI.† No appreciable differences were found with regard to the prevalence of exchange effects in this description.

Basis set size and the anomeric effect

Some time ago, Molteni and Parrinello[32] mentioned a reduction of the theoretically predicted anomeric effect as the size of the basis set increases, casting some doubts about its existence in the gas-phase. However, recent reports from Simons and co-workers show that, in a solvent free environment,[33] the preference for the A anomer is still experimentally observed. Thus, a reliable gas-phase model of the anomeric effect must be able to properly describe this preference. A more detailed investigation of the influence of the basis set size on the energetic differences shows that the smallest basis set able to describe all important terms that determine the behaviour of these systems is the 6-31G(d,p) basis set.[34] All of the studies mentioned by Molteni and Parrinello refer to comparisons between this basis set and smaller ones.[35,36]

To better understand the influence of the basis set on the computation of the anomeric effect, new geometry optimisation calculations were performed for the 2-F– and 2-OH–THP compounds with different basis sets. In the latter case, these calculations were performed only for the most stable rotamer of each anomer. From Fig. 4, we can determine that, for the 2-F–THP description using Pople's basis set family, the anomeric difference slightly decreases as the quality of the basis set is improved from 4-31G(d,p) to 6-311G(d,p). However, the changes are almost negligible, and the values for the anomeric difference are acceptable in all cases. Even for the smallest anomeric difference (obtained with the 6-311G(d,p) basis set), the predominance of exchange effects is still observed and is responsible for approximately 2/3 of the final total energy difference value. It is important to note that, in the Pople family, the 4-31G(d,p) basis set shows the highest (and the only positive) value for the ΔV_{el} component, whereas ΔK presents its most prominent value.

The anomeric difference in 2-OH–THP is less sensitive to the size of the basis set than in 2-F–THP within the Pople family, presenting almost negligible fluctuations as the size of the basis set increases. In all cases the exchange effects dominate ΔE_{tot} between the considered anomers.

The same trend is not reproduced in the Dunning–Huzinaga basis set family, but two cases might not be enough to allow for a more definite conclusion about the behaviour of this basis set family. Curiously, both compounds present the same behaviour when this basis set is used.

Geometric aspects

Some geometric evidence related to the anomeric effect refers to a decrease in the length of the Y–C bond (O5–C1, in the compounds studied) in the preferential A anomer, when compared to the same bond in the E anomer. This decrease in bond length is accompanied by an increase of the C–X bond length (C1–X, in Fig. 1). The absolute values for bond distances can be found in the ESI† and are in good agreement with previous studies of the same systems.[11,13,29] Fig. 5 reports the differences in bond lengths between the A and E anomers for all THP derivatives studied in this work. In the case of the OH and NH_2 substituents, the values for the most stable rotamer are reported.

As observed in Fig. 5, the geometric features of the anomeric effect are well described at the HF level. These geometric features are an increase in the C5–O5 and C1–X bond lengths and a decrease in the O5–C1 bond length in the A anomer when compared to the corresponding parameters in the E anomer for the F, OH and CN substituents. Note that the NH_2 substituent does not show the same trend, as expected because it does not show the anomeric effect. The intensity of the changes correlates with the intensity of the anomeric effect, which is dependent upon the substituent. In our proposal, because exchange effects are responsible for the anomeric effect, they might be related to this bond length shortening. As already mentioned, K receives contributions from all electrons with the same spin. Therefore, even though it has a global character, these exchange effects may receive larger

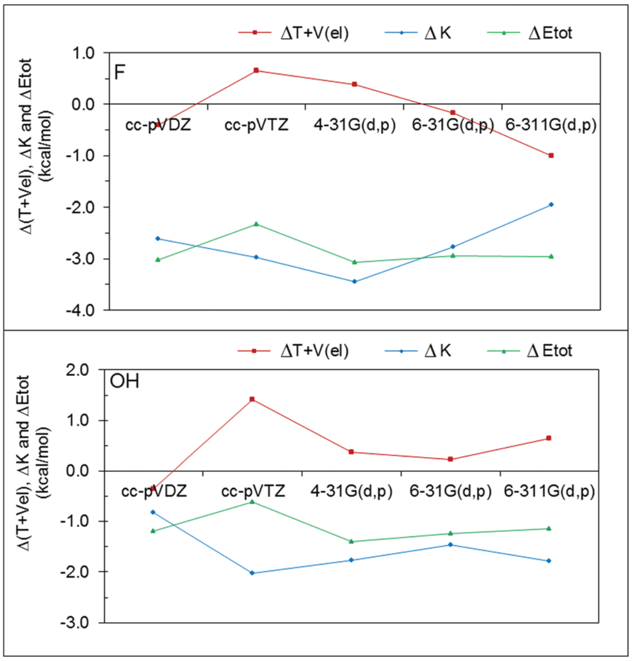

Fig. 4 Effects of the basis set on the anomeric difference for 2-F–THP and 2-OH–THP.

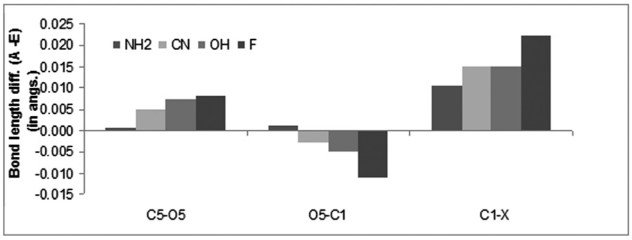

Fig. 5 Bond length differences (A–E), in Å for 2-NH_2–, 2-CN–, 2-OH– and 2-F–THP compounds.

Table 5 Electronic energy in the gas-phase (E_{gas}), electrostatic component of the energy in solution (G_{elec}), energy of the solvated system (G_{solv}), solvation energy ($\Delta G_{(Solv\text{-}Gas)}$), dipole moment ($\mu$), standard enthalpy of the solvated system ($H°_{298.15\ K}$), entropic contribution (–TS), and standard Gibbs free energy ($G°_{298.15\ K}$) of the solvated system

	2-OH–THP			2-F–THP		
	Axial	Equatorial	Δ(A–E) kcal mol^{-1}	Axial	Equatorial	Δ(A–E) kcal mol^{-1}
E_{gas} (a.u.)	−344.90357	−344.90160	−1.24	−368.89900	−368.89431	−2.95
G_{elec} (a.u.)	−344.91114	−344.91047	−0.42	−368.90465	−368.90160	−1.92
G_{solv} (a.u.)	−344.90999	−344.90955	−0.28	−368.90379	−368.90088	−1.82
$\Delta G_{(Solv\text{-}Gas)}$ (kcal mol^{-1})	4.03	4.99		3.01	4.12	
μ (D)	0.42	2.83		2.58	4.13	
$H°_{298.15K}$ (a.u.)	−344.74098	−344.74091	−0.05	−368.74840	−368.74574	−1.67
–TS (kcal mol^{-1})	−23.13	−23.29	0.16	−22.86	−22.90	0.04
$G°_{298.15K}$ (a.u.)	−344.77784	−344.77802	0.11	−368.78482	−368.78223	−1.63

contributions from some functional groups located in particular regions of the molecule. Such regions suffer the impact of these interactions in their geometries. In fact, in the literature there are indications that exchange effects decrease some bond lengths.[37,38]

Preliminary comments about solvation

Because this work proposes that the anomeric effect has no electrostatic basis, it is important to rationalise some of the solvation aspects related to the experimental evidence that the E anomer is preferred over the A anomer in systems which present the anomeric effect, in the presence of solvents with high permittivity values.

The stereoelectronic proposal for the origin of the anomeric effect suggests that the prevalence of the E anomer over the A anomer is a consequence of the minimisation of the supposed electrostatic repulsion between the lone pairs of X and Y atoms due to their interaction with the solvent. Such a proposition assumes that the anomeric effect is depreciated in polar solvents. However, another possible explanation for the preference for the E anomer in polar solvents is that a different effect may appear in polar solvents, which is in competition with the anomeric effect and stabilises the E anomers more than the A anomers. To further investigate both possibilities, the most stable rotamer of each anomer of 2-OH–THP and both anomers of 2-F–THP were described in aqueous solution, using the integral equation version[39] of the Polarizable Continuum Model (PCM).[40] The solvation was restricted to these two anomers of 2-OH–THP because they are also the most stable ones in aqueous solutions.[13]

In the PCM, the solute is immersed in a cavity opened inside a continuum dielectric. This cavity has a molecular shape, defined by interlocking spheres centered on atoms or groups of atoms. The radii of the spheres used in this work are 2.40 Å for CH or CH_2 groups, 1.76 Å for fluorine, 1.80 Å for oxygen atoms and 1.44 Å for the hydrogen atoms of the hydroxyl group.[41] The polarisation of the solvent due to solute presence is described by charges located on the cavity surface, regularly tessellated in small area units. The energy of the solvated system (G_{solv}) is defined by the sum of electrostatic (G_{elec}) and non-electrostatic ($G_{non\text{-}elec}$) components. The non-electrostatic component is obtained as a sum of the cavitation, repulsion and dispersion components. The computational code used to describe the solvated anomers was Gaussian03.[42]

In Table 5, some energetic quantities related to the solvation process of 2-OH– and 2-F–THP are reported.

From Table 5 it can be observed that, for the OH substituent, the E anomer has a higher dipole moment than the A anomer. As a consequence of this, it is most likely better solvated than the A anomer. The E anomer has a decrease in energy upon solvation of 4.99 kcal mol^{-1}, while the decrease for the A anomer is 4.03 kcal mol^{-1}. However, although the E anomer is more stabilised than the A anomer in aqueous solution, this predominantly electrostatic stabilisation is not enough to eliminate the preference for the axial anomer at equilibrium. The anomeric ratio is shifted in favour of the E anomer only after entropic contributions are incorporated into the quantitative description. These findings are in complete agreement with other results using different solvation models for the same system,[13] and with our unpublished results for xylose and glucose solutions. Similar observations regarding differences in the solvation patterns of equatorial and axial anomers are also made by Molteni and Parrinello.[32]

For the F substituent, the same pattern is observed: the E anomer has a higher dipole moment than the A anomer, and its stabilisation from solvation is 4.12 kcal mol^{-1}, while that of the A anomer is 3.01 kcal mol^{-1}. However, the entropy in an aqueous solution of the E anomer is not much greater than that of the A anomer and is not able to eliminate the preference for the A anomer. As for the OH substituent, electrostatic interactions stabilise the E anomers more than the A anomers. However, this is not necessarily related to the supposed lone pair repulsions, which would, in theory, be the cause of the anomeric effect. If this were true, the anomeric effect in 2-F–THP would be more intense than in 2-OH–THP because the repulsion between the X–Y lone pairs would be greater, and the stabilisation in polar solvents would be more efficient than for the 2-OH–THP compound.

As a final remark, to reinforce the idea that the preference of E anomers over A anomers in polar solvents is not only due to solute–solvent electrostatic interactions, it is important to recall that there are some monosaccharides like mannose and lyxose (C2-epimers of glucose and xylose, respectively) which present A : E anomeric ratios in aqueous solution[10] of 65 : 35

and 71 : 29. They, of course, demonstrate an anomeric effect, which is apparently preserved in aqueous solution.

The previous discussion is very preliminary, but was presented here to show that the experimental evidence related to the solvation of molecules which present anomeric effects does not contradict the hypothesis of a non-electrostatic origin for the anomeric effect. It is important to mention that all energetic quantities evaluated in Table 5 are very small, and need to be more deeply investigated, not only with more accurate methods, but especially in different systems, to better determine the trend for different molecules. This work is in progress for glucose and xylose monosaccharides, systems where the number of physically relevant conformations for each anomer is greater than in the molecules analysed here.[4,9a]

Nevertheless, this discussion provides a possible alternative to the purely electrostatic model involving solvation, which is not able to completely explain experimental data concerning the behaviour of these systems in solution.

Conclusions

Taking into account the discussion presented, it is possible, at least in the context of the Hartree–Fock theory, to make a clear distinction between the two supposedly related anomeric and reverse anomeric effects. The anomeric effect has its origin in the exchange terms of the energy, and has no electrostatic origin. In turn, the reverse anomeric effect is merely the consequence of differences in the electrostatic potential and the kinetic energy ($T + V_{\mathrm{el}}$) between differing geometries.

The explanation presented here for the anomeric effect has two implications: it establishes a physical model that is able to properly quantify this effect, and it is a serious candidate for replacing its empirical definition, which was inspired by experimentally determined equilibrium compositions and only makes use of an unexpected behaviour with respect to bond distances and the preferred molecular conformations. Though qualitatively useful, the empirical definition is purely phenomenological and prevents a deeper understanding of the matter at hand.

Clearly, a more detailed investigation is needed to verify our hypothesis. For instance, it is necessary to access the contributions of each electronic pair to K to better evaluate the contributions of the functional group to the global character of this quantity. Another relevant question to be addressed is why the A anomer has exchange effects magnified with respect to the E anomer. However, the correlations between ΔE_{tot} and ΔK that were highlighted remain unchanged independently of the answers to these questions.

Notes and references

1 V. S. R. Rao, P. K. Qasba, P. V. Baslaji and R. Chandrasekaran, in *Conformation of Carbohydrates*, Hardwood Academic, Amsterdam, 1998.
2 C. O. Silva, A. O. Menezes, A. V. Coelho, V. O. Paralovo and C. S. Soares, in *Strategies for the Determination of Carbohydrate Structure and Conformation*, ed. H. Verli, Transworld Research Network, Kerala, 2010, ch. 1, pp. 1–37.
3 M. R. Wormald, A. J. Petrescu, Y.-L. Pao, A. Glithero, T. Elliott and R. A. Dwek, *Chem. Rev.*, 2002, **102**, 371–386.
4 (*a*) R. R. Andrade and C. O. da Silva, *Carbohydr. Res.*, 2012, **350**, 62–67; (*b*) C. O. da Silva and B. Mennucci, *J. Chem. Theory Comput.*, 2007, **3**, 62–70.
5 J. T. Edward, *Chem. Ind. (London)*, 1955, 1102–1104.
6 R. U. Lemieux and P. Chü, *133rd National Meeting of the American Chemical Society*, 1958, 31N.
7 I. Tvaroška and T. Bleha, *Adv. Carbohydr. Chem. Biochem.*, 1989, **47**, 45–123.
8 E. Juaristi and G. Cuevas, *Tetrahedron*, 1992, **48**, 5019–5087.
9 (*a*) C. O. da Silva, B. Mennucciand and T. Vreven, *J. Org. Chem.*, 2004, **69**, 8161–8164; (*b*) J. C. Corchado, M. L. Sanchez and M. A. Aguilar, *J. Am. Chem. Soc.*, 2004, **126**, 7311–7319.
10 K. Matsuo and K. Gekko, *Carbohydr. Res.*, 2004, **339**, 591–597.
11 Y. Mo, *Nature Chem.*, 2010, **2**, 666–671.
12 J. K. Badenhoop and F. Weinhold, *J. Chem. Phys.*, 1997, **107**, 5406–5421.
13 I. Tvaroška and J. P. Carver, *Carbohydr. Res.*, 1998, **309**, 1–9.
14 F. M. Bickelhaupt and E. J. Baerends, *Angew. Chem., Int. Ed.*, 2003, **42**, 4183–4188.
15 Y. Mo, W. Wu, L. Song, M. Lin, Q. Zhang and J. Gao, *Angew. Chem., Int. Ed.*, 2004, **43**, 1986–1990.
16 F. Weinhold, *Angew. Chem., Int. Ed.*, 2003, **42**, 4188–4194.
17 V. F. Weisskopf, *Science*, 1975, **187**, 605–612.
18 Y. Huang, A.-G. Zhong, Q. Yang and S. Liu, *J. Chem. Phys.*, 2011, **134**, 084103, DOI: 10.1063/1.3555760.
19 E. P. Raman, O. Guvench and A. D. MacKerell Jr., *J. Phys. Chem. B*, 2010, **114**, 12981–12994.
20 (*a*) H. Booth, K. A. Khedhair and S. A. Readshaw, *Tetrahedron*, 1987, **43**, 4699–4723; (*b*) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, 1968, **33**, 3754–3758.
21 *Jaguar, version 7.6, Schrödinger*, LLC, New York NY, 2009.
22 (*a*) J. A. Pople, J. S. Binkley and R. Seeger, *Int. J. Quantum Chem.*, 1976, **S10**, 1–19; (*b*) M. J. Frisch, M. Head-Gordon and J. A. Pople, *Chem. Phys. Lett.*, 1990, **166**, 275–280; (*c*) C. M. Aikens, S. P. Webb, R. L. Bell, G. D. Fletcher, M. W. Schmidt and M. S. Gordon, *Theor. Chem. Acc.*, 2003, **110**, 233–253.
23 P. Piecuch, S. A. Kucharski, K. Kowalski and M. Musial, *Comput. Phys. Commun.*, 2002, **149**, 71–96.
24 GAMESS v.25mar2010 (R2); M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1347–1363.
25 A. M. Silva, E. C. da Silva and C. O. da Silva, *Carbohydr. Res.*, 2006, **341**, 1029–1040.
26 I. Tvaroška and J. P. Carver, *J. Phys. Chem.*, 1994, **98**, 6452–6458.

27 I. Tvaroška and J. P. Carver, *J. Phys. Chem.*, 1994, **98**, 9477–9485.

28 S. E. Barrows, F. J. Dulles, C. J. Cramer, A. D. French and D. G. Truhlar, *Carbohydr. Res.*, 1995, **276**, 219–251.

29 M. H. Benn, Y. Y. Huang, F. Johannsen, M. O'Reilly, M. Parvez, A. Rauk and T. Sorensen, *Can. J. Chem.*, 2010, **88**, 831–838.

30 R. S. Bitzer, A. G. H. Barbosa, C. O. da Silva and M. A. C. Nascimento, *Carbohydr. Res.*, 2005, **340**, 2171–2184.

31 O. J. Sovers, C. W. Kern, R. M. Pitzer and M. Karplus, *J. Chem. Phys.*, 1968, **49**, 2592–2599.

32 C. Molteni and M. Parrinello, *J. Am. Chem. Soc.*, 1998, **120**, 2168–2171.

33 E. J. Cocinero, P. Çarçabal, T. D. Vaden, J. P. Simons and B. G. Davis, *Nature*, 2011, **469**, 76–80.

34 (*a*) G. I. Csonka, *J. Mol. Struct. (THEOCHEM)*, 2002, **584**, 1–4; (*b*) G. I. Csonka, A. D. French, G. P. Johnson and C. A. Stortz, *J. Chem. Theory Comput.*, 2009, **5**, 679–692.

35 P. L. Polavarapu and C. S. Ewig, *J. Comput. Chem.*, 1992, **13**, 1255–1261.

36 K. A. Jebber, K. Zhang, C. J. Cassady and A. Chung-Phillips, *J. Am. Chem. Soc.*, 1996, **118**, 10515–10524.

37 S. A. Egorov, N. H. March and R. Santamaria, *Int. J. Quantum Chem.*, 1992, **42**, 1641–1649.

38 R. A. Ballinger and N. H. March, *Nature*, 1954, **174**, 179.

39 B. Mennucci, E. Cancès and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032–3041.

40 R. Cammi and J. Tomasi, *J. Comput. Chem.*, 1995, **16**, 1449–1458.

41 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–451.

42 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03 (Revision C.01)*, Gaussian, Inc., Wallingford CT, 2004.