

# Computational evidence that hyperconjugative interactions are not responsible for the anomeric effect

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**The 'anomeric effect' is the thermodynamic preference for polar substituents to occupy the axial position in the chair conformation of various heterocycles. The most common explanation given for this effect at present is hyperconjugation from the lone pairs on the ring heteroatom to the antibonding orbital between the anomeric carbon and its linking substituent. Alternatively, the anomeric effect could be explained by intramolecular electrostatic interactions between local dipoles. Few models can provide convincing data for either theory at the quantum-mechanical level. Now, using the extended block-localized wavefunction method, which is the simplest form of valence bond theory, we have evaluated the degree of hyperconjugation in various compounds that display the anomeric effect and have interpreted their conformational preferences in terms of steric, hyperconjugation and dispersion effects. The results provide strong evidence that hyperconjugative interactions are not responsible for the anomeric effect and that it is better interpreted in terms of electrostatic interactions.**

The 'anomeric effect' is a stereoelectronic effect that was discovered by Edward<sup>1</sup> in 1955 while studying carbohydrates; the term was later coined by Lemieux and Chü<sup>2</sup> in 1958. It refers to the thermodynamic preference for electronegative (polar) substituents bonded to C<sub>1</sub> (the anomeric carbon shown in Fig. 1 in a substituted tetrahydropyran) to take up an axial position ( $\alpha$ -anomer) rather than an equatorial position ( $\beta$ -anomer) in the chair conformation of a monosaccharide<sup>3</sup>. The anomeric centre is critical to the reactivity of carbohydrates because it is the site at which ring opening occurs, producing the important functional carbonyl group. The preference for the  $\alpha$ -anomer diastereomer increases as the electron-withdrawing capability of the anomeric substituent Y increases. When Y is a carbon atom substituent such as a methyl group, however, the  $\beta$ -anomer is favoured so that steric repulsions between the ring and the substituent are minimized.

Although the anomeric effect was initially found in carbohydrates and ubiquitously exists in monosaccharides and their derivatives, the concept has now been generalized to saturated heterocycles and acyclic systems containing heteroatoms. Many experimental and theoretical studies have been conducted regarding the understanding and utilization of this peculiar effect<sup>4–9</sup>, which plays a central role in conformational analysis in modern organic chemistry<sup>10</sup>.

The most intriguing issue surrounding the anomeric effect is why it occurs. When Edward<sup>1</sup> proposed the anomeric effect, he intuitively linked it to the lone pairs on the ring oxygen. This idea later developed into the electrostatic model, which states that the preference for the  $\alpha$ -anomer arises from the favourable local dipole–dipole interaction, as illustrated in Fig. 2a (ref. 11). This electrostatic model is in agreement with the experimental evidence, which suggests that aqueous solvation effects stabilize the  $\beta$ -anomer and thus reduce anomeric stabilization in many systems such as tetrahydropyranosyls<sup>12,13</sup>. It has also been claimed that the electrostatic model is unable to explain the variations in bond distances and angles around the anomeric carbon atom, such as the shortening of the O–C<sub>1</sub> bond and the lengthening of the C<sub>1</sub>–Y

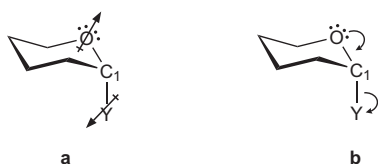
bond<sup>14</sup>. However, this has been refuted by Perrin and colleagues, who showed that the electrostatic model can rationalize the geometrical variations at least in 2-methoxy-1,3-dimethylhexahydropyrimidine<sup>15</sup>. Further refinements of this electrostatic model include the consideration of favourable C–H...O hydrogen bonds<sup>16</sup>.

An alternative and popular rationalization of the anomeric effect is based on electron delocalization from the oxygen lone pairs to the vacant antibonding orbital  $\sigma_{\text{CY}}^*$  (Fig. 2b)<sup>17</sup>. This kind of  $n \rightarrow \sigma^*$  negative hyperconjugative interaction can explain the geometry changes, because the electron delocalization increases the double-bond character of the O–C<sub>1</sub> bond but weakens the C<sub>1</sub>–Y bond. The hyperconjugation model, however, is inconsistent with the reverse anomeric effect, where the equatorial conformation is preferred<sup>5,18</sup>, and some researchers have questioned the validity of the  $n \rightarrow \sigma^*$  hyperconjugation model<sup>16,19</sup>. A compromise that takes into account such different views is that both the dipole–dipole and hyperconjugative interactions contribute to the anomeric effect<sup>18</sup>.

Although extensive computational studies have correctly described and predicted the conformational features of compounds exhibiting the anomeric effect, few have been able to differentiate various factors such as steric (Pauli exchange), electrostatic and electronic interactions at the quantum-mechanical level. Individual estimates of various interactions can provide deep insights into the origin of the anomeric effect. Perrin and colleagues examined the change in the anomeric effect when the oxygen of an anomeric molecule was replaced by nitrogen<sup>15</sup>. Owing to its lower electronegativity when compared with oxygen, nitrogen would have weaker electrostatic interactions and stronger hyperconjugative interactions. The results revealed that the anomeric effect is weaker in the nitrogen analogue and that 2-aminotetrahydropyran exhibits the reverse anomeric effect<sup>20</sup>, suggesting that electrostatic interactions predominate. However, the hyperconjugation model is greatly supported by direct computations of the  $n \rightarrow \sigma^*$  and  $\sigma \rightarrow \sigma^*$  stabilization energies based on the natural bond orbital (NBO) method<sup>21</sup>. It has been pointed out, however, that the NBO method tends to highly overestimate stabilizing electron



**Figure 1 | Anomeric effect in substituted tetrahydropyran.** The anomeric effect refers to the preference for polar substituents to occupy the axial, rather than equatorial, position in a chair conformation. This is illustrated here with the thermodynamic equilibrium between  $\alpha$  (right side) and  $\beta$  (left side) anomers of a substituted tetrahydropyran where Y is an electronegative substituent.



**Figure 2 | Two most common explanations for the anomeric effect.** **a**, The electrostatic model states that the preference for the  $\alpha$ -anomer arises from favourable local dipole–dipole interactions. **b**, The hyperconjugation model is based on the stabilization gained from electron delocalization from the oxygen lone pairs to the vacant antibonding orbital  $\sigma_{C_1Y}^*$ .

delocalization energies (DEs) due to the non-optimization of bond orbitals, as exemplified by the recent controversy over the nature of the ethane rotation barrier<sup>22–26</sup>.

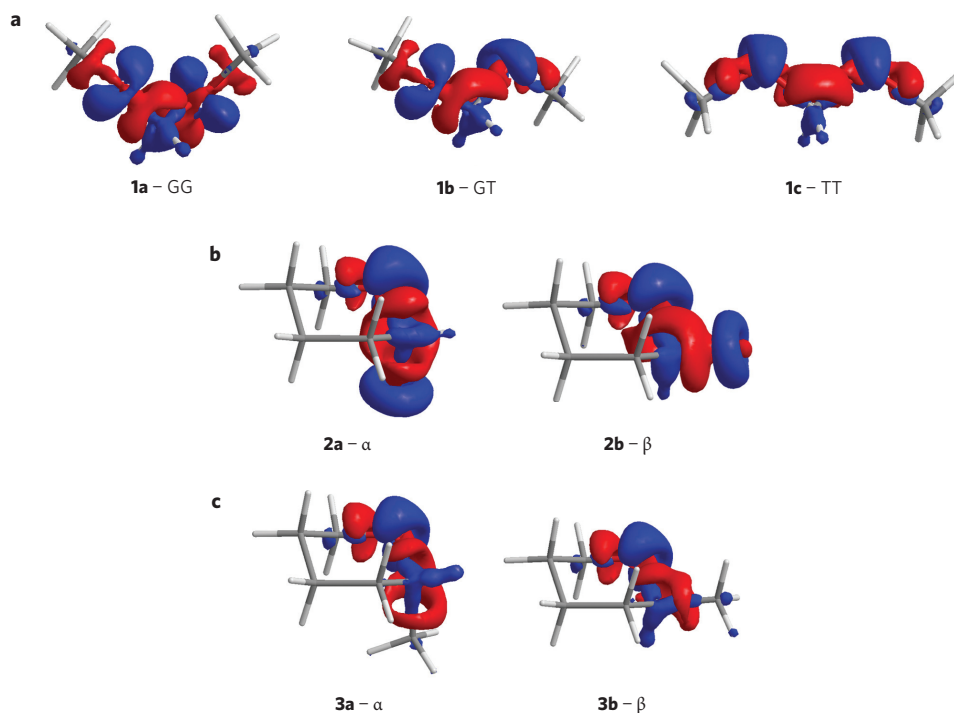
One plausible way by which to determine the impact of conjugative and hyperconjugative electron delocalization is to use *ab initio* valence bond (VB) theory<sup>27,28</sup>, which can define wavefunctions for individual resonance structures. Among all possible resonance structures with electrons strictly localized on bonds or atoms, the one with the lowest energy is taken as the reference to measure the electron delocalization effect<sup>29</sup>. Although *ab initio* VB

methods are computationally demanding due to the non-orthogonality of orbitals, the introduction of doubly occupied (a feature of molecular orbital (MO) theory) but strictly localized (a feature of VB theory) bond orbitals can significantly simplify the computational process. Following this strategy, the wavefunction of an electron-localized reference Lewis structure can be derived by partitioning the system into several mutually interacting subgroups and restricting the expansion of each MO in only one subspace. All block-localized MOs are self-consistently optimized<sup>30–35</sup>. Our block-localized wavefunction (BLW) method can not only decompose the intermolecular interaction energy into a few physically meaningful terms<sup>36</sup>, but can also probe the electron delocalization within a molecule. Similar approaches have been successfully applied by others to study conjugation and hyperconjugation effects<sup>23,37–41</sup>.

In this work, we studied molecules that exemplify the anomeric effect, including dimethoxymethane and substituted tetrahydropyrans, as well as the reference molecules dimethyl ether, tetrahydropyrans and substituted cyclohexanes, which have no anomeric effect. The BLW method was applied to these systems to quantify the electron delocalization and steric effects and subsequently critically examine the role of hyperconjugative interactions in the anomeric effect.

## Results

**Dimethoxymethane.** Dimethoxymethane is the simplest example with which to illustrate the anomeric effect: its *gauche* conformation around the C–O bonds is more stable than the *trans* conformation. Moreover, as there are two anomeric centres, the most stable conformer, namely the *gauche–gauche* (GG) conformer shown in Fig. 3 (1a), is 3–5 kcal mol<sup>−1</sup> more stable than 1c the *trans–trans* (TT) conformer; this effect is about twice as big as that in sugars. Dimethoxymethane has therefore been widely selected as the prototype for computational studies on the anomeric effect<sup>19,42–44</sup>.



**Figure 3 | Electron density difference (EDD) maps showing electron delocalization within compounds displaying the anomeric effect.** **a–c**, Electron delocalization between the oxygen atoms and methyl groups in dimethoxymethane (GG, GT and TT conformers, isodensity 0.003 a.u.) (**a**), the oxygen atom and substituted groups in 2-fluorotetrahydropyran ( $\alpha$ - and  $\beta$ -anomers, isodensity 0.002 a.u.) (**b**) and the oxygen atom and substituted groups in 2-methyltetrahydropyran ( $\alpha$ - and  $\beta$ -anomers, isodensity 0.002 a.u.) (**c**). The red colour denotes a gain and the blue colour a loss of electron density.

**Table 1 | Absolute energies and relative and delocalization energies for various conformers of dimethoxymethane.**

Basis Set	Conformer	$E(\Psi^{\text{Del}}, \text{MP2})$	$E(\Psi^{\text{Del}}, \text{HF})$	$E(\Phi_L, \text{BLW})$	DE* (kcal mol <sup>-1</sup> )
6-31 + G(d)	GG	-268.71788	-267.95848	-267.87335	53.42
	GT	3.37	2.32	2.82	53.92
	TT	7.52	5.52	6.48	54.38
6-311 + G(d,p)	GG	-268.88891	-268.03024	-267.93984	56.72
	GT	2.74	2.07	2.94	57.59
	TT	6.56	5.20	7.02	58.55

For GG,  $E$  is given as absolute values in Hartree; for GT and TT,  $E$  is given as values relative to GG in kcal mol<sup>-1</sup>. \*DE =  $E(\Phi_L, \text{BLW}) - E(\Psi^{\text{Del}}, \text{HF})$ .

**Table 2 | Absolute energies (a.u.) of  $\alpha$ -anomers and relative energies of  $\beta$ -anomers and the delocalization energies in substituted tetrahydropyrans (C<sub>5</sub>OH<sub>2</sub>Y, Y = F, OH, Cl, NH<sub>2</sub> and CH<sub>3</sub>).**

Y	Anomer	$E(\Psi^{\text{Del}}, \text{MP2})$	$E(\Psi^{\text{Del}}, \text{HF})$	$E(\Phi_L, \text{BLW})$	DE (kcal mol <sup>-1</sup> )
F	$\alpha$	-369.90446	-368.89261	-368.83684	35.00
	$\beta$	3.41	2.80	3.46	35.66
OH	$\alpha$	-345.91027	-344.88796	-344.83107	35.69
	$\beta$	1.32	0.77	2.19	37.11
Cl	$\alpha$	-729.90042	-728.92888	-728.87242	35.43
	$\beta$	2.69	2.46	1.76	34.73
NH <sub>2</sub>	$\alpha$	-326.06039	-325.05242	-324.99628	35.23
	$\beta$	-2.73	-3.07	-2.45	35.84
CH <sub>3</sub>	$\alpha$	-310.02913	-309.05549	-309.00804	29.77
	$\beta$	-3.30	-3.48	-2.31	30.95

We investigated three stationary structures of dimethoxymethane—GG, GT (*gauche-trans*) and TT—the geometries of which were optimized at the MP2/6-31 + G(d) level (second-order Møller–Plesset (MP2) theory is an electron-correlated method compared with the Hartree–Fock (HF) approximation). Of these structures, GG represents the ground state, but all show no imaginary frequency. Table 1 presents a compilation of the relative MP2 and HF energies of these three conformers with the basis sets of 6-31 + G(d) and 6-311 + G(d,p). Because enlargement of the basis set reduces the relative energies at the correlated MP2 level more than at the uncorrelated HF level, we conclude that electron correlation increases the preference for a *gauche* conformer. This is due to the dispersion effect, which favours close contact between functional groups in *gauche* conformers.

As our interests lie in the  $n \rightarrow \sigma^*$  hyperconjugative interactions, we built the BLW of the primary Lewis structure where all electrons are strictly localized on their respective functional groups. In other words, all electron delocalization effects are deactivated. For the case of dimethoxymethane (for which the partition scheme is outlined in the Supplementary Information), we localized the C–H bonds within their own methyl or methylene groups, while constraining the oxygen lone electron pairs to individual oxygen atoms. Finally, each C–O  $\sigma$  bond was strictly localized between the two bonding atoms. Nine blocks were defined, each containing an even number of electrons. Any MO was expanded within only one block or subgroup and doubly occupied. Energies of the strictly localized structures,  $E(\Phi_L)$ , and the regular HF energy  $E(\Psi^{\text{Del}})$  are listed in Table 1. The energy difference DE between BLW and HF represents the magnitude of electron delocalization. However, it should be noted that DE includes not only the vicinal  $n \rightarrow \sigma^*$  and  $\sigma \rightarrow \sigma^*$  hyperconjugative interactions, but also the geminal interactions among the bonds sharing common apex atoms<sup>45</sup>. The hyperconjugative and geminal interactions occur simultaneously and in general cannot effectively be separated, but the latter are essentially conserved in different conformers. Computational results with the basis sets 6-31G(d) and 6-311 + G(d,p) are presented in Table 1.

Although a modest basis set effect was observed, the most significant finding is that the DEs are very comparable for all conformers. In fact, the overall delocalization stabilization in the *trans* conformer is even slightly greater than in the *gauche* conformer. For example,

with the 6-311 + G(d,p) basis set the DE values for conformers GG, GT and TT are 56.7, 57.6 and 58.6 kcal mol<sup>-1</sup>, respectively, indicating that each *trans* structure is nearly 1 kcal mol<sup>-1</sup> more stable than the *gauche* structure as a result of electron delocalization. This is completely different from the popular hyperconjugation model, suggesting that the overall stability of the GG conformer relative to the TT conformer must not result from hyperconjugative interactions. It should be stressed that when we claim that hyperconjugation is not responsible for the anomeric effect, we are not denying the existence of this important interaction within molecules. This is quite similar to the case of ethane, for which it was found that hyperconjugation between two methyl groups makes a secondary contribution (0.7–0.8 kcal mol<sup>-1</sup>) to the rotation barrier (3.0 kcal mol<sup>-1</sup>), but in both eclipsed and staggered conformers there are still considerable hyperconjugative interactions (5.6–7.3 kcal mol<sup>-1</sup>)<sup>26</sup>.

**Substituted tetrahydropyrans (C<sub>5</sub>OH<sub>2</sub>Y; Y = F, OH, Cl, NH<sub>2</sub> and CH<sub>3</sub>).** Among the five substituted tetrahydropyrans, 2-fluorotetrahydropyran, 2-chlorotetrahydropyran and 2-tetrahydropyranol favour the  $\alpha$ -anomers, thus exhibiting a significant anomeric effect, as shown in Table 2. 2-Aminotetrahydropyran and 2-methyltetrahydropyran, however, are more stable with the  $\beta$ -anomer. In particular, the reverse anomeric effect in 2-aminotetrahydropyran is well known both computationally and experimentally, and steric repulsions have been cited as the cause<sup>20</sup>. This indicates that the dipole of the substituent as shown in Fig. 2 is not determined by the polarity of the C<sub>1</sub>–Y bond alone, but also by the lone pair(s) and other atoms within the substituent group. Electron correlation is more pronounced in  $\alpha$ -anomers than in their corresponding  $\beta$ -anomers, indicating the stabilizing role of dispersion in more crowded conformers. Overall, the strength of the anomeric effect is dictated by the identity of the substituents in the following order, F > Cl > OH > NH<sub>2</sub> > CH<sub>3</sub>, in agreement with previous findings.

To evaluate the impact of hyperconjugation on the anomeric effect, from both the ring oxygen and the substituent, we computed the delocalization energy by partitioning a substituted tetrahydropyran (C<sub>5</sub>OH<sub>2</sub>Y) into six overlapping blocks (see Supplementary Information), one including the cyclic C<sub>5</sub>H<sub>9</sub> fragment with 36 electrons, two corresponding to the two C–O  $\sigma$  bonds, with two electrons for each block, the fourth consisting of the two lone pairs on

**Table 3 | Energy differences ( $\Delta E_{\alpha \rightarrow \beta}$ ) between axial and equatorial conformations with decomposed contributions from electron delocalization ( $\Delta E_{\text{del}}$ ), steric effects ( $\Delta E_{\text{s}}$ ) and dispersion effects ( $\Delta E_{\text{disp}}$ ).**

Y	$\Delta E_{\alpha \rightarrow \beta}$ (kcal mol <sup>-1</sup> )	$\Delta E_{\text{s}}$ (kcal mol <sup>-1</sup> )	$\Delta E_{\text{del}}$ (kcal mol <sup>-1</sup> )	$\Delta E_{\text{disp}}$ (kcal mol <sup>-1</sup> )
Substituted tetrahydropyran				
F	3.41	3.46	-0.66	0.61
OH	1.32	2.19	-1.42	0.55
Cl	2.69	1.76	0.70	0.33
NH <sub>2</sub>	-2.73	-2.45	-0.61	0.34
CH <sub>3</sub>	-3.30	-2.31	-1.18	0.18
Substituted cyclohexane				
F	0.09	-0.07	-0.01	0.17
OH	-0.40	-0.60	-0.09	0.29
Cl	-0.96	-1.00	-0.17	0.21
NH <sub>2</sub>	-1.71	-2.02	-0.03	0.33
CH <sub>3</sub>	-2.19	-2.23	-0.16	0.19

the oxygen, the fifth consisting of the  $\sigma$  bond between the anomeric centre C<sub>1</sub> and its linking atom from the substituent group Y, and the final sixth block comprising the substituent group alone. Clearly, the BLW  $\Phi_{\text{L}}$  for the electron-localized diabatic state deactivates not only the hyperconjugative interactions from the oxygen lone pairs to the substitute group Y, but also the geminal interactions from these two groups as well as the exo-anomeric effect from Y to the ring. Table 2 listed the energies of the diabatic states for all five substituted tetrahydropyrans. BLW computations revealed no change in the relative stability between  $\alpha$ - and  $\beta$ -anomers for all species following quenching of electron delocalization, once again proving that hyperconjugation has no role in influencing the anomeric effect. In fact, with the exception of 2-chlorotetrahydropyran, for which the exo-anomeric effect from chlorine favours the  $\alpha$ -anomer, the DEs in  $\beta$ -anomers are even slightly higher than in the corresponding  $\alpha$ -anomers. These findings are consistent with the above studies on dimethoxymethane. Of the five substituted tetrahydropyrans, the delocalization energies in four species (Y = F, OH, Cl, NH<sub>2</sub>) are comparable within a narrow range of 35–37 kcal mol<sup>-1</sup>. The low delocalization stabilization in 2-methyltetrahydropyran is obviously due to the lack of lone electrons in the substituted group. The capability for electron delocalization from the substituted groups can be justified from the computations for tetrahydropyran. BLW computations at the same level resulted in a DE value of 22.7 kcal mol<sup>-1</sup>. Taking the difference in DEs for 2-methyltetrahydropyran and tetrahydropyran, it is possible to estimate that hyperconjugation between the methyl group and the ring is about 7–8 kcal mol<sup>-1</sup>. This is very close to the hyperconjugative stabilization energy in ethane<sup>26</sup>.

## Discussion

The BLW computations for dimethoxymethane and substituted tetrahydropyrans confirm the persistence of the anomeric effect, even when all intramolecular electron delocalization is quenched. Thus, the hyperconjugation model is unable to explain the anomeric effect.

To visualize the electron delocalization effect within the molecular system, we plotted the electron density difference (EDD) between the delocalized and localized wavefunctions. Figure 3 shows the EDD maps for the three conformers of dimethoxymethane (1) and the  $\alpha$ - and  $\beta$ -anomers of 2-fluorotetrahydropyran (2) and 2-methyltetrahydropyran (3), where the red colour denotes a gain and the blue refers to a loss of electron density. For 1, the delocalization reduces the electron density around the oxygen atoms, but the central methylene group also loses electrons. All these lost electrons flow to the C–O bond regions. If there were only  $n \rightarrow \sigma_{\text{CO}}^*$  interactions, we would observe a significant electron density increase in the two central C–O bonds. However, the EDD maps in Fig. 3a show the comparable changes in central and terminal C–O bonds. As a consequence, both the geminal delocalization, which can be described in terms of re-hybridization of the oxygen orbitals, and hyperconjugative delocalization are involved and

collectively cause the scenario shown by the EDD maps. To distinguish the  $n \rightarrow \sigma_{\text{CO}}^*$  hyperconjugative interactions from the geminal interactions, we used the dimethyl ether as a reference and similarly computed the DE with a wavefunction of five blocks. For the MP2/6-31 + G(d) geometry, the DE in dimethyl ether is 27.1 or 28.6 kcal mol<sup>-1</sup> with the basis sets 6-31 + G(d) or 6-311 + G(d,p). Because the antibonding CO orbital is much lower in energy than the antibonding CH orbital, the fact that the delocalization energy in dimethoxymethane is nearly twice that of the DE in dimethyl ether suggests that both the  $n \rightarrow \sigma_{\text{CO}}^*$  and  $n \rightarrow \sigma_{\text{CH}}^*$  hyperconjugative interactions are fairly weak and the  $n \rightarrow \sigma_{\text{CO}}^*$  hyperconjugation thus cannot be the cause of the anomeric effect.

Similarly, for 2, both oxygen and fluorine delocalize their lone pairs to the adjacent bonds (C–F and C–O), resulting in the reduction of electron densities on oxygen and fluorine but the enhancement of these bonds. The EDD maps in Fig. 3c for 3, however, are more illustrative, confirming the hyperconjugative interactions from oxygen lone pairs to the C<sub>1</sub>–CH<sub>3</sub> bond. As there is very little electron density change in the methyl group, in accordance with the weak hyperconjugative capability, there is an obvious increase in the electron density in the C<sub>1</sub>–CH<sub>3</sub> bond, and this electron flux must predominantly come from the oxygen, indicating  $n \rightarrow \sigma_{\text{CC}}^*$  hyperconjugative interactions.

The confirmation of hyperconjugative interactions, however, does not indicate that they should be responsible for the anomeric effect, as our BLW computations have profoundly demonstrated. Further evidence can be taken from a comparison with substituted cyclohexanes (C<sub>6</sub>H<sub>11</sub>Y), as the energy difference between the equatorial and axial conformations of substituted cyclohexane is often taken as a reference with which to measure the magnitude of the anomeric effect<sup>18</sup>. However, the greater length of the C–C bond in C<sub>6</sub>H<sub>11</sub>Y compared with the C–O bond in C<sub>5</sub>OH<sub>9</sub>Y relieves the steric repulsion and consequently underestimates the anomeric effect<sup>46,47</sup>. (Computational results for substituted cyclohexanes are presented in the Supplementary Information.) Owing to steric effects, except for F, which is neutral with regard to axial or equatorial positions, all substituents prefer the equatorial position. It is noteworthy that the electron delocalization effect in the  $\alpha$ - and  $\beta$ -anomers of each molecule is particularly close.

To explain the origin of the anomeric effect in substituted tetrahydropyrans, we decomposed the axial–equatorial energy differences ( $\Delta E_{\alpha \rightarrow \beta}$ ) at the MP2 level into three components, namely electron delocalization ( $\Delta E_{\text{del}}$ ), steric effect ( $\Delta E_{\text{s}}$ ) and dispersion ( $\Delta E_{\text{disp}}$ ), as

$$\begin{aligned}
 \Delta E_{\alpha \rightarrow \beta} &= E_{\beta}(\text{MP2}) - E_{\alpha}(\text{MP2}) = E_{\beta}(\text{HF}) - E_{\alpha}(\text{HF}) + \Delta E_{\text{disp}} \\
 &= E_{\beta}(\text{BLW}) - E_{\alpha}(\text{BLW}) + \Delta E_{\text{del}} + \Delta E_{\text{disp}} \\
 &= \Delta E_{\text{s}} + \Delta E_{\text{del}} + \Delta E_{\text{disp}}
 \end{aligned}
 \quad (1)$$



The steric energy term consists of both the electrostatic interaction (stabilizing or destabilizing) and Pauli repulsion. Table 3 contains the energy terms for substituted tetrahydropyrans and cyclohexanes. It is clear that the steric effect dominates in the conformational preferences for all cases. Except for 2-chlorotetrahydropyran, for which a significant exo-anomeric effect favours the  $\alpha$ -anomer, all species exhibit stronger hyperconjugative interactions in the equatorial conformers than in the axial conformers. In addition, the dispersion effect stabilizes all axial forms, although the magnitude is small.

One further support for the electrostatic explanation comes from analysis of the relative orientations of the local dipoles in substituted tetrahydropyrans (see Fig. 2). We used model molecules  $\text{CH}_3\text{—O—CH}_3$  and  $\text{CH}_3\text{—Y}$  at the exact positions of the substituted tetrahydropyran to compute the orientations of the local dipoles (listed in the Supplementary Information). The data are in agreement with the conformational preferences.

In summary, to evaluate the stabilization energy due to electron delocalization (or electron transfer) at the quantitative level, it is essential to derive the wavefunction for the electron-localized diabatic state for reference. We have proposed a general BLW method, which can be regarded as the simplest variant of *ab initio* VB theory. Applications of the BLW method to dimethoxymethane and substituted tetrahydropyrans demonstrated that electron delocalization slightly favours the *trans* conformer of dimethoxymethane and equatorial anomers of substituted tetrahydropyrans ( $\text{C}_5\text{OH}_2\text{Y}$ ,  $\text{Y} = \text{F}, \text{OH}, \text{NH}_2$  and  $\text{CH}_3$ ) with the exception of 2-chlorotetrahydropyran. However, even for the latter, the stabilization energy due to the hyperconjugation from chlorine to the ring accounts for only a small portion of the axial–equatorial energy difference. Thus, our BLW computations do not support the currently popular hyperconjugation explanation for the anomeric effect. Energy analyses revealed that the steric effect, which includes both electrostatic interaction and Pauli repulsion, dominates conformational preferences. An alternative explanation such as the electrostatic model must therefore be introduced to interpret the anomeric effect.

## Methods

The significant difference between the MO and VB theories is that, by definition, the latter can construct wavefunctions for individual resonance structures or diabatic states where each pair of electrons is strictly localized on one atom or two bonding atoms, with the expense of increased computational costs due to the non-orthogonality of the orbitals. In contrast, MO theory allows all orbitals to delocalize over the whole system with the constraint of orthogonality, and is therefore unable to define diabatic states. In VB theory, the wavefunction for a resonance structure  $L$  (here we assume closed-shell cases, that is,  $N$  is an even number) can be expressed by a Heitler–London–Slater–Pauling (HLSP) function as

$$\Phi_L = N_L \hat{A} \left\{ (\varphi_1 \varphi_2 \varphi_3 \cdots \varphi_N) \prod_j [\alpha(i)\beta(j) - \beta(i)\alpha(j)] \right\} \quad (2)$$

where  $N_L$  is the normalization constant,  $\hat{A}$  is an antisymmetrizer and in the above resonance structure  $L$ , two electrons on orbitals  $\varphi_i$  and  $\varphi_j$  form a chemical bond. The overall wavefunction  $\Psi$  is a superposition of all independent resonance structures, and the delocalization energy can be generally 'obtained by subtracting the actual energy of the molecule in question from that of the most stable contributing structure'<sup>29</sup>. Apparently, each HLSP can be expanded into  $2^{N/2}$  Slater determinants, so the electron correlation is taken into account.

One way to dramatically simplify HLSP functions yet retain the VB characteristics of localization is to make two bonding orbitals  $\varphi_i$  and  $\varphi_j$  equal but strictly localized on their bonding area. As such, equation (2) will be reduced to only one Slater determinant. A general extension of this idea is the BLW method<sup>33,34</sup>, in which all primitive orbitals and electrons are partitioned into  $K$  blocks (or groups), and each MO is allowed to expand only in one block. Although block-localized MOs (BL-MOs) in the same block are constrained to be orthogonal, BL-MOs between different blocks are non-orthogonal. However, the above partition is not enough for general cases in which certain primitive orbitals may be involved in more than one block. A further generalized BLW method defines each block with a subspace of all primitive orbitals, without imposing the limit that any primitive orbital can appear only once in blocks. In such a way, equation (2) can be simplified to the form

$$\Phi_L = N_L \hat{A} \{\Omega^1 \Omega^2 \cdots \Omega^K\} \quad (3)$$

where  $\Omega^A$  is a successive product of  $n_A$  occupied spin-orbitals in subgroup  $A$ :

$$\Omega^A = \psi_1^A \alpha \psi_1^A \beta \cdots \psi_{n_A/2}^A \beta \quad (4)$$

If we allow all orbitals to expand in the whole space of primitive orbitals, equation (3) will be equivalent to the familiar Hartree–Fock (or Kohn–Sham with density functional theory) wavefunction  $\Psi^{\text{Del}}$ , corresponding to a delocalized, adiabatic state, which is implicitly a superposition of all electron-localized states. If we choose the resonance structure  $L$  as the most stable resonance structure, the energy difference between  $\Phi_L$  and  $\Psi^{\text{Del}}$  is generally defined as the delocalization energy (or resonance energy, RE):

$$\text{DE} = E(\Phi_L) - E(\Psi^{\text{Del}}) \quad (5)$$

In applications, however, we can generally define blocks in a much more flexible way by focusing on the specific delocalization effect. For instance, a negative hyperconjugation can be studied by localizing the lone pairs and adjacent bonds only in  $\Phi_L$ ; consequently the DE measures the hyperconjugative interactions between these lone pairs and surrounding bonds.

In this work, all geometries were optimized at the MP2/6-31 + G(d) level and subsequent BLW calculations were carried out using the Xiamen Valence Bond (XIMVB) program<sup>48</sup> and a modified version of GAMESS<sup>49</sup>.

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### Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at [www.nature.com/naturechemistry](http://www.nature.com/naturechemistry). Reprints and permission information is available online at <http://npg.nature.com/reprintsandpermissions/>. Correspondence and requests for materials should be addressed to Y.M.