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# The Reverse Fluorine Perlin-like Effect and Related Stereoelectronic Interactions

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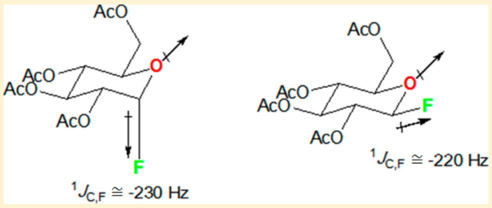
Supporting Information

**ABSTRACT:** A similar effect to the well-known reverse Perlin effect was observed on the $^1J_{C-F}$ coupling constants of $\alpha$- and $\beta$-D-glucopyranosyl fluoride tetracetate, both in nonpolar and polar solution. This can be called "reverse fluorine Perlin-like effect", and it is shown to be ruled by dipolar interactions rather than by hyperconjugation. The reverse fluorine Perlin-like effect does not have a general relationship with the anomeric effect, and it can be useful to determine the structure and stereochemistry of organofluorine compounds.



Spin−spin coupling constants (SSCCs) have been useful to determine the structure and stereochemistry of molecules, particularly the $^3J_{H,H}$ SSCC, which is dependent on the dihedral angle H−C−C−H, according to the well-known Karplus curve.[1] $^1J_{C-H}$ SSCCs have also shown structural dependence, giving rise to the Perlin effect,[2] which is observed in some cyclohexane and tetrahydropyran derivatives.[3,4] The Perlin effect refers to the smaller $^1J_{C-Hax}$ SSCC in comparison to the corresponding $^1J_{C-Heq}$ value in 6-membered rings. Originally, this phenomenon was attributed to the fact that C−$H_{ax}$ bonds are longer than C−$H_{eq}$ ones, due to the preferred electron delocalization involving antiperiplanar orbitals bearing $H_{ax}$ rather than $H_{eq}$, namely, the $\sigma_{CH} \rightarrow \sigma^*_{C-Hax}$ interaction in cyclohexane derivatives and the $n_O \rightarrow \sigma^*_{C-Hax}$ interaction in tetrahydropyran derivatives, like pyranoside sugars. The reverse Perlin effect corresponds to larger $^1J_{C-Hax}$ SSCC than $^1J_{C-Heq}$ in some dithianes, due to better $\sigma_{CS} \rightarrow \sigma^*_{C-Heq}$ electron transfer than $n_S \rightarrow \sigma^*_{C-Hax}$.[5]

Because of the interpretation based on hyperconjugation, the Perlin effect has been frequently related to the anomeric effect, which is a concept in carbohydrate chemistry and can be defined as the preference of electronegative substituents (X) attached to the anomeric carbon to occupy an *axial* orientation ($\alpha$-anomer) instead of the less hindered *equatorial* orientation ($\beta$-anomer) that would be expected from steric considerations of a chair conformation.[6] The relationship between both effects comes from the fact that the elongated $C_2$−$H_{ax}$ bond relative to the $C_2$−$H_{eq}$ bond in tetrahydropyran (THP) would be the consequence of the hyperconjugative origin of the anomeric effect (the $n_O \rightarrow \sigma^*_{C-Hax}$ interaction in THP or $n_O \rightarrow \sigma^*_{CX}$ in 2-X-THP)[7] and the cause of the Perlin effect ($^1J_{C-Hax} < {}^1J_{C-Heq}$, since longer C−H bonds make difficult the coupling transmission). It is worth mentioning that structural effects on C−H bonds not associated with hyperconjugation were reported in six-membered heterocycles.[8] In addition, electrostatic effects are also operative and have been invoked to explain both effects.[9] Recently, Cuevas et al.[10] found that the angular dependence of $^1J_{C-H}$ is not consistent with hyperconjugation for tetrahydropyran, but it was likely to be related with electrostatic effects. In line with this, since the C−F bond is more polar than the C−H one, electrostatic effects in organofluorine compounds would be more evident on $^1J_{C-F}$ than in $^1J_{C-H}$ coupling constants. Indeed, the angular dependence of $^1J_{C-F}$ upon rotation of the C−O−C−F dihedral angle in fluoro(methoxy)methane was calculated to be exponentially related with the molecular dipole moment ($\mu$), but no relationship with the $n_O \rightarrow \sigma^*_{CF}$ hyperconjugative interaction was found;[11] i.e., the absolute $^1J_{C-F}$ value decreases exponentially with increasing $\mu$, giving support for the electrostatic nature of the here called reverse fluorine Perlin-like effect. The same tendency is observed in the anesthetic sevoflurane, whose absolute $^1J_{C-F}$ SSCC is smaller in the conformation containing the *anti* F−C−O−C dihedral angle (matching the *equatorial* orientation of the fluorine atom in 2-fluorotetrahydropyran) than in the *gauche* arrangement (matching the *axial* 2-fluorotetrahydropyran).[11] This behavior can give important insights about the structure and stereochemistry of organofluorine compounds.

2-Fluorotetrahydropyran analogues are the best models to experimentally probe both effects, which are especially useful for the study of the stereochemistry of sugar derivatives. 2-Fluorotetrahydropyran is computationally known to exhibit the anomeric effect (the *axial* form is more stable than the *equatorial* one, by more than 2 kcal mol$^{-1}$),[9,12] but no experimental data for this compound and corresponding derivatives have been found to test the theoretical findings. On the other hand, the $^1J_{C-Fax}$ and $^1J_{C-Feq}$ SSCCs in other fluorinated 6-membered rings have been measured and the

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absolute $^1J_{C-Feq}$ value has been shown to be larger than the $^1J_{C-Fax}$ (Figure 1).[13,14]

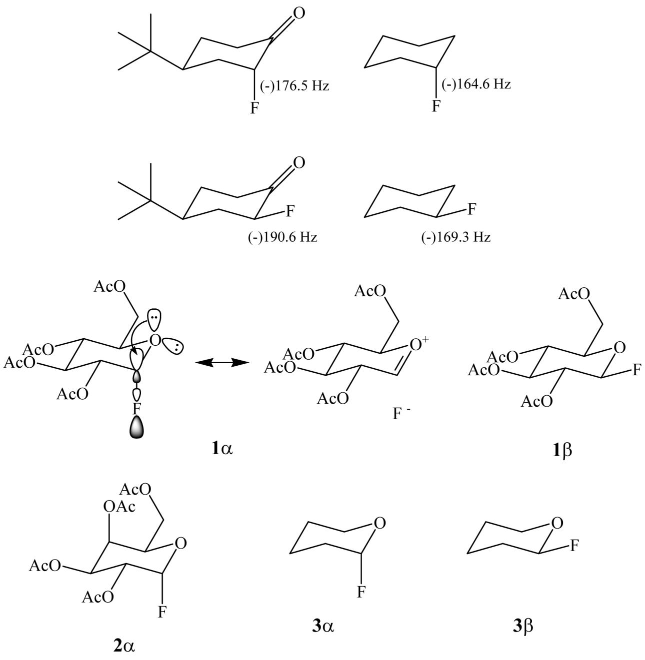

**Figure 1.** Some fluorinated 6-membered rings and the corresponding $^1J_{C-F}$ coupling constant, the studied D-glucopyranosyl fluoride tetracetate (**1**), *α*-D-galactopyranosyl fluoride tetracetate (**2*α***), and 2-fluorotetrahydropyran (**3**).

The NMR spectra of the *α* and *β* anomers of D-glucopyranosyl fluoride tetracetate (**1*α*** and **1*β***, Figure 1) were analyzed to give insight about the origin of the anomeric effect and also to investigate the manifestation of the (reverse) fluorine Perlin-like effect. The acetate derivatives were employed rather than the 2-fluoro-2-deoxy-D-glucose to avoid any interference from possible internal hydrogen bonds among hydroxyl groups. Preliminary coupling constant calculations at the *ω*B97X-D/6-311+G(d,p) level[15] indicated that the absolute value for the $^1J_{C-Fax}$ coupling constant is larger than $^1J_{C-Feq}$, which is in agreement with the experimental data (Table 1). Thus, **1** experiences the reverse fluorine Perlin-like effect, while the ketones and fluorocyclohexane of Figure 1 exhibit the fluorine Perlin-like effect. Moreover, **1*α*** was calculated to be significantly more stable than **1*β*** both in the gas phase and implicit (using the polarizable continuum model) solution (Table 1), at the *ω*B97X-D/6-31G(d,p) level,[16] indicating that the anomeric effect is operative. This theoretical level includes dispersion effects and has shown good agreement with CCSD results for aromatic systems.[17] The geometries of **1*α*** and **1*β*** used in the DFT optimization were selected from previous conformational search using the Monte Carlo approach at the semiempirical AM1 method.[18]

The resonance structure of **1*α*** giving the dissociated fluoride, which is consistent with the hyperconjugation model for the anomeric effect, should shield the axial fluorine in the $^{19}$F NMR spectrum; indeed, $\delta_{Fax}$ in **1*α*** relative to $CFCl_3$ is −150.88 ppm in $C_6D_{12}$ and −147.90 ppm in DMSO-$d_6$, while the respective $\delta_{Feq}$ values for **1*β*** are −136.17 and −142.53 ppm. Accordingly, the CHELPG charges[19] on the fluorine atom in **1*α*** and **1*β*** are −0.218 and −0.202, while the calculated C−F bond distances are 1.384 Å for **1*α*** and 1.357 Å for **1*β***, in the gas phase (despite angular dependence between $d_{C-F}$ and $n_O \rightarrow \sigma^*_{C-F}$ was not found for 2-fluoromethanol[20]). The values for **1*α*** are consistent with those obtained for *α*-D-galactopyranosyl fluoride tetracetate, **2*α*** (−151.99 ppm in $C_6D_{12}$ solution and −148.90 ppm in DMSO-$d_6$ solution). Such a behavior cannot be clearly explained using the electrostatic model for the anomeric effect. The stabilizing $n_O \rightarrow \sigma^*_{C-F}$ electron delocalization in **1*α***, obtained by natural bond orbital (NBO)[21] analysis, contributes for its overall hyperconjugative stabilization (Table 2).

**Table 2. NBO Data for 1*α* and 1*β* (in kcal mol$^{-1}$), Obtained at the *ω*B97X-D/6-31G(d,p) Level (Δ = 1*α* − 1*β*)**

| parameter | gas | $C_6H_{12}$ | DMSO |
|---|---|---|---|
| $\Delta E_{full}$ | −5.8 | −5.4 | −4.5 |
| $\Delta E_{Steric}$ | 4.7 | 4.9 | −6.3 |
| $\Delta E_{Electrostatic}$ | −1.5 | −1.7 | 16.1 |
| $\Delta E_{Hyperconjugation}$ | −8.0 | −8.6 | −14.3 |
| $n_O \rightarrow \sigma^*_{C-F}$ | 22.0 | 22.1 | 22.4 |

According to the energy decomposition scheme $E_{full} = E_L + E_{NL}$ ($E_L = E_{Steric} + E_{Electrostatic}$ and $E_{NL} = E_{Hyperconjugation}$), hyperconjugation is the main effect governing the anomeric effect of **1** in the gas phase and nonpolar solution. In polar solution (DMSO), the dipolar interaction between the endocyclic oxygen and fluorine is attenuated and, consequently, overall electrostatic repulsions are reduced in **1*β*** relative to **1*α***. In the gas phase, hyperconjugation is the main factor controlling the anomeric effect in **1*α***, while in DMSO both hyperconjugation in **1*α*** and reduced dipolar repulsion in **1*β*** and the balance between these similar competitive forces rules the anomeric effect in **1**, such as found in the literature for 2-fluorotetrahydropyran.[12]

It is well-known that $^1J_{XY} = {}^1J^{b} + \Sigma^1J^{ob} + \Sigma^1J^{LP}$, where X and Y are the coupled nuclei (C and F for **1**), the first term is always positive and corresponds to the X−Y bond connecting the coupled nuclei, the second term is always negative and corresponds to other bond contributions (ob refers to any bond containing either the X or Y atom, but it is a bond other than the X−Y one), and the third term is the X and/or Y lone pair contributions, which is always negative.[13] Because the fluorine atom bears lone pairs of electrons with strong *s* character, the overall $^1J_{C-F}$ is negative, while $^1J_{C-H}$ is positive. The absolute $^1J_{C-Fax}$ SSCC in the less polar **1*α*** is larger than $^1J_{C-Feq}$ in **1*β*** (Table 1), and is quantitatively in agreement with

**Table 1. Calculated $E_{rel}$ in kcal mol$^{-1}$ [*ω*B97X-D/6-31G(d,p) level], *J* in Hz [*ω*B97X-D/6-311+G(d,p)] (the Experimental *J* Values Are Given in Parentheses), Molecular Dipole Moments (*μ*, in Debye), and C−F Bond Lengths (in Å), for 1*α* and 1*β***

| | gas | | | | $C_6H_{12}$ | | | | DMSO | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| cpd | $E_{rel}$ | $^1J_{C-F}$ | $\mu$ | $d_{C-F}$ | $E_{rel}$ | $^1J_{C-F}$ | $\mu$ | $d_{C-F}$ | $E_{rel}$ | $^1J_{C-F}$ | $\mu$ | $d_{C-F}$ |
| **1*α*** | 0.0 | −233.0 | 1.2 | 1.384 | 0.0 | −232.1 (−229.6) | 1.3 | 1.385 | 0.0 | −231.2 (−226.3) | 1.7 | 1.386 |
| **1*β*** | 5.8 | −230.2 | 2.7 | 1.357 | 5.4 | −227.1 (−220.7) | 2.8 | 1.359 | 4.5 | −222.4 (−213.7) | 2.6 | 1.363 |

$^1J_{\mathrm{C-Fax}}$ for the similar compound **2**$\alpha$ (−228.8 Hz in $C_6D_{12}$ and −226.2 Hz in DMSO-$d_6$). In addition, the trend in $J$ is extended for the parent compound 2-fluorotetrahydropyran (**3**), whose calculated $^1J_{\mathrm{C-F}}$ SSCC are −227.6 Hz for **3**$\alpha$ and −220.4 Hz for **3**$\beta$. The opposite is found for fluorocyclohexane,[14] as well as in *cis-* and *trans*-4-*tert*-butyl-2-fluorocyclohexanone[13] (Figure 1); tentatively, the endocyclic oxygen bearing lone pairs of electrons plays the determinant role for the difference between **1** and fluorocyclohexane and 4-*tert*-butyl-2-fluorocyclohexanone. The dipolar effect between two polar bonds (two bonding orbitals) on the $^1J_{\mathrm{C-F}}$ SSCC is opposite to the effect caused by the interaction between a polar bond (C−F) and oxygen lone pairs (Figure 2), i.e., between bonding and nonbonding orbitals (compare the angular dependence of $^1J_{\mathrm{C-F}}$ in the small molecules 1,2-difluoroethane[22] and fluoro(methoxy)methane[11]). For instance, in addition to the case of the 2-fluorocyclohexanones of Figure 1, the polar 8-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (with interacting C═O and C−F dipole moments) exhibits a $^1J_{\mathrm{C-F}}$ SSCC of −265.9 Hz, while the corresponding value for the less polar 7-fluoro-3,4-dihydronaphthalen-1(2*H*)-one is −247.6 Hz.[23]

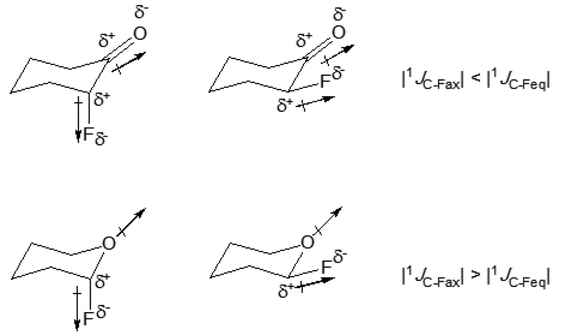

**Figure 2.** Example of local dipoles originated from bonding and nonbonding orbitals. The electrostatic interaction between polar bonds causes $|^1J_{\mathrm{C-Fax}}| < |^1J_{\mathrm{C-Feq}}|$, while the interaction between dipoles from polar bond and electron lone pairs causes $|^1J_{\mathrm{C-Fax}}| > |^1J_{\mathrm{C-Feq}}|$.

The Fermi contact (FC, responsible for the magnitude of $^1J$ coupling constants) in C−H bonds, as well as the bond distance, is strongly influenced by hydridization in the bond forming carbon; the larger the *s*-character, the larger the FC term and the shorter the C−H bond.[24] This trend is also calculated for the C−F bond in 2-fluorocyclohexanone, i.e., for the *axial* conformer: $d_{\mathrm{C-Fax}} = 1.406$ Å, $^{\mathrm{FC}\text{-}1}J_{\mathrm{C-Fax}} = -255.7$ Hz, $s_{\mathrm{C}} = 17.7\%$, and $s_{\mathrm{Fax}} = 27.5\%$; while for the *equatorial* conformer: $d_{\mathrm{C-Feq}} = 1.381$ Å, $^{\mathrm{FC}\text{-}1}J_{\mathrm{C-Feq}} = -259.9$ Hz, $s_{\mathrm{C}} = 19.0\%$, and $s_{\mathrm{Feq}} = 28.6\%$. Interestingly, the FC term for **1** does not follow this trend nor the Ramsey expression for the FC term,[25] since the *s*-character (%) for the *axial* and *equatorial* C−F bonds in **1**, in the gas phase (the *s*-character did not vary in PCM, see Supporting Information), is $18.9_{\mathrm{C}}$ and $28.7_{\mathrm{Fax}}$ versus $19.6_{\mathrm{C}}$ and $29.8_{\mathrm{Feq}}$, respectively, contributing for $^{\mathrm{FC}\text{-}1}J_{\mathrm{C-Fax}}$ of −253.8 Hz and $^{\mathrm{FC}\text{-}1}J_{\mathrm{C-Feq}}$ of −243.0 Hz.

According to the hyperconjugative model, the C−F distance in **1**$\alpha$ should be longer, and therefore, $^1J_{\mathrm{C-Fax}}$ should be smaller than $^1J_{\mathrm{C-Feq}}$ In addition, there is not any relationship between the angular dependence of $^1J_{\mathrm{C-F}}$ with the angular dependence of the $n_{\mathrm{O}} \rightarrow \sigma^*_{\mathrm{C-F}}$ interaction for fluoro(methoxy)methane,[11] which contains the same C−O−C−F fragment as **1**. However, a correlation between $^1J_{\mathrm{C-F}}$ and the molecular dipole moment (governed by the mutual orientation of the C−F bond and oxygen electron lone pairs) for this compound was found. In addition, the calculated difference between $^1J_{\mathrm{C-F}}$ for the *gauche* and *anti* conformers of fluoro(methoxy)methane using implicit acetonitrile as solvent was larger than in the gas phase, which is parallel to the behavior found for the angular dependence of the molecular dipole moment;[11] this behavior is well reproduced experimentally for **1**, since $\Delta^1J_{\mathrm{C-F(ax\text{-}eq)}}$ in the polar DMSO-$d_6$ solvent was −12.6 Hz, while the corresponding value in the nonpolar $C_6D_{12}$ solvent was −8.9 Hz. Thus, the origin of the reverse fluorine Perlin-like effect in **1** does not appear to be due to hyperconjugation, similarly to that found for the Perlin effect in tetrahydropyran.

Overall, spectroscopic and theoretical outcomes indicate that the main origin of the anomeric effect can be either hyperconjugative or electrostatic, depending on the molecular system, substituents and media; in **1**, the nature of the anomeric effect was found to be due especially to hyperconjugation in the gas phase and nonpolar solution, but these effects are competitive in DMSO solution. However, the general interpretation for the so-called reverse fluorine Perlin-like effect is based predominantly on dipolar interactions. Thus, such effect does not have any relationship with the anomeric effect. This can be extended to acyclic organofluorine compounds in order to determine structural properties and the stereochemistry of, e.g., anesthetic-like molecules, like sevoflurane.

## ■ EXPERIMENTAL SECTION

The global minima for **1**$\alpha$, **1**$\beta$ and **2**$\alpha$ were first searched using Monte Carlo distribution at the AM1 level.[18] Further calculations were performed over the selected conformers: geometry optimization and NBO calculations at the $\omega$B97X-D/6-31G(d,p) level,[16] and coupling constants calculations at the $\omega$B97X-D/6-311+G(d,p) level.[15] These calculations were performed using the Gaussian 09 program.[26] The NMR experiments for **1** and **2**$\alpha$ (commercially available) were carried out at 499.87 MHz for $^1$H, 125.69 MHz for $^{13}$C and 470.34 MHz for $^{19}$F, for ca. 20 mg mL$^{-1}$ solutions in $C_6D_{12}$ and DMSO.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Cartesian coordinates and NMR spectra for the $\alpha$- and $\beta$-D-glucopyranosyl fluoride tetracetate. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES

(1) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11−15. (b) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870−2871. (c) Barfield, M.; Karplus, M. *J. Am. Chem. Soc.* **1969**, *91*, 1−16.

(2) Perlin, A. S.; Casu, B. *Tetrahedron Lett.* **1969**, *10*, 2921−2924.

(3) Wolfe, S.; Pinto, B. M.; Varma, V.; Leung, R. Y. N. *Can. J. Chem.* **1990**, *68*, 1051−1062.
(4) Anderson, J. E.; Bloodworth, A. J.; Cai, J.; Davies, A. G.; Tallant, N. A. *J. Chem. Soc., Chem. Commun.* **1992**, 1689−1690.
(5) Juaristi, E. *J. Org. Chem.* **2012**, *77*, 4861−4884.
(6) Eliel, E. *Angew. Chem., Int. Ed.* **1972**, *11*, 739−750.
(7) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910−3919.
(8) Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014−14031.
(9) Mo, Y. *Nat. Chem.* **2010**, *2*, 666−671.
(10) Cuevas, G.; Martínez-Mayorga, K.; Fernández-Alonso, M. C.; Jiménez-Barbero, J.; Perrin, C. L.; Juriasti, E.; López-Mora, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2360−2364.
(11) Freitas, M. P.; Bühl, M.; O'Hagan, D.; Cormanich, R. A.; Tormena, C. F. *J. Phys. Chem. A* **2012**, *116*, 1677−1682.
(12) Freitas, M. P. *Org. Biomol. Chem.* **2013**, *11*, 2885−2890.
(13) Contreras, R. H.; Peralta, J. E. *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *37*, 321−425.
(14) Abraham, R. J.; Edgar, M.; Griffiths, L.; Powell, R. L. *J. Chem. Soc., Perkin Trans. 2* **1995**, 561−567.
(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (b) Barone, V. In *Recent Advances in Density Functional Methods, Part I*; Chong, D. P., Ed.; World Scientific Publ. Co.: Singapore, 1996.
(16) (a) Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615−6620. (b) Frisch, J. M.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265−3269.
(17) Josa, D.; Rodríguez-Otero, J.; Cabaleiro-Lago, E. M.; Rellán-Piñero, M. *Chem. Phys. Lett.* **2013**, *557*, 170−175.
(18) Dewar, M. J. S.; Jie, C.; Yu, G. *Tetrahedron* **1993**, *23*, 5003−5038.
(19) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361−373.
(20) Silla, J. M.; Freitas, M. P. *Comput. Theor. Chem.* **2014**, *1037*, 49−52.
(21) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Landis, C. R.; Weinhold, F. *NBO 6.0*; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 2013; http://nbo6.chem.wisc.edu/.
(22) Freitas, M. P.; Bühl, M.; O'Hagan, D. *Chem. Commun.* **2012**, *48*, 2433−2435.
(23) Podány, B.; Keresztúri, G.; Vasvári-Debreczy, L.; Hermecz, I.; Tóth, G. *Magn. Reson. Chem.* **1996**, *34*, 972−978.
(24) Rusakov, Y. Y.; Krivdin, L. B. *Russ. Chem. Soc.* **2013**, *82*, 99−130.
(25) Ramsey, N. F. *Phys. Rev.* **1953**, *91*, 303−307.
(26) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.