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Absolute Configuration through the DFT Simulation of the Optical Rotation. Importance of the Correct Selection of the Input Geometry: A Caveat

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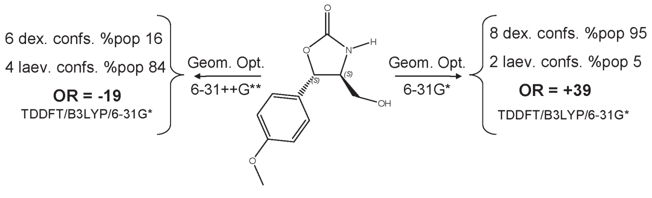

In ab initio calculation of ORs of flexible molecules, the input geometries and conformer populations obtained at different levels of theory can yield opposite OR values. Therefore, when at the commonly used DFT/B3LYP/6-31G* level several conformers result, even showing the same sign of OR, additional geometry optimization at a higher level of theory will be absolutely required.

The recent progress in computational chemistry has made available powerful ab initio methods for the simulation[1] of electronic chiroptical properties (OR, ECD) which, in principle, allow a safe assignment of the molecular absolute configuration (AC). In fact, these methods are increasingly used by the experimental organic chemists to assign the AC of new synthetic and natural compounds.[2] The ab initio simulation of the OR at a certain wavelength, usually 589 nm, represents a particularly appealing method to the practicing organic chemist owing to its experimental simplicity. In spite of all these progresses, some difficulties are still present. In fact, Stephens and co-workers[3] wrote that the ab initio calculation of the OR (and of ECD) provides a reliable answer only by the use of TDDFT method with extended basis sets (i.e., including both polarization and diffuse functions). They proposed the following protocol: use of the TDDFT method with the state-of-the-art hybrid functional B3LYP and an extended basis set (aug-cc-pVDZ) or higher, upon input geometries generally obtained at the DFT/B3LYP/6-31G* level, as a reliable and largely applicable[2] calculation technique. Clearly, such a recipe makes compulsory the use of powerful computing systems when a large size, and often the most attractive organic molecules are treated. Additional problems also exist in the treatment of medium-size flexible and transparent molecules. In such cases, the presence of a large number of conformers and of only high-energy Cotton effects also requires high-level calculations and powerful computational resources. The problem associated with the choice of method and basis set has been recently addressed in a recent review by Autschbach.[4] In any case, the geometry problem, as we shall see in the next section, appears to be of primary importance. In this paper, we shall show that while the DFT/B3LYP/6-31G*, the standard most common method to obtain input geometries for OR calculations, usually works well, sometimes it can be unsuitable leading to erroneous results. The latter include a conformationally flexible molecule where the presence of multiple conformers requires more sophisticated levels of theory. For a number of reasons, many of the problems associated with opposite-signed OR for different conformers, like those described in the following text, have been highlighted in the specialized literature.[5]

We shall consider first the cases of those molecules which are rigid systems, show intense ($\Delta\varepsilon > 10$) Cotton effects in their near-UV ECD spectra, and possess high OR values (>200 deg [dm g/cm^3]$^{-1}$), determined in sign and order of magnitude by the lowest energy ECD bands. We call them "class a) compounds".[6a] Let us consider the (+)-*syn*-benzotricamphor (**1**) as the first example (Chart 1).[6b]

Compound **1** shows $[\alpha]_D = +690$ (*c* 1.4, $CHCl_3$) and +660 (*c* 0.4, CH_3CN); i.e., the OR in practice is independent of the solvent. The lowest energy Cotton effects contribution[6b] to

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[†] Dedicated to the memory of Professor Carlo Rosini (1948−2010), an unforgettable mentor and a dear friend, in recognition of his outstanding contribution to chiroptical spectroscopy.

(1) For a general discussion of the ab initio calculation of chiroptical properties, see: (a) Polavarapu, P. L. *Chirality* **2002**, *14*, 768–781. (b) Pecul, M.; Ruud, K. *Adv. Quantum Chem.* **2006**, *50*, 185–227. (c) Crawford, T. D. *Theor. Chem. Acc.* **2006**, *115*, 227–245. (d) Crawford, T. D.; Tam, M. C.; Abrams, M. L. *J. Phys. Chem. A* **2007**, *111*, 12057–12068. (e) Polavarapu, P. L. *Chem. Rec.* **2007**, *7*, 125–136. (f) Autschbach, J. *Chirality* **2009**, *21*, S116–S152.

(2) See, for instance: (a) Synthetic compounds: Xu, D.; Wang, Y.; Luo, S.; Zhong, A.; Chen, H.; Xu, Z. *Adv. Synth. Cat.* **2008**, *350*, 2610–2616. Gioia, C.; Fini, F.; Mazzanti, A.; Bernardi, L.; Ricci, A. *J. Am. Chem. Soc.* **2009**, *131*, 9614–9615. (b) Natural products: Ge, H. M.; Zhu, C. H.; Da, H. S.; Zhang, L. D.; Xie, D. Q.; Yang, J.; Ng, S. W.; Tan, R. X. *Chem.—Eur. J.* **2008**, *14*, 376–381. (c) Hussain, H.; Akhtar, N.; Draeger, S.; Schulz, B; Pescitelli, G.; Salvadori, P.; Antus, S.; Kurtan, T.; Khron, K. *Eur. J. Org. Chem.* **2009**, 749–756. Kwit, M.; Sharma, N. D.; Boyd, D. R.; Gawronski, J. *Chem.—Eur. J.* **2007**, *13*, 5812–5821. See also: Bringmann, G; Gulder, T. A. M.; Reichert, M.; Gulder, T. *Chirality* **2008**, *20*, 628–642. Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem.* **2009**, 2717–2727 and references cited therein.

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(4) Autschbach, J. *Chirality* **2009**, *21*, E116–E152.

(5) (a) Kundrat, M. D.; Autschbach, J. *J. Phys. Chem. A* **2006**, *110*, 4115–4123. (b) Kundrat, M. D.; Autschbach, J. *J. Phys. Chem. A* **2006**, *110*, 12908–12917. (c) Kundrat, M. D.; Autschbach, J. *J. Am. Chem. Soc.* **2008**, *101*, 4404–4414.

(6) (a) Mennucci, B.; Claps, M.; Evidente, A.; Rosini, C. *J. Org. Chem.* **2007**, *72*, 6680–6691. (b) Mazzeo, G.; Giorgio, E.; Rosini, C.; Fabris, F.; Fregonese, E.; Toniolo, U.; De Lucchi, O. *Chirality* **2009**, *21*, S86–S97.

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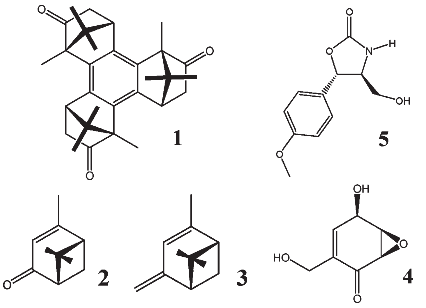
CHART 1



the OR at the sodium D line is +547; i.e., the OR of **1** is determined in sign, and order of magnitude, by the lowest energy Cotton effects. **1** exists as a single conformer, and OR values have been computed with the TDDFT/B3LYP method and 6-31G* basis set using Gaussian03[7] for a number of input geometries obtained at different levels of theory: DFT/B3LYP/6-31G* geometry optimization of Gaussian03,[7] the semiempirical AM1, PM3, and molecular mechanics (MMFF94s) methods of SPARTAN02.[8] The results are collected in Table 1 of the Supporting Information and can be discussed as follows: (i) The use of the TDDFT/B3LYP/6-31G* method upon a DFT/B3LYP/6-31G* geometry provides an OR value (+713) which is in excellent agreement with the experiment. (ii) The use of input geometries obtained with the semiempirical or the molecular mechanics methods provide OR value in good agreement with experiment (runs 2−4). Clearly, due to the rigid skeleton of **1**, the final theoretically derived structure does not depend (at least to a large extent) on the optimization technique. It seems therefore, that at least in this case, the quality of the input geometry does not affect significantly the computed OR values. One could argue that we have examined a particularly easy case owing to its high rotatory power. So let us study a case of a molecule with a smaller OR: (−)-verbenone (**2**), with $[\alpha]_D = -175$ (hexane), for which we measured an OR value at $c \to 0$, −192 (hexane). It shows the lowest energy Cotton effect at 338 nm ($\Delta\varepsilon$ −1.3, R −9.5)[9] that provides a contribution at 589 nm of −285 against the experimental OR of −192 (hexane).

In this case as well, the lowest energy Cotton effect dominates the OR at the sodium D line, i.e., (−)-verbenone is a class a) molecule. In Table 1 are reported OR values obtained at two levels of theory (TDDFT/B3LYP/6-31G* and 6-31++G**), while for the geometry optimization the DFT/B3LYP/6-31G* and 6-31++G**, semiempirical and molecular mechanics, MM, were employed.

A TDDFT/B3LYP/6-31G* OR calculation upon a geometry obtained at the same level of theory, provides −251, i.e., a value which is correct in sign and order of magnitude (and therefore useful for the AC assignment), even though the theoretical absolute value is larger (1.3 times) than the experimental one (−192). From the data of Table 1, it can be concluded that for rigid, class a) systems, with high (say 200 deg [dm g/cm^3]$^{-1}$) OR values, the calculated OR data at the TDDFT/B3LYP/6-31G* level upon input geometries at the DFT/B3LYP/6-31G*, semiempirical or molecular mechanics level, agree well in sign and order of magnitude with the experimental OR data. Therefore, any of the approaches shown in Table 1 can be confidently employed for AC assignments since an enhanced level of theoretical OR computations does not significantly improve the predicted values by bringing them much closer to the experimental data. We have studied also (−)-4-methylverbenene (**3**), which is another example for rigid molecules belonging to class a).[10] We found that even though its experimental $[\alpha]_D$ value is much smaller, ca. 50 deg [dm g/cm^3]$^{-1}$, the calculations of input geometries and OR at any level of theory provide satisfactory results. The estimated OR values are of correct sign and correct order of magnitude, although three times larger than the experimental ones.

TABLE 1. $[\alpha]_D$ Values of 2 (in deg [dm g/cm^3]$^{-1}$), Obtained at the TDDFT/B3LYP/BASIS SET Level of Calculation Using Geometries Calculated with Different Optimization Methods

run	opt method	6-31G*	6-31++G**
1	DFT/B3LYP/6-31++G**	−246	−250
2	DFT/B3LYP/6-31G*	−251	−256
3	AM1	−232	−219
4	PM3	−216	−205
5	MM	−223	−231
6	exp.OR (hexane)	−192	

Again, the use of the more extended 6-31++G** basis set in the OR calculation, has no effect. Certainly, a better agreement between the theoretical vs experimental values would require research efforts that are beyond the aims of the present study. The results shown in Tables 1 and 2 lead to the *first lesson*: for rigid molecules with large OR values at 589 nm (at least ca. 100 deg [dm g/cm^3]$^{-1}$) whose signs and magnitudes are determined by the lowest energy Cotton effect, the use of higher level computation for geometry optimization is of no particular importance. Even if the OR values are smaller it is still possible to predict the correct sign and order of magnitude by using DFT/B3LYP/6-31G* for the input geometry. Yet, in regard to absolute values, a good agreement of experimental vs theoretical values cannot be reached, even using high levels of theory for both the geometry optimization and the OR calculation.

Let us consider the case of (+)-epoxidone (**4**), $[\alpha]_D$ +93, in methanol. Its analysis provides another, perhaps more important, lesson.

For (2*R*,3*R*,4*R*)-epoxidone (**4**) five stable conformers can be found[6a] in the gas phase. The population of these conformers, as well as the corresponding ORs are reported in Table 3 and in Supporting Information, Table 2.

The data reported in Table 3 (and in Table 2 of Supporting Information) show that for this compound a calculation at the TDDFT/B3LYP/6-31G* level for OR, using an input geometry obtained at the DFT/B3LYP/6-31G* level, revealed the most stable conformer (population 54.4%) to be strongly

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TABLE 2. $[\alpha]_D$ Values of 3 (in deg $[\mathrm{dm\ g/cm^3}]^{-1}$), Obtained at the TDDFT/B3LYP/BASIS SET Level of Calculation, Using Geometries Calculated with Different Optimization Methods

run	opt method	6-31G*	6-31++G**
1	DFT/B3LYP/6-31++G**	−124	−120
2	DFT/B3LYP/6-31G*	−121	−115
3	AM1	−115	−87
4	PM3	−121	−105
5	MM	−150	−160
6	exp.OR (hexane)	−42	

TABLE 3. $[\alpha]_D$ (in deg $[\mathrm{dm\ g/cm^3}]^{-1}$) for Each Conformer of (2*R*,3*R*,4*R*)-Epoxidone 4 in the Gas Phase and the Corresponding Averaged Values[a]

conf	% pop 6-31G* (6-31++G**)	6-31G*// 6-31G*	6-31G*// 6-31++G**
1	7.6 (22.1)	29	38
2	54.4 (42.4)	−98	−62
3	10.9 (9.1)	14	23
4	17.6 (18.5)	130	122
5	9.6 (7.8)	71	76
	average	**-20**	**13**
exp.OR (methanol)		+92	

[a] X//Y means that the TDDFT/B3LYP/X basis set level of calculation has been used for [α], while the DFT/B3LYP/Y basis set level have been used for the calculation of geometries and populations.

laevorotatory (−98) while all remaining conformers appeared as dextrorotatory. The final averaged value (6-31G* basis set) is then −20 a number which represents only the 25% of the experimental value, and moreover it is opposite in sign. Clearly, one cannot draw conclusions in these conditions about a configurational assignment. It is noteworthy that even improving the level of OR calculation upon the 6-31G* geometries still gives (fourth column in Table 2 of the Supporting Information, Table 2) an average OR which is wrong in sign, because conformer 2 remains levorotatory while the others remain dextrorotatory. A different outcome, however, was attained when the geometry optimization was performed at the DFT/B3LYP/6-31++G** level (see Tables 2 and 3 of the Supporting Information). In this case, the quality of the basis set has a profound effect, in particular on the populations (Table 3). This fact is really important since the new structural parameters, even at a 6-31G* OR calculation, provide an average OR which is correct in sign although of lower absolute values ($[\alpha]_D$ +13). Furthermore, the use of the same high level of theory to obtain input geometries and OR values (Supporting Information, Table 2, third column) provides more satisfactory results ($[\alpha]_D$ +28). Table 2 of the Supporting Information shows also that employment of even higher basis sets (aug-cc-pVDZ) for both geometry and OR calculations leads to a higher OR value (+57) and then to a better agreement with the experimentally observed values.

In summary, when some conformers exhibit an OR of opposite sign, it is critical to obtain more precise input conformations rather than use higher levels for OR calculations. This is the *second, important lesson:* if the common level of geometry optimization (i.e., DFT/B3LYP/6-31G*) shows several conformers of opposite OR values, a search of more reliable geometries and populations by extended basis sets should become an essential necessary step of the entire analysis.

The case of trans-(4*S*,5*S*)-isocytoxazone (**5**) is even more complex but very instructive.

TABLE 4. Populations and OR Values of (4*S*,5*S*)-5 from Ref 11 (Columns 2 and 3), DFT/B3LYP/6-31++G Populations (Column 4), and TDDFT/B3LYP/6-31G*//DFT/B3LYP/6-31++G** OR (Column 5)**

conf	% pop	589 nm	% pop	589 nm
1	3.8	−25	19.2	−67
2	43.8	58	17.4	−2
3	36.9	16	14.9	−26
4	2.2	32	5.7	28
5	3	32	20.5	−21
6	1.8	−43	3.4	−46
7	1.8	251	1.0	184
8	2.5	11	8.1	−18
9	3	103	3.6	53
10	2.2	51	6.2	3.4
average		**39**		**-19**
exp. OR (methanol)		−94		

We have recently carried out the OR theoretical study of **5**, and other related analogues,[11] with the purpose of determining its absolute configurations. In this study, we assigned a *trans*-4*S*,5*S*-configuration to the dextrorotatory enantiomer of **5** based on theoretically predicted positive ORD curve for this arbitrary chosen absolute configuration.

***trans*-(4*S*,5*S*)-Isocytoxazone, $[\alpha]_D > 0$.**

In this study,[11] we have used one of the most common geometry-optimization techniques, i.e., DFT/B3LYP/6-31G*, which provided at room temperature 10 different structures, eight of which represent 95% of the overall population and show positive OR values (see the Supporting Information, Table 3). There was no doubt, therefore, that the predicted positive average value of +39 for the *trans*-4*S*,5*S*-configuration represents a strong evidence that the dextrorotatory **5** (with $[\alpha]_D$ +79 (THF) and $[\alpha]_D$ +94 (MeOH)) should indeed possess the 4*S*,5*S* absolute configuration. A few years later, Rozwadowska and Tomczak reported[12] that *trans*-(4*S*,5*S*)-isocytoxazone, prepared by a stereocontrolled chemical procedure starting from (+)-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol, was, on the contrary, levorotatory. This surprising finding prompted us to reoptimize the structures of the 10 conformers found in our previous study. When our work was in progress, employing a higher level (DFT/B3LYP/6-31++G**) of theory, Kwit et al. reported[13] that, at higher levels of theory in the geometry optimization and in the OR calculation (they indeed took in account even solvent effects), they reached a configurational assignment of **5** in full agreement with the chemical correlation by Rozwadowska et al.[12]

***trans*-(4*S*,5*S*)-Isocytoxazone, $[\alpha]_D < 0$.**

Here we report our new results on the geometry reoptimization at the DFT/B3LYP/6-31++G** level of the previously reported ten structures[11] and OR calculations of new resulted geometries at the TDDFT/B3LYP/6-31G* level of **5** (see Table 4). The most important observations are as follows: First, the new conformers have populations which are completely different from those of ref 11: in particular, note that conformer 1 for which the old population was 43.8% is now 17.4%, while for conformer 3 the population that was 36.9% is now 14.9%. In other words, the effect of the basis set on the structure appears to be really significant! Second, at the

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TDDFT/B3LYP/6-31G* level (i.e., the same level of theory used in ref 11), the OR values of the new conformers 2, 3, 5, and 8 become negative while the OR value of conformer 1 becomes more negative and that of conformer 7 becomes less positive, so the overall result is the 589 nm OR becomes negative, as well as all the values at the other wavelengths, Table 4 (Supporting Information). Third, the predicted, from new analysis, average $[\alpha]_D$ −19 at 589 nm for (4*S*,5*S*)-**5** came in agreement with the AC assignment of ref 12. Clearly, Kwit at al., who have employed[13] higher levels of theory in the calculations, have obtained a better agreement between theoretical and experimental values. However, it is important to emphasize that even upon DFT/B3LYP/6-31++G** geometry calculation, a lower level then that applied in ref 13, the weighted average OR value has changed from dextrorotatory to a levorotatory. Thus, the AC assignment becomes (−)-(4*S*,5*S*), in agreement with reported[12] experimental data. Of course, taking into account the solvent effects has resulted in a better agreement between predicted and experimental data.[12,13]

The erroneous configurational assignment of *trans*-isocytoxazone **5**[11] by us when DFT/B3LYP/6-31G* was used for conformational analysis gives a *third lesson*: when dealing with flexible substrate the geometry calculation by DFT/B3LYP/6-31G* provides several, different structures, even with OR of the same sign, and a reoptimization of geometry at a higher level of theory (e.g., at least the DFT/B3LYP/6-31++G** level) becomes absolutely necessary.

We want to clarify that we are far from recommending the use of DFT/B3LYP/6-31++G** method as a general and reliable protocol. We fully agree with a reviewer of this paper who noticed that "...(B3LYP/6-31++G**) is in fact a very unbalanced basis set. Diffuse functions on a very incomplete double-ζ basis can lead to huge (intramolecular in this case) basis set superposition errors (BSSE). For B3LYP such a basis simulates to some extent the intrinsically missing medium and large range correlation effects, and therefore the results are seemingly better." This suggest some "uncontrollable error compensation [which] may not always work". All in these lines, a need of general protocol for finding a correct input geometry emerges as a new challenge for the theoreticians in the field. Actually, some deficiencies of the hybrid B3LYP functional have been recently underscored,[14] and at the same time, more accurate geometry-optimization techniques have been pointed out.[13,15]

Since we have consistently obtained geometries and populations at the same level of theory, one of the reviewers has suggested a way to find out whether optical rotations of (2*R*,3*R*,4*R*)-epoxidone (**4**) and *trans*-(4*S*,5*S*)-isocytoxazone (**5**) are more sensitive to geometry or populations. Accordingly, for both **4** and **5** we have calculated higher level DFT/B3LYP/6-311++G(2d,2p) single-point electronic energies for the conformational structures obtained at the DFT/B3LYP/6-31G* level. Then, we have computed E_{mix} as follows: E_{mix} = free energy(B3LYP/6-31G*) − electronic energy(B3LYP/6-31G*) + electronic energy(B3LYP/6-311++G(2d,2p)). E_{mix} represents one energy that contains the vibrational contribution from a simple frequency calculation at the B3LYP/6-31G* level and the electronic contribution from a higher level B3LYP/6-311++G(2d,2p) calculation. E_{mix} values have been used to obtain a new set of improved Boltzmann populations to work out OR predictions at TDDFT/B3LYP/6-31G*//DFT/B3LYP/6-31G*. In this way, we obtain $[\alpha]_D = +3$ for (2*R*,3*R*,4*R*)-epoxidone (**4**) and $[\alpha]_D = +28$ for *trans*-(4*S*,5*S*)-isocytoxazone (**5**) (see Table 5 of the Supporting Information for details on populations). These results demonstrate that the improved Boltzmann populations suffice to change the OR sign only of **4**, while for **5** the wrong AC assignment still remains. For the latter, the structural parameters seem to play a major role. In order to elucidate this point, we have considered conformer 2 of **5** which provides the largest contribution to the wrong OR prediction. Let us recall that for this conformer the computed OR values at 598 nm are: +58 using TDDFT/B3LYP/6-31G*//DFT/B3LYP/6-31G* and −2 using TDDFT/B3LYP/6-31G*//DFT/B3LYP/6-31++G**. Moreover, its geometry has been fully optimized at the DFT/B3LYP/6-311++G(2d,2p) level too, and the corresponding calculated TDDFT/B3LYP/6-31G* OR values at 589 nm is +1. At a first glance, the three structures look quite similar. However, a closer inspection reveals that only one of the four dihedral angles associated to internal rotations, i.e., those describing the orientation of the two rings, displays some differences, the remaining being almost unchanged. Values of this dihedral are 45.1 (6-31G*), 50.1 (6-31++G**), and 49.5 (6-311++G(2d,2p)) (see the Supporting Information for the optimized structures). Therefore, here we document that a change of only 5 degrees (from 45 to 50) for the internal rotation about the bond connecting the two rings of *trans*-(4*S*,5*S*)-isocytoxazone (**5**) provides a variation of the OR by as large as 60 deg $[\mathrm{dm\ g/cm^3}]^{-1}$. In other words, the OR calculation is very sensitive to seemingly small geometry variations. All together, these results demonstrate that while it is critical to get the correct Boltzmann populations it is very important as well to obtain the reliable conformer geometries.

In summary, this study underscores the importance of geometry optimization as a fundamental step before carrying out reliable OR calculations and AC assignment. Another more specific conclusion comes to mind in relation to *trans*-isocytoxazone problem. How safe are in general the AC assignments based on predicted OR data when no additional proofs by other more direct methods, such as chemical correlation or X-ray analysis exist? The need to check out our theoretical AC assignment[11] became obvious only after (−)-(4*S*,5*S*)-*trans*-isocytoxazone was synthesized from the known (+)-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol.[12] We hope that our study unveils reasonable concerns and calls for a particular caution about AC assignments of flexible compounds where the danger of making an erroneous AC conclusion as result of conformational analysis at insufficiently high level of theory is expected to be the highest.

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Supporting Information Available: Computational detail populations and OR data at different levels of theory for compounds **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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