JOC Article

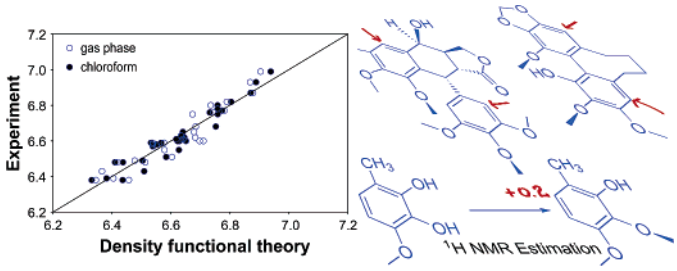
Stereoelectronic Effects on ^{1}H Nuclear Magnetic Resonance Chemical Shifts in Methoxybenzenes

Maja Lambert, Lars Olsen, and Jerzy W. Jaroszewski*

Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen, Denmark

jj@dfuni.dk

Received August 25, 2006



Investigation of all O-methyl ethers of 1,2,3-benzenetriol and 4-methyl-1,2,3-benzenetriol (**3**−**16**) by ^{1}H NMR spectroscopy and density-functional calculations disclosed practically useful conformational effects on ^{1}H NMR chemical shifts in the aromatic ring. While the conversion of phenol (**2**) to anisole (**1**) causes only small positive changes of ^{1}H NMR chemical shifts ($\Delta\delta < 0.08$ ppm) that decrease in the order $H_{ortho} > H_{meta} > H_{para}$, the experimental O-methylation induced shifts in ortho-disubstituted phenols are largest for H_{para}, $\Delta\delta = 0.19 \pm 0.02$ ppm ($n = 11$). The differences are due to different conformational behavior of the OH and OCH_3 groups; while the ortho-disubstituted OH group remains planar in polyphenols due to hydrogen bonding and conjugative stabilization, the steric congestion in ortho-disubstituted anisoles outweighs the conjugative effects and forces the Ar−OCH_3 torsion out of the ring plane, resulting in large stereoelectronic effects on the chemical shift of H_{para}. Conformational searches and geometry optimizations for **3**−**16** at the B3LYP/6-31G** level, followed by B3LYP/6-311++G-(2d,2p) calculations for all low-energy conformers, gave excellent correlation between computed and observed ^{1}H NMR chemical shifts, including agreement between computed and observed chemical shift changes caused by O-methylation. The observed regularities can aid structure elucidation of partly O-methylated polyphenols, including many natural products and drugs, and are useful in connection with chemical shift predictions by desktop computer programs.

Introduction

Conformation of the methoxy group in anisole (methoxybenzene, **1**, Figure 1), its phase dependence, and the effects of substituents have been the subject of many experimental and theoretical studies.[1] The energy barrier for rotation of the methoxy group (Ar−OCH_3) in unsubstituted anisole in the gas phase was determined to be roughly 10 kJ/mol,[2] and thus only the planar conformation (conformation A, Figure 1), stabilized by conjugative effects, is observed. Stable planar conformations are retained in the presence of a single ortho substituent.[3] However, perpendicular conformation of the methoxy group (conformation B) is imposed in 2,6-disubstituted anisoles, and the resulting redistribution of electron density is known to affect ^{13}C NMR chemical shifts.[4,5] Thus, the chemical shift of the methyl groups in the planar conformation A is about δ 56, changing to about δ 61 when the methoxy group is forced out of the aromatic ring plane.[4]

By contrast, effects of methoxy group rotation on ^{1}H NMR chemical shifts have not been studied, even though conformation-dependent electron density release from the oxygen atom is expected to influence chemical shifts of the aromatic ring hydrogen atoms considerably and may be useful as a structural assignment tool.[6] ^{1}H NMR chemical shifts of simple aromatic compounds can be calculated quite accurately by use of empirical substituent rules or database-derived predictions incorporated in widely used desktop computer programs for prediction of ^{1}H NMR spectra.[7] However, the absence of explicit

10.1021/jo061757x CCC: $33.50
Published on Web 11/11/2006

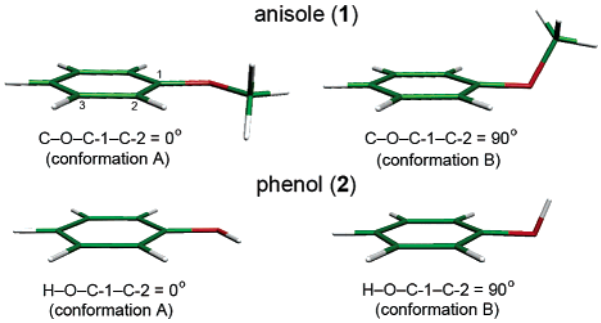


FIGURE 1. Minimum- and maximum-energy conformations of anisole (**1**) and phenol (**2**).

correction for stereoelectronic effects of methoxy groups, resulting from different conformational behavior of hydroxy and alkoxy groups, may lead to substantial differences between calculated and observed chemical shifts. Due to the stereoelectronic effects, the O-methylation induced shifts of aromatic ring hydrogen atoms in ortho-disubstituted phenols[6] are very much different than those in phenol[8] (**2**) itself. In this work we demonstrate, by investigation of ^{1}H NMR spectra of a series of model compounds, that the effects of methoxy group conformation can be easily generalized, affording a set of practically useful rules. The experimental data are corroborated by calculations with density functional theory (DFT) method,[9] which reproduces the effects very well.

Results and Discussion

Synthesis and ^{1}H NMR Spectra of Model Compounds. The complete series of methyl ethers of 1,2,3-benzenetriol (**3**−**8**) and 4-methyl-1,2,3-benzenetriol (**9**−**16**) were included in the investigation. The latter compounds were prepared by reduction of 2,3,4-trihydroxybenzaldehyde or 2,3,4-trimethoxybenzaldehyde followed by partial O-methylation or demethylation.[10] The products were isolated by preparative HPLC and their structures were confirmed by 1D and 2D NMR experiments.

^{1}H NMR spectra of **3**−**16** were recorded in chloroform-*d* with 50−70 mM solutions. To ensure that the determined chemical shifts are not influenced by intermolecular interactions, the spectra were recorded again after dilution of the samples by a factor of 20, which did not affect the observed chemical shifts. The changes of ^{1}H NMR chemical shifts observed upon stepwise O-methylation of **3** and **9** are shown in Schemes 1 and 2, respectively. The absolute chemical shift values are reported in the Supporting Information (Table S1). Whenever necessary, heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC), and nuclear Overhauser effect (NOESY) spectra were recorded for unambiguous resonance assignments.

In the simplest possible case of O-methylation of a phenol group, the conversion of phenol (**2**) to anisole (**1**) causes only a small chemical shift change of H_{ortho} ($\Delta\delta = 0.08$ ppm) and H_{meta} ($\Delta\delta = 0.04$ ppm), and has nearly no effect on H_{para}.[8] However, for the methyl ethers of 1,2,3-benzenetriol (**3**) and 4-methyl-1,2,3-benzenetriol (**9**), entirely different relationships are observed (Schemes 1 and 2). Notably, O-methylation of ortho-disubstituted hydroxyl groups caused a large shift of H_{para} by $\Delta\delta = 0.19 \pm 0.02$ ppm (mean ± standard deviation; $n = 11$), whereas only approximately half as large a shift of H_{para} was observed in the case of ortho-monosubstituted hydroxy groups, $\Delta\delta = 0.11 \pm 0.01$ ppm ($n = 4$). The remaining shifts were considerably smaller. Thus, the shift of H_{ortho} upon O-methylation of ortho-monosubstituted hydroxy groups was $\Delta\delta = -0.03 \pm 0.03$ ppm ($n = 8$). The O-methylation-induced shifts of H_{meta} were likewise small, $\Delta\delta = 0.05 \pm 0.02$ ppm ($n = 8$) and $\delta = 0.01 \pm 0.02$ ppm ($n = 12$) for ortho-disubstituted and ortho-monosubstituted phenol groups, respectively. It is apparent that O-methylation-induced changes of aromatic ring

(1) (a) Baddeley, G.; Smith, N. H. P. *J. Chem. Soc*. **1961**, 2516−2519. (b) Grubb, E. L.; Smyth, C. P. *J. Am. Chem. Soc.* **1962**, *83*, 4873−4878. (c) Baddeley, G.; Vickars, M. A. *J. Chem. Soc*. **1963**, 765−770. (d) Clark, E. R.; Williams, S. G. *J. Chem. Soc. B* **1967**, 859−866. (e) Aroney, J. M.; Le Févre, R. J. W.; Pierens, P. K.; The, M. G. N. *J. Chem. Soc. B* **1969**, 666−669. (f) Owen, N. L.; Hester, R. E. *Spectrochim. Acta, Part A* **1969**, *25*, 343−354. (g) Helgstrand, E. *Acta Chem. Scand.* **1970**, *24*, 3687−3696. (h) Seip, H. M.; Seip, R. *Acta Chem. Scand.* **1973**, *27*, 4024−4027. (i) Tylli, H.; Konshchin, H. *J. Mol. Struct.* **1977**, *42*, 7−12. (j) Emsley, J. W.; Exon, C. M.; Slack, S. A.; Giroud, A. M. *J. Chem. Soc., Perkin Trans. 2* **1978**, 928−931. (k) Anderson, G. M.; Kollman, P. A.; Domelsmith, L. N.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 2344−2352. (l) Friege, H.; Klessinger, M. *Chem. Ber.* **1979**, *112*, 1614−1625. (m) Konschin, H.; Tylli, H.; Grundfelt-Forsius, C. *J. Mol. Struct.* **1981**, *77*, 51−64. (n) Klessinger, M.; Zywietz, A. *THEOCHEM* **1982**, *7*, 341−350. (o) Gerhards, J.; Ha, T. K.; Perlia, X. *Helv. Chim. Acta* **1982**, *65*, 105−121. (p) Schaefer, T.; Wildman, T. A.; Peeling, J. *J. Magn. Reson.* **1984**, *56*, 144−148. (q) Schaefer, T.; Laatikainen, R.; Wildman, T. A.; Peeling, J.; Penner, G. H.; Baleja, J.; Marat, K. *Can. J. Chem.* **1984**, *62*, 1592−1597. (r) Nagy, L. T.; Jancarova, M. *Chem. Pap.* **1985**, *39*, 289−294. (s) Schaefer, T.; Salman, S. R.; Wildman, T. A.; Penner, G. H. *Can. J. Chem.* **1985**, *63*, 782−786. (t) Onda, M.; Toda, A.; Mori, S.; Yamaguchi, I. *J. Mol. Struct.* **1986**, *144*, 47−51. (u) Schaefer, T.; Penner, G. H. *Can. J. Chem.* **1988**, *66*, 1635−1640. (v) Schaefer, T.; Sebastian, R. *Can. J. Chem.* **1989**, *67*, 1148−1152. (w) Breen, P. J.; Bernstein, E. R.; Secor, H. V.; Seeman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 1958−1968. (x) Biekofsky, R. R.; Pomilio, A. B.; Aristegui, R. A.; Contreras, R. H. *J. Mol. Struct.* **1995**, *344*, 143−150. (y) Facelli, J. C.; Orendt, A. M.; Jiang, Y. J.; Pugmire, R. J.; Grant, D. M. *J. Phys. Chem.* **1996**, *100*, 8268−8272. (z) Dolgounitcheva, O.; Zakrzewski, V. G.; Ortiz, J. V.; Ratovski, G. V. *Int. J. Quant. Chem.* **1998**, *70*, 1037−1043.

(2) (a) Spellmeyer, D. C.; Grootenhuis, P. D. J.; Miller, M. D.; Kuyper, L. F.; Kollman, P. A. *J. Phys. Chem.* **1990**, *94*, 4483−4491. (b) Rumi, M.; Zerbi, G. *J. Mol. Struct.* **1999**, *509*, 11−28. (c) Bzhezovskii, V. M.; Kapustin, E. G. *Russ. J. Org. Chem.* **2002**, *38*, 564−572. (d) Bossa, M.; Morpurgo, S.; Stranges, S. *THEOCHEM* **2002**, *618*, 155−164. (e) Kieninger, M.; Ventura, O. N.; Diercksen, G. H. F. *Chem. Phys. Lett.* **2004**, *389*, 405−412.

(3) (a) Gerzain, M.; Buchanan, G. W.; Driega, A. B.; Facey, G. A.; Enright, G.; Kirby, R. A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2687−2693. (b) Popik, M. V.; Novikov, V. P.; Vilkov, L. V.; Samdal, S.; Tafipolsky, M. A. *J. Mol. Struct.* **1996**, *376*, 173−181. (c) Tsuzuki, S.; Houjou, H.; Nagawa, Y.; Hiratani, K. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1271−1273. (d) Novikov, V. P.; Vilkov, L. V.; Oberhammer, H. *J. Phys. Chem. A* **2003**, *107*, 908−913.

(4) (a) Makriyannis, A.; Knittel, J. J. *Tetrahedron Lett.* **1979**, *20*, 2753−2756. (b) Calvert, D. J.; Cambie, R. C.; Davis, B. R. *Org. Magn. Reson.* **1979**, *12*, 583−586. (c) A Makriyannis, A.; Fesik, S. *J. Am. Chem. Soc.* **1982**, *104*, 6462−6463. (d) Roitman, J. N.; James, L. F. *Phytochemistry* **1985**, *24*, 835−848. (e) Joseph-Nathan, P.; García-Martínez, C.; Morales-Ríos, M. S. *Magn. Reson. Chem.* **1990**, *28*, 311−314. (f) Simonsen, H. T.; Larsen, M. D.; Nielsen, M. W.; Adsersen, A.; Olsen, C. E.; Strasberg, D.; Smitt, U. W.; Jaroszewski, J. W. *Phytochemistry* **2002**, *60*, 817−820.

(5) (a) Dhami, K. S.; Stothers, J. B. *Can. J. Chem.* **1966**, *44*, 2855−2866. (b) Buchanan, G. W.; Montaudo, G.; Finocchiaro, P. *Can. J. Chem.* **1974**, *52*, 767−774. (c) Fujita, M.; Yamada, M.; Nakajima, S.; Kawai, K.-I.; Nagai, M. *Chem. Pharm. Bull.* **1984**, *32*, 2622−2627.

(6) Lambert, M.; Stærk, D.; Hansen, S. H.; Sairafianpour, M.; Jaroszewski, J. W. *J. Nat. Prod.* **2005**, *68*, 1500−1509.

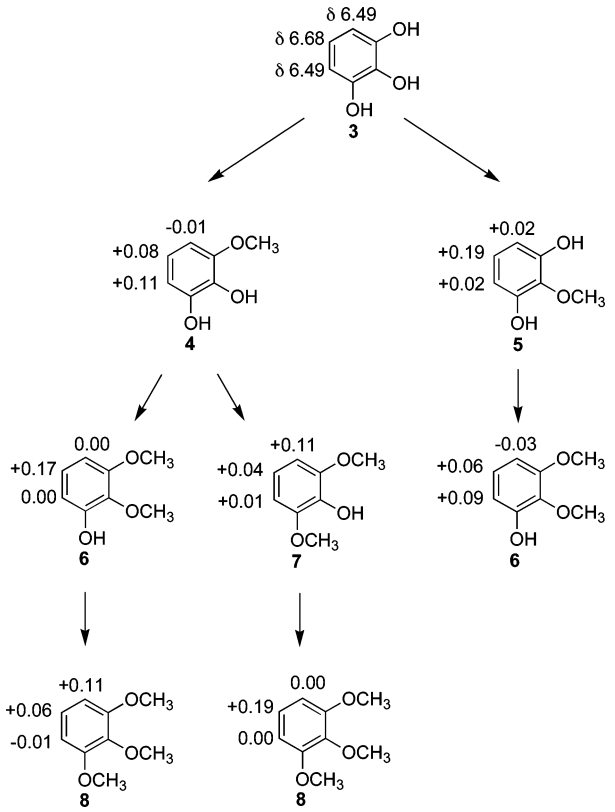
(7) (a) ChemNMR Pro incorporated in ChemDraw, v. 10.0, CambridgeSoft Corp., Cambridge, MA. (b) ACD/HNMR Predictor, v. 9.0, ACD/Labs, Toronto, Canada.

(8) Abraham, R. J.; Reid, M. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1081−1091.

(9) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793−1873.

(10) (a) Pattekhan, H. H.; Divakar, S. *J. Mol. Catal. A* **2001**, *169*, 185−191. (b) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 664−671. (c) Carvalho, C. F.; Russo, A. V.; Sargent, M. V. *Aust. J. Chem.* **1985**, *38*, 777−792.

SCHEME 1. Changes of ^1H NMR Chemical Shifts of Aromatic Hydrogen Atoms during Stepwise O-Methylation of 1,2,3-Benzenetriol (3)[a]



[a] For spectra (600 MHz) in chloroform-*d*.

hydrogens in polyoxygenated benzenes decrease in the order $H_{para} \gg H_{meta} \approx H_{ortho}$ and are entirely different from those observed in phenol, where the shifts are small and decrease in the order $H_{ortho} > H_{meta} > H_{para}$.[8] The particularly large shifts are observed when the O-methylated hydroxy group is flanked by two ortho substituents. Thus, while the effect of O-methylation of phenol is attributable to differences in electronegativity between the hydroxy and the methoxy group, the effects observed in substituted anisole derivatives are stereoelectronic in nature. The effect appears to be general and independent of whether the ortho substituents are OCH_3, OH, or CH_3.

Stereoelectronic Effects of Methoxy Group Rotation on ^1H Nuclear Shieldings in DFT Calculations. Three simple model compounds, anisole (**1**), phenol (**2**), and 2-methoxyphenol (guaiacol, **17**), were studied by use of B3LYP theory in order to assess trends on the ^1H nuclear shielding constants. Initially, differences between nuclear shieldings in the two conformations of anisole (A and B, Figure 1) were calculated with different basis sets (Table 1). Good basis-set independence was observed, and further calculations were performed at the B3LYP/6-311++G(2d,2p) level.[11] Energy differences and nuclear shielding constants for planar and nonplanar conformations of **1** and **2** (Figure 1), as well as for four low-energy conformations of **17** (Figure 2), which represents a structural motif present in many of the compounds in Schemes 1 and 2, are shown in Table 2. The calculations[12] were performed for molecules in vacuum as well as in chloroform, by use of the conductorlike polarized continuum (CPCM) solvent model.[13]

The calculated rotational barriers for anisole (**1**) and phenol (**2**) were about 12 and 15 kJ/mol, respectively. The increased energy for the nonplanar conformation of **2** as compared to **1** (Tables 1 and 2) is in agreement with previous results.[2,14] Solvent effects on the calculated rotational barriers in **1** and **2** were small (Table 2). For partially O-methylated polyphenol derivatives, hydrogen bonding is expected to contribute to relative stability of individual conformers.[15,16] The hydrogen-bond enthalpy in 2-methoxyphenol (**17**) was previously estimated to be 18.4 kJ/mol in vacuo,[15] diminishing to below 3 kJ/mol in polar hydroxylic solvents.[16] Accordingly, the DFT calculations identified the planar conformation A stabilized by an intramolecular hydrogen bond as a global energy minimum (Table 2, Figure 2), in agreement with previous theoretical end experimental studies.[15−17] Interestingly, the next most stable conformation identified in this work, both in vacuum and in chloroform, was that with the methoxy group perpendicular to the aromatic ring plane (conformation C, Figure 2), which still allows for the intramolecular hydrogen bond. The energy difference between conformations A and C of **17** corresponded to the energy difference between conformations A and B of **2** (Table 2). Conformations without the intramolecular hydrogen bond were considerably higher in energy, with a significant difference between gas-phase and chloroform stability of conformations B and D, which have a solvent-exposed hydroxy group.

The change of the orientation of the ArO−H and ArO−CH_3 bonds in anisole (**1**) and phenol (**2**) from planar toward perpendicular (Figure 1) leads to systematic and significant

(11) For a review and selected recent examples of DFT chemical shift calculations, see (a) Helgaker, T.; Jaszunski, M.; Ruud, K. *Chem. Rev.* **1999**, *99*, 293−352. (b) Jolibois, F.; Soubias, O.; Reat, V.; Milon, A. *Chem. Eur. J.* **2004**, *10*, 5996−6004. (c) Pihlaja, K.; Tahtinen, P.; Klika, K. D.; Jokela, T.; Salakka, A.; Wahala, K. *J. Org. Chem.* **2003**, *68*, 6864−6869. (d) Bifulco, G.; Gomez-Paloma, L.; Riccio, R.; Gaeta, C.; Troisi, F.; Neri, P. *Org. Lett.* **2005**, *7*, 5757−5760. (e) Roslund, M. U.; Klika, K. D.; Lehtila, R. L.; Tahtinen, P.; Sillanpaa, R.; Leino, R. *J. Org. Chem.* **2004**, *69*, 18−25. (f) Sefzik, T. H.; Turco, D.; Iuliucci, R. J.; Facelli, J. C. *J. Phys. Chem. A* **2005**, *109*, 1180−1187. (g) Hennig, M.; Munzarova, M. L.; Bermel, W.; Scott, L. G.; Sklenar, V.; Williamson, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 5851−5858. (h) Perez, M.; Peakman, T. M.; Alex, A.; Higginson, P. D.; Mitchell, J. C.; Snowden, M. J.; Morao, I. *J. Org. Chem.* **2006**, *71*, 3103−3110.

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

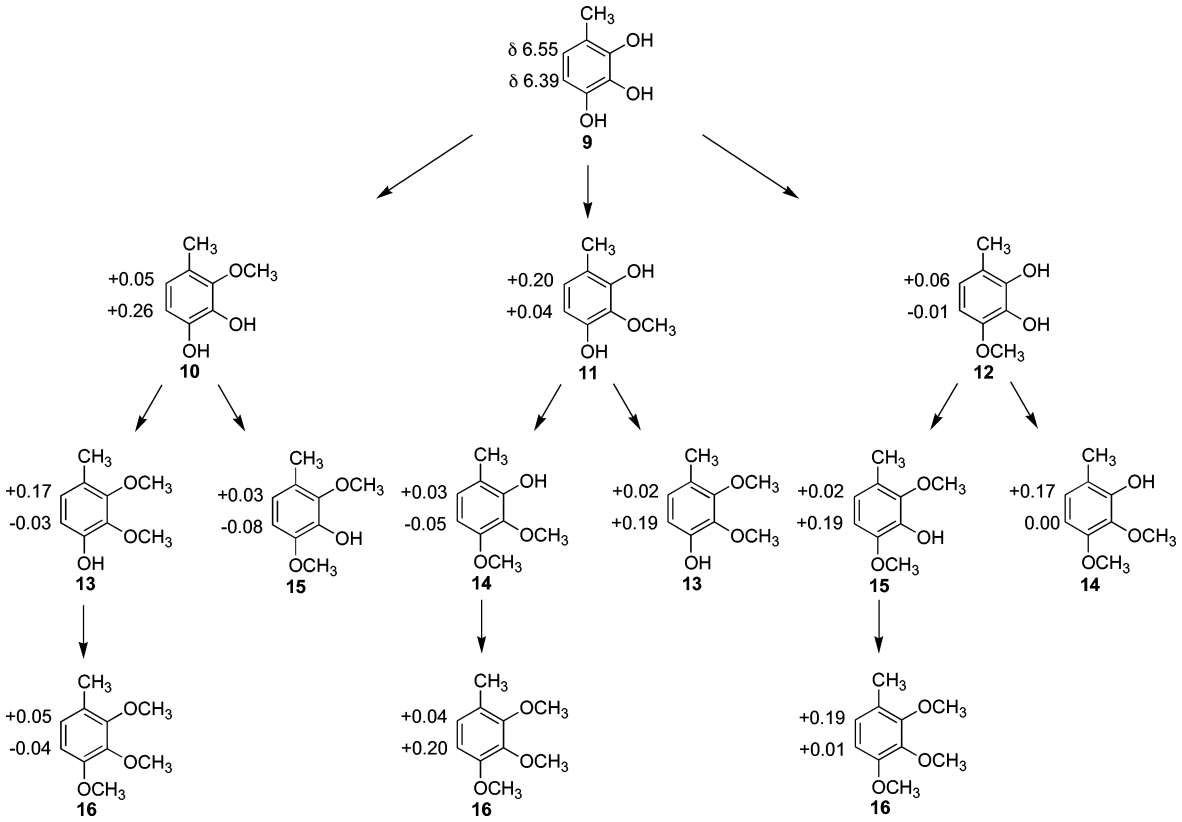
(13) Cossi, M.; Rega, N.; Giovanni, S.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681.

(14) (a) Larsen, N. W. *J. Mol. Struct.* **1979**, *51*, 175−190. (b) Schaefer, T.; Wildman, T. A.; Sebastian, R. *THEOCHEM* **1982**, *89*, 93−101. (c) Konschin, H. *THEOCHEM* **1983**, *92*, 173−189. (d) Bock, C. W.; Trachtman, M.; George, P. *THEOCHEM* **1986**, *139*, 63−74. (e) Politzer, P.; Sukumar, N. *THEOCHEM* **1988**, *179*, 439−449. (f) Puebla, C.; Ha, T.-K. *THEOCHEM* **1990**, *204*, 337−351. (g) Portalone, G.; Schultz, G.; Domenicano, A.; Hargittai, I. *Chem. Phys. Lett.* **1992**, *197*, 482−488. (h) Buemi, G. *Chem. Phys.* **2002**, *282*, 181−195.

(15) Korth, H.-G.; de Heer, M. I.; Mulder, P. *J. Phys. Chem. A* **2002**, *106*, 8779−8789.

(16) Lithoxoidou, A. T.; Bakalbassis, E. G. *J. Phys. Chem. A* **2005**, *109*, 366−377.

SCHEME 2. Changes of ^{1}H NMR Chemical Shifts of Aromatic Hydrogen Atoms during Stepwise O-Methylation of 4-Methyl-1,2,3-benzenetriol (9)[a]



[a] For spectra (600 MHz) in chloroform-*d*.

TABLE 1. Energy Differences and Differences in ^{1}H Nuclear Shieldings (σ) between Planar and Nonplanar Conformations of Anisole (1) Calculated with Different Basis Sets

	nuclear shielding difference $\Delta\sigma$,[a] ppm				
atom	6-31G**	6-311++G(2d,2p)	aug-cc-pVDZ	aug-cc-pVTZ	aug-cc-pVQZ
H-2	−0.53	−0.45	−0.47	−0.39	−0.38
H-3	−0.10	−0.06	−0.02	−0.06	−0.04
H-4	−0.24	−0.25	−0.23	−0.25	−0.21
H-5	−0.08	−0.07	−0.08	−0.10	−0.05
H-6	−0.25	−0.21	−0.15	−0.10	−0.14
OCH_3	0.01	0.02	0.01	0.01	0.02
relative energy,[a] kJ/mol	12.9	12.4	13.7	13.2	13.3

[a] Conformation B relative to conformation A (see Figure 1).

changes of nuclear shielding of the hydrogen atoms in the aromatic ring (Table 3), whereas practically no changes are observed for the methoxy group itself (Table 2). The most significant changes upon the rotation are observed for H_{ortho} that is originally syn-oriented to the OR group (H-2; $\Delta\sigma$ = −0.45 ppm for **1** and −0.75 ppm for **2**) as well as for H_{para} (H-4; $\Delta\sigma$ = −0.25 ppm for **1** and −0.29 ppm for **2**), whereas H_{meta} (H-3, H-5) are only weakly affected (Table 3). The trends observed in vacuum and in chloroform are identical (Table 2). For **1** and **2** in vacuum, the chemical shielding of H_{ortho} changes by 0.25 and 0.45 ppm, respectively, as the Ar−OR torsion changes by 180° between the two isoenergetic conformations with the ArO−R bond in the aromatic ring plane. The respective differences diminish to 0.18 and 0.21 ppm in chloroform. In **17**, the out-of-plane rotation of the methoxy group caused changes of nuclear shieldings that closely parallel those observed in **1** (Table 2). It is therefore concluded that neither the presence of an ortho-oxygen atom nor hydrogen bonding influences the stereoelectronic effect of the methoxy group on ^{1}H shieldings in the aromatic ring significantly.

Shieldings in Methyl Ethers of Polyphenols. The MMFF force field[18] was used to generate initial conformations of compounds **3**−**16** by a Monte Carlo search. All conformations within at least 25 kJ/mol from the calculated lowest-energy conformation were geometry-optimized by use of B3LYP/6-

(17) (a) Vokin, A. I.; Frolov, Y. L.; Medvedev, S. A.; Dyachkova, S. G. *Russ. Chem. Bull.* **1993**, *42*, 1680−1683. (b) Konijn, S. W.; Steenvoorden, R. J. J. M.; Kistemaker, P. G.; Weeding, T. L. *J. Phys. Chem.* **1994**, *98*, 5399−5403. (c) Matos, M. A. R.; Miranda, M. S.; Morais, V. M. F. *J. Chem. Eng. Data* **2003**, *48*, 669−679.

(18) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

TABLE 2. ^1H Nuclear Shieldings (σ) and Relative Energies of Planar (A) and Nonplanar (B) Conformations of Anisole (1) and Phenol (2), and Conformations A−D of 2-Methoxyphenol (17)[a]

	nuclear shielding constant σ, ppm															
	anisole (**1**)				phenol (**2**)				2-methoxyphenol (**17**)							
	gas phase		chloroform		gas phase		chloroform		gas phase				chloroform			
nucleus	A	B	A	B	A	B	A	B	A	B	C	D	A	B	C	D
H-2	24.71	24.26	24.39	23.97	24.93	24.18	24.47	23.94								
H-3	24.14	24.08	23.82	23.77	24.25	24.12	23.95	23.83	24.80	24.58	24.35	24.32	24.47	24.38	24.02	24.05
H-4	24.51	24.26	24.22	23.94	24.56	24.27	24.31	24.00	24.65	24.69	24.65	24.60	24.33	24.45	24.33	24.35
H-5	24.16	24.09	23.85	23.77	24.16	24.12	23.89	23.83	24.56	24.84	24.39	24.50	24.30	24.53	24.09	24.17
H-6	24.46	24.25	24.21	23.95	24.48	24.18	24.26	23.94	24.50	25.07	24.42	24.89	24.25	24.57	24.14	24.41
OCH_3	27.87	27.89	27.77	27.81					27.77	27.33	27.92	27.87	27.68	27.27	27.85	27.82
relative energy,[b] kJ/mol	0.0	12.4	0.0	11.5	0.0	14.5	0.0	15.2	0.0	29.6	11.2	24.7	0.0	21.0	10.2	12.0

[a] Structures were optimized with the B3LYP/6-31G** method and the energies as well as NMR shieldings were calculated at the B3LYP/6-311++G(2d,2p) level in gas phase or by use of the CPCM model for chloroform. [b] Relative to conformation A (see Figures 1 and 2).

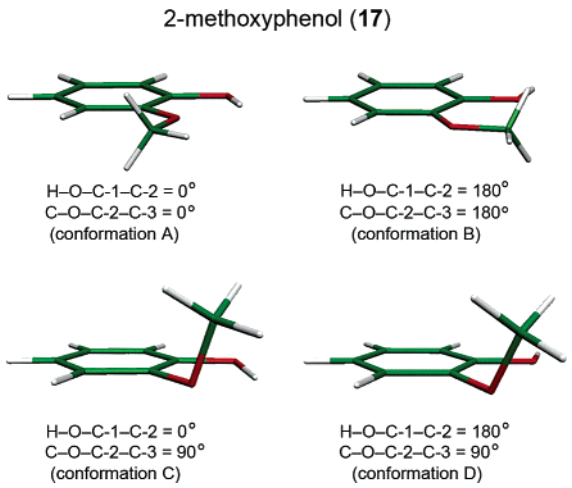


FIGURE 2. Four low-energy conformations of 2-methoxyphenol (**17**).

TABLE 3. Stereolectronic Effects of the Methoxy Group Rotation in Anisole (1) and of the Hydroxy Group Rotation in Phenol (2) on ^1H Nuclear Shieldings (σ)[a]

	nuclear shielding for C−O−C1−C2 torsion angle						
atom	0°	30°	60°	90°	120°	150°	180°
			Anisole (**1**)				
H-2	0	−0.17	−0.50	−0.45	−0.36	−0.27	−0.25
H-3	0	−0.03	−0.03	−0.06	−0.02	0.06	0.02
H-4	0	−0.03	−0.15	−0.25	−0.15	−0.03	0
H-5	0	0.05	−0.03	−0.07	−0.04	−0.04	−0.02
H-6	0	−0.02	−0.11	−0.21	−0.25	0.08	0.25
relative energy,[b] kJ/mol	0	4.7	11.1	12.4	11.1	4.7	0
			Phenol (**2**)				
H-2	0	−0.18	−0.52	−0.75	−0.72	−0.53	−0.45
H-3	0	−0.02	−0.09	−0.13	−0.12	−0.10	−0.09
H-4	0	−0.07	−0.20	−0.29	−0.20	−0.07	0
H-5	0	−0.02	−0.03	−0.04	0.00	0.07	0.09
H-6	0	−0.08	−0.26	−0.30	−0.06	0.27	0.45
relative energy,[b] kJ/mol	0	3.3	10.5	14.5	10.5	3.3	0

[a] Calculated in the gas phase at the B3LYP/6-311++G(2d,2p) level; shieldings for 0 torsion angles are set to zero. [b] Relative to conformation A; the energies were calculated by use of B3LYP/6-311++G(2d,2p).

31G**. Single-point energies and the ^1H NMR shielding constants were calculated with the 6-311++G(2d,2p) basis set, both in the gas phase and in chloroform with the CPCM model (Supporting Information, Tables S2−S7).[12]

For three of the compounds (**4**, **12**, and **13**), the differences in energy between the most stable and the next most stable conformations were larger than 20 kJ/mol, both in the gas phase and in the solvent (Table 4). The most stable conformations of these compounds are those stabilized by intramolecular hydrogen bonds (Figure 3). The stable conformations of **4** and **12** are essentially planar, with two hydrogen bonds each; the high-energy conformations of **4** and **12** are also nearly planar but are stabilized with only one hydrogen bond. In the most stable conformation of **13**, the two ortho-disubstituted methoxy groups are rotated out of plane by about 70° to the opposite faces of the benzene ring (Figure 3). The stable conformations of **4**, **12**, and **13**, identified as deep, global energy minima, can be regarded as accurate representations of actual structures present during acquisition of the experimental ^1H NMR data (Table S1). The ^1H NMR shieldings calculated for these conformations, both in gas phase and in chloroform (Table 5), are plotted against the experimental chemical shifts in Figure 4. The nuclear shieldings calculated for the low-energy conformations of **4**, **12**, and **13** correlated far better with the experimental values than those calculated for the high-energy conformations (Figure 3).

TABLE 4. Calculated Conformational Energies of Compounds 3−16

		relative energy,[a] kJ/mol	
compd	conformation[b]	gas phase	chloroform
3	2	9.4	5.9
4	2	27.8	20.9
5	2	13.8	10.1
6	2	7.7	8.5
7	2	9.4	16.2
8	2	4.7	7.3
8	3	10.6	15.2
8	4	13.8	16.0
9	2	1.8	10.0
9	3	10.0	6.2
10	2	16.2	11.5
11	2	6.9	8.8
11	3	13.1	9.9
12	2	29.6	31.1
13	2	38.4	39.8
14	2	7.0	7.7
15	2	1.0	−6.1
15	3	5.4	0.2
16	2	5.3	7.2
16	3	5.6	4.5
16	4	11.4	11.4
16	5	12.4	11.7

[a] Relative to conformation 1; the energies were calculated by use of B3LYP/6-311++G(2d,2p). [b] The conformations are labeled according to increasing energy in the gas phase.

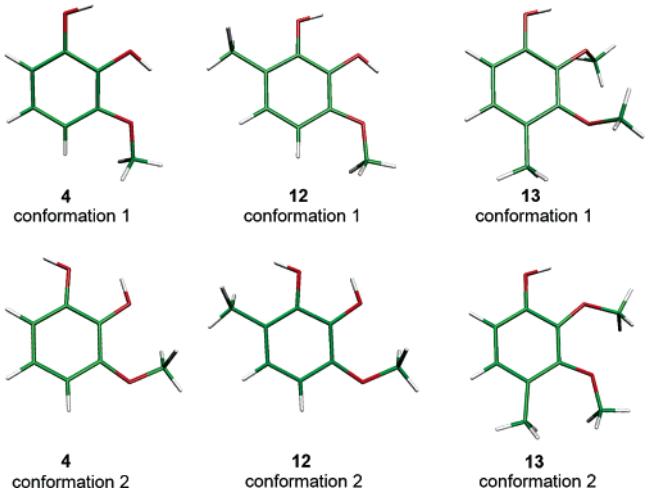


FIGURE 3. Global energy minima (conformation 1) and next lowest-energy conformations (conformation 2) of compounds **4**, **12**, and **13**.

TABLE 5. Calculated ^{1}H Nuclear Shieldings (σ) for Compounds 4, 12, and 13[a]

		calculated nuclear shielding σ, ppm			
		gas phase		chloroform	
H-atom	experimental chemical shift, δ	conf. 1	conf. 2	conf. 1	conf. 2
		Compound **4**			
H-4	6.48	25.24	24.99	24.88	24.84
H-5	6.76	24.73	24.97	24.44	24.68
H-6	6.60	24.80	25.34	24.60	24.88
CH_3	3.88	27.79	27.28	27.69	27.23
		Compound **12**			
H-4	6.38	25.36	25.11	25.04	24.94
H-5	6.61	24.89	25.05	24.61	24.76
CH_3	2.20	29.41	29.52	29.39	29.43
OCH_3	3.85	27.82	27.34	27.74	27.29
		Compound **13**			
H-5	6.77	24.67	25.19	24.38	24.91
H-6	6.62	24.82	25.12	24.57	24.90
CH_3	2.18	29.48	29.01	29.44	28.95
2-OCH_3	3.92	27.68	27.31	27.62	27.25
3-OCH_3	3.83	27.73	27.43	27.68	27.35

[a] Calculated at the B3LYP/6-311++G(2d,2p) level; conformations 1 and 2 refer to the most stable and the next most stable conformation, respectively; nuclear shieldings for all compounds **3**−**16** are given in the Supporting Information (Tables S6 and S7).

The regression lines for all types of hydrogen atoms of the low-energy conformations of compounds **4**, **12**, and **13** are $\delta = -0.969\sigma + 30.748$, with correlation coefficient $R^2 = 0.997$ and mean average error (MAE) of 0.07 ppm, in the gas phase and $\delta = -0.914\sigma + 29.128$ ($R^2 = 0.999$, MAE 0.06) in chloroform. For the aromatic ring hydrogens only, $R^2 = 0.902$ (MAE 0.10) in the gas phase and $R^2 = 0.968$ (MAE 0.07) in chloroform. Thus, the calculated data (σ) in chloroform correlate better with the experimental δ values (obtained in chloroform-*d*).

For the remaining compounds (**3**, **5**−**11**, and **14**−**16**), energy calculations suggest the presence of multiple conformations close in energy (Table 4). In some cases (compounds **9**, **15**, and **16**) the relative stability of conformers changes between the gas phase and chloroform (Table 4). Because the real, quantitative conformer distributions for **3**, **5**−**11**, and **14**−**16** cannot be reliably deduced from the calculated relative energies, the calculated nuclear shielding were averaged for all low-energy conformers within either 4 or 8 kJ/mol and converted to chemical shifts by use of the above regression equations obtained for **4**, **12**, and **13**. The scatter plots in Figure 5 show the relationships between the calculated and experimental chemical shifts of the aromatic ring hydrogens, both for the lowest-energy conformers and for averaged chemical shifts of all conformers having relative energies within 4 or 8 kJ/mol.

Mean average errors for chemical shifts calculated by this method are 0.11, 0.09, and 0.06 ppm for the minimum energy conformations of **3**−**16**, conformations with relative energies up to 4 kJ/mol, and conformations with relative energies up to 8 kJ/mol, respectively, for the gas-phase conformations. For chloroform data, the respective errors are 0.08, 0.08, and 0.06 ppm. It is apparent that chemical shifts averaged for the conformer ensembles with energies within 8 kJ/mol from the calculated lowest-energy conformations give the best agreement with the experimental data. Mean average errors for individual conformations of **3**−**16** are shown in Table S8 in the Supporting Information. There is a clear tendency that less stable conformations give higher average errors. However, in many cases the lowest-energy conformations are clearly not representative for the experimental data. For example, the two most conspicuous outliers in the vacuum data are the chemical shift of H-6 in conformation 1 of compound **9** and the chemical shift of H-5 in conformation 1 of compound **15** (Figure 5). Conformation 1 of compound **9** has two hydrogen bonds with all hydroxy groups in the ring plane and the hydroxy group at C-1 pointing toward H-6, whereas conformation 2 of **9** has all hydroxy groups rotated by 180°, which changes the chemical shift of H-6 significantly (cf. Tables 2 and 3). Therefore, even a small contribution from conformation 2 is expected to affect the average chemical shift of H-6 significantly. For compound **15**, conformation 1, identified as a global energy minimum in vacuum, is considerably less stable than conformation 2 in chloroform (Table 4). It is therefore clear that conformation 1 of **15** is a very poor representation of the real conformer population. Conformations 1 and 2 of **15** differ in the torsion angle of the methoxy group at C-2, leading to substantial error of the chemical shift of H-5. Therefore, the limited ability to identify correct conformer populations that represent the actual solution situation, rather than the ability of the DFT calculations to reproduce the stereoelectronic effects, is the major source of discrepancies between the calculated and the experimental results.

When averaged shieldings of all conformations within 8 kJ/mol for all compounds (**3**−**16**) are plotted against experimental chemical shifts (i.e., without prior validation of the results for the most reliably predicted conformations of **4**, **12**, and **13**) and converted to calculated chemical shifts by use of the resulting regression lines ($\delta = -0.635\sigma + 22.440$, $R^2 = 0.876$ in the gas phase; $\delta = -0.665\sigma + 22.987$, $R^2 = 0.913$ in chloroform), the calculated and experimental chemical shifts agree with MAE = 0.045 ppm (gas phase) or MAE = 0.038 ppm (in chloroform); see Figure 6.

Calculation of O-Methylation-Induced Shifts. The conformational behavior of an Ar−OR bond (R = H, CH_3) in a polyphenol is governed by three major effects. The first is stabilization of the planar conformation by delocalization of nonbonding oxygen electrons into the aromatic ring (Table 2). This is reflected by shortening of the Ar−OCH_3 bond in **1** from 1.382 Å in the perpendicular conformation B to 1.367 Å in the planar conformation A (Figure 1), as calculated in the present work (the corresponding values for the Ar−OH bond in **2** are 1.389 and 1.368 Å). The energy of this stabilization is at least

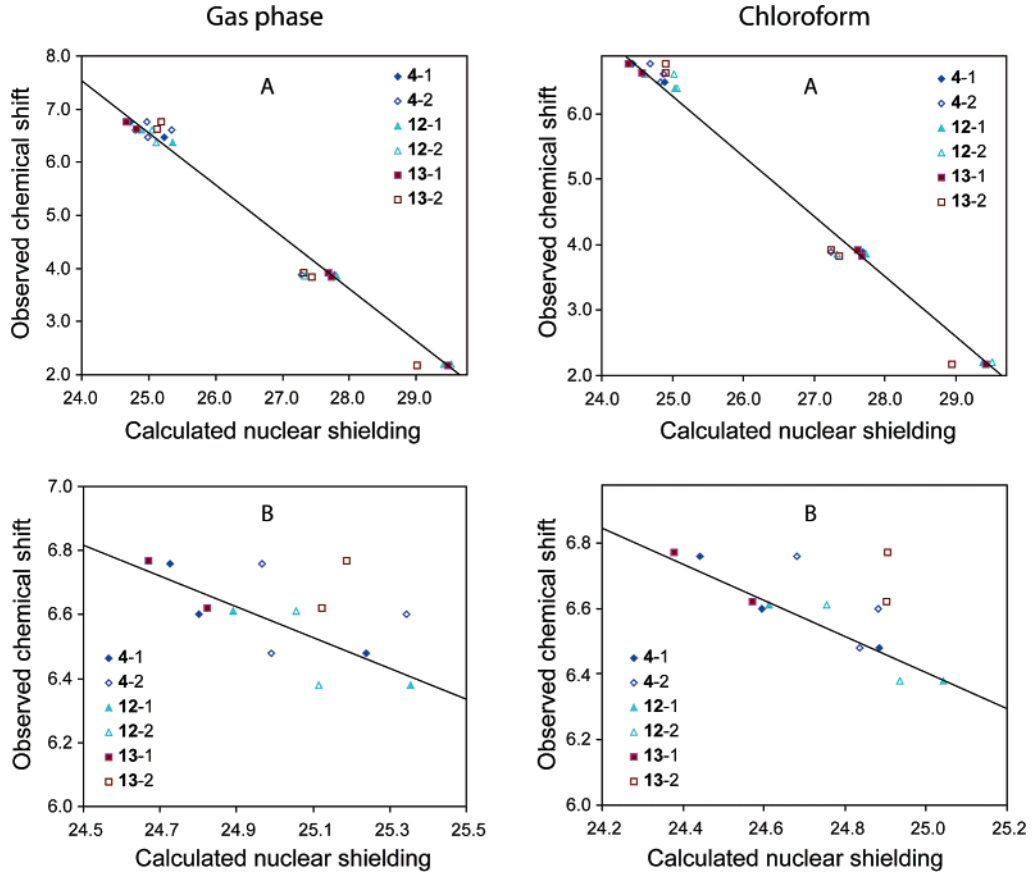


FIGURE 4. (A) Relationship between observed [1]H NMR chemical shifts (δ) and calculated nuclear shieldings (σ) for **4**, **12**, and **13** in gas phase and chloroform; solid and open symbols represent the lowest and the next-lowest energy conformations (conformations 1 and 2, respectively; cf. Figure 3). (B) Expansions of regions corresponding to hydrogen atoms attached to the aromatic ring. Solid lines represent best fits for the most stable conformations (see text).

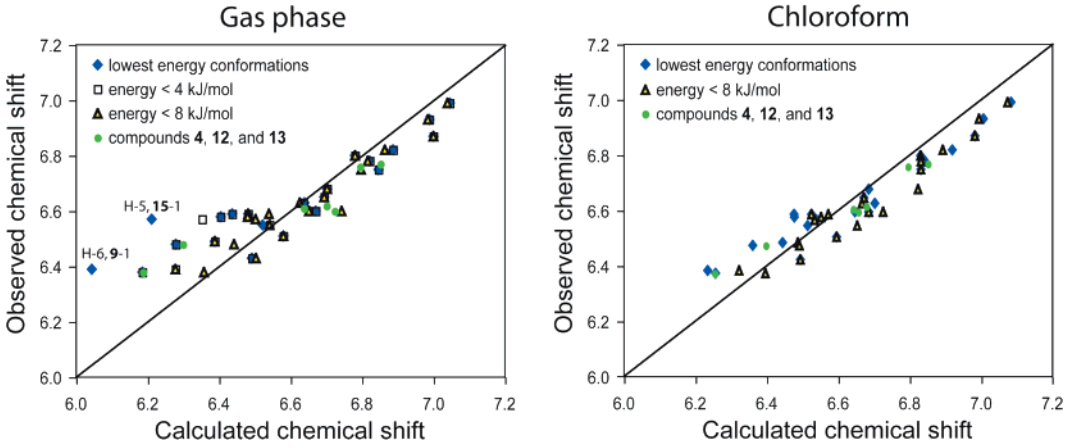


FIGURE 5. Comparison of observed and calculated chemical shifts of **3**−**16**. For compounds **3**, **5**−**11**, and **14**−**16**, the calculated nuclear shieldings were converted to chemical shifts by use of the regression equations derived for all chemical shifts of compounds **4**, **12**, and **13** (Figure 4). Calculated chemical shifts for the minimum-energy conformations, averaged chemical shifts for all conformations with calculated energies within 4 kJ/mol, and averaged chemical shifts for all conformations with calculated energies within 8 kJ/mol are displayed separately.

12 kJ/mol (Tables 1 and 2). The second effect is the intramolecular hydrogen bonding that stabilizes planar conformation of the Ar−OH groups in a solvent-dependent manner.[15,16] The energy cost of breaking the hydrogen bond by rotation of the Ar−OH bond away from a planar OCH_3 acceptor group is quite high,[15,16] for example, 21 kJ/mol for **17** in chloroform (Table 2). This hydrogen-bond strength appears to be largely retained when the OCH_3 acceptor group is rotated out-of-plane, as the energy difference between the hydrogen-bonded conformations A and C of **17** equals the energetic penalty of rotation of the Ar−OCH_3 torsion out-of-plane in **1** (Table 2). The third effect that controls the Ar−OR torsional angle is the steric repulsion by neighboring ortho-substituents. As seen in Tables 4, S2, and S3, the energetic penalty of retaining a planar conformation in

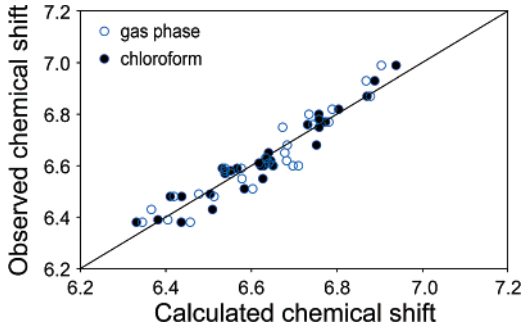


FIGURE 6. Comparison of observed and calculated chemical shifts of **3**−**16**. Calculated nuclear shieldings averaged for all conformations within 8 kJ/mol were converted to calculated chemical shifts by use of the regression equations for all compounds (see text).

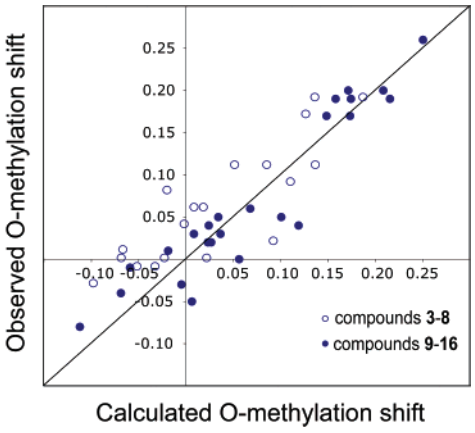


FIGURE 7. Comparison of observed and calculated O-methylation shifts in **3**−**16** (cf. Schemes 1 and 2).

ortho-disubstituted anisoles varies between about 10 kJ/mol in cases where the OCH_3 group acts at a hydrogen-bond acceptor (conformation 2 of **5**, conformation 3 of **11**) to at least 16 kJ/mol (conformation 4 of **8**, conformation 2 of **13**; Tables 4, S2, and S3). The balance between these three effects determines the conformer distribution for a particular, partly O-methylated polyphenol, and the resulting Ar−OR torsion angle determines the ^{1}H NMR chemical shifts in the aromatic ring through torsion-dependent electron density release into the aromatic ring.

Thus, the calculations confirm a very strong preference of the hydroxy group to remain in the plane of the aromatic ring, even for ortho-disubstituted phenols.[19] In all but two cases of hydroxy group conformations in compounds **3**−**16** (Tables 4, S2, and S3), the hydroxy group is essentially coplanar with the aromatic ring, regardless of whether the hydroxy group has one or two ortho substituents (torsion angle 3.0° ± 4.1° in gas phase and 4.4° ± 6.2° in chloroform, n = 46). The two exceptions are the 2-OH group in conformation 2 of **3** and the 2-OH group in conformation 3 of **9**. In these two cases the central hydroxy group is essentially orthogonal to the ring and acts as a hydrogen-bond acceptor for the two flanking hydroxy groups (Tables S2 and S3). The energy of these conformations, which must be considered specific for the 1,2,3-benzenetriol systems, is about 6 kJ/mol higher than the energy of the conformations with the central hydroxy group in the ring plane (in chloroform, Table 4). In all other occurrences of the ortho-disubstituted hydroxy groups in compounds **3**−**16** (n = 21), the hydroxy group is planar. Thus, in the case of ortho-disubstituted phenol groups, the steric congestion never outweighs the stabilization by hydrogen bonding. By contrast, the ortho-disubstituted methoxy groups are always out-of-plane in all conformations within 10 kJ/mol. Therefore, the O-methylation of an ortho-disubstituted phenol group will cause rotation of the Ar−OR torsion angle out of plane of the benzene ring as the steric effects outweigh the conjugative effects, resulting in predictable (cf. Table 3) changes of the chemical shifts.

A comparison between the experimental O-methylation shifts (Schemes 1 and 2) and the O-methylation shifts calculated from data in Figure 6 (calculated chemical shifts averaged for all conformations within 8 kJ/mol, in chloroform) are shown in Figure 7. Considering that the calculated O-methylation shifts are differences between small numbers representing δ values of parent phenols and the corresponding methyl ethers, the correlation must be considered as very good (MAE = 0.033 ppm). The correlation is considerably better for compounds **9**−**16** (R^2 = 0.888, MAE 0.026 ppm) than for **3**−**8** (R^2 = 0.648, MAE 0.044 ppm). The DFT-calculated O-methylation shift of H_{para} in ortho-disubstituted phenols is $\Delta\delta$ = 0.18 ± 0.04 ppm (n = 11), in excellent agreement with the experimental results ($\Delta\delta$ = 0.19 ± 0.02 ppm).

Applications. The downfield shift of H_{para} of 0.2 ppm observed upon O-methylation (and presumably upon O-alkylation in general) of ortho-disubstituted phenols must be regarded as a useful structure elucidation aid. Many drugs, including colchicine, etoposide, mescaline, podophylotoxin, reserpine, and trimethoprim, contain a 1,2,3-trimethoxybenzene moiety. Their metabolism involves demethylation to give partly O-methylated 1,2,3-benzenetriol derivatives.[20] Moreover, a vast number of natural products contain partially O-methylated 1,2,3-benzenetriol moieties. Structure elucidation of such compounds can present a considerable challenge, requiring time-consuming 2D NMR experiments.[6,21] Examples confirming the large shift of H_{para} upon O-methylation of an ortho-disubstituted phenol group include isoflavans,[6] isoflavanones,[6] natural dibenzocyclooctadienes,[21a] natural terphenyls,[21b] isoflavones,[21c] acridone alkaloids,[21d] homoflavonoids,[21e] and lignans.[22] On the basis of the observations described herein, the hydroxy and methoxy substituents attached to C-3 and C-5 in the natural lignan rupestrin C, recently described by Suo et al.,[22] should be interchanged.[23]

(19) (a) Allinger, N. L.; Maul, J. J.; Hickey, J. H. *J. Org. Chem.* **1970**, *36*, 2747−2752. (b) Brewster, M.; Pop, E.; Huang, M.-J.; Bodor, N. *THEOCHEM* **1994**, *303*, 25−38. (c) Shigematsu, M.; Kobayashi, T.; Yoshitani, K.; Tanahashi, M. *J. Comput. Chem. Jpn.* **2002**, *1*, 129−134.

(20) See, for example, (a) Kawashiro, T.; Yamashita, K.; Zhao, X. J.; Koyama, E.; Tani, M.; Chiba, K.; Ishizaki, T. *J. Pharmacol. Exp. Ther.* **1998**, *286*, 1294−1300. (b) Wu, D.; Otton, S. V.; Inaba, T.; Kalow, W.; Sellers, E. M. *Biochem. Pharmacol.* **1997**, *53*, 1605−1612. (c) Tateishi, T.; Soucek, P.; Caraco, Y.; Guengerich, F. P.; Wood, A. J. *Biochem. Pharmacol.* **1997**, *53*, 111−116. (d) van Maanen, J. M.; de Vries, J.; Pappie, D.; van den Akker, E.; Lafleur, V. M.; Retel, J.; van der Greef, J.; Pinedo, H. M. *Cancer Res.* **1987**, *47*, 4658−4662. (e) Friis, C.; Gyrd-Hansen, N.; Nielsen, P.; Nordholm, L.; Rasmussen, F. *Pediatr. Pharmacol. (New York)* **1984**, *4*, 231−238.

(21) For selected, recent examples of natural products identified by use of 2D NMR that exhibit the expected O-methylation shifts of H_{para}, see (a) Shen, Y. C.; Liaw, C. C.; Cheng, Y. B.; Ahmed, A. F.; Lai, M. C.; Liou, S. S.; Wu, T. S.; Kuo, Y. H.; Lin, Y. C. *J. Nat. Prod.* **2006**, *69*, 963−966. (b) Zhang, C, Ondeyka, J. G.; Herath, K. B.; Guan, Z.; Collado, J.; Pelaez, F.; Leavitt, P. S.; Gurnett, A.; Nare, B.; Liberator, P.; Singh, S. B. *J. Nat. Prod.* **2006**, *69*, 710−712. (c) Maver, M.; Queiroz, E. F.; Wolfender, J.-L.; Hostettmann, K. *J. Nat. Prod.* **2005**, *68*, 1094−1098. (d) Naidoo, D.; Coombes, P. H.; Mulholland, D. A.; Crouch, N. R.; van den Bergh, A. J. J. *Phytochemistry* **2005**, *66*, 1724−1728. (e) Lin, Y.-L.; Shen, C.-C.; Huang, Y.-J.; Chang, Y.-Y. *J. Nat. Prod.* **2005**, *68*, 381−384.

Thus, simple comparison of ^{1}H NMR chemical shift of aromatic ring hydrogens of polyphenolic natural products and their O-methylated analogues can provide immediate structural clues or suggest a need of revision of a published structure.[6,21,22] The ability to extract as much information as possible from 1D ^{1}H NMR spectra alone is of special interest in cases where 2D NMR experiments are not readily accessible, for example, when modern high-throughput hyphenated HPLC−NMR methods[24] or NMR probes with microcoils for mass-limited samples[25] are used.

Since the use of *ab initio* methods for ^{1}H NMR spectra predictions for large, conformationally flexible systems is computationally and conceptually demanding,[11] other approaches to calculation of ^{1}H NMR chemical shifts acquire growing popularity.[7] Recognition of the fact that out-of-plane rotation of an OR group attached to a benzene ring causes an additional downfield shift of H_{para} by 0.2 ppm can improve the spectral predictions, regardless of whether the predictions are based on tabulated substituent effects or databases of experimental chemical shifts.[7] More importantly, similar effects are expected to be considerable for a number of other heteroatom-containing substituents. The assessment of stereoelectronic effects of such substituents on ^{1}H NMR chemical shifts by the DFT approach with simple model compounds, similarly to what was done for the OR substituent in the present work, can be regarded as a general approach leading to improved prediction of ^{1}H NMR chemical shifts in aromatics, heteroaromatics, and olefins.

Conclusions

The stereoelectronic effects of hydroxy and methoxy group rotation in substituted benzenes on ^{1}H NMR chemical shifts were demonstrated in a series of model compounds and reproduced well by DFT calculations. The differences between conformational properties of ortho-disubstituted hydroxy and methoxy group, resulting from a balance between electronic, steric, and hydrogen-bonding effects, cause stereoelectronic effects on the ^{1}H NMR chemical shifts that are useful for determination of O-methylation patterns in polyphenols, the structural motifs found in many natural products and some drugs. This work demonstrates a general approach to improvement of ^{1}H NMR chemical shift predictions by inclusion of stereoelectronic effects that are identified in simple model compounds.

Experimental Section

Synthesis of Compounds 9−16. 2,3,4-Trihydroxybenzaldehyde (3 g, 20 mmol) was dissolved in 1 M NaOH (25 mL) and stirred with $(CH_3)_2SO_4$ (4.6 mL, 50 mmol) for 3 h at 80 °C under nitrogen; approximately 35 mL of 1 M NaOH was added during this period to maintain basic pH. The reaction mixture was stirred at room temperature for 12 h and was then acidified with 4 N H_2SO_4 and extracted with CH_2Cl_2, to yield 2.6 g of a mixture of mono- and di-O-methylated 2,3,4-trihydroxybenzaldehydes.[10a] The mixture was dissolved in THF (60 mL) and treated with $NaBH_3CN$ (5.2 g, 83 mmol) in nitrogen atmosphere, after which 2 N HCl (45 mL) was added over a period of 30 min; the stirring was continued for 2.5 h, H_2O (100 mL) was added, and the solution was extracted with diethyl ether.[10b] This yielded 2.4 g of a mixture consisting of **9**−**14** and a number of dimerization products. Compounds **9** and **11**−**14** were isolated by preparative HPLC; compound **10** was characterized by NMR in mixture with **11**. Compound **16** was prepared in approximately 50% yield by reduction of 2,3,4-trimethoxybenzaldehyde (1.4 g, 7 mmol) with $NaBH_3CN$ (4 g, 65mmol) by the above-described procedure. Compound **15** was prepared by demethylation of **16** (0.45 g, 2.5 mmol) with BCl_3 (1 M in CH_2Cl_2, 0.3 mL) in CH_2Cl_2 under nitrogen.[10c] After 2.5 h the reaction mixture was quenched with ice and extracted with diethyl ether, the extract was washed with saturated aqueous sodium tetraborate,[10c] and pure **15** was isolated by preparative HPLC. The phenols (especially **13**−**15**) were air-sensitive, their dilute solutions being progressively oxidized to quinones and dimerization products.

Acknowledgment. Financial support to L.O. from the Carlsberg Foundation is gratefully acknowledged. We are also indebted to Drs. H. Franzyk and C. A. Olsen for valuable discussions.

Supporting Information Available: General experimental and computational procedures, experimental ^{1}H NMR shift data for **3**−**16** (Table S1), models and atomic coordinates of low-energy conformers of **3**−**16** (Tables S2−S5), calculated nuclear shieldings for all low-energy conformers of **3**−**16** in vacuum and in chloroform (Tables S6 and S7), mean average errors of calculated chemical shifts (Table S8), and ^{1}H NMR spectra of **9**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061757X

(22) Suo, M.-R.; Yang, J.-S.; Liu, Q.-H. *J. Nat. Prod.* **2006**, *69*, 682−684.

(23) This conclusion is also supported[4] by the ^{13}C NMR data reported by Suo et al.[22] For reference values, see (a) Assoumatine, T.; Datta, P. K.; Hooper, T. S.; Yvon, B. L.; Charlton, J. L. *J. Org Chem.* **2004**, *69*, 4140−4144. (b) Wang, B. G.; Ebel, R.; Wang, C. Y.; Edrada, R. A.; Wray, V.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 682−684. (c) DellaGreca, M.; Pinto, G.; Pollio, A.; Previtera, L.; Temussi, F. *Tetrahedron Lett.* **2003**, *44*, 2779−2780. (d) Neudorffer, A.; Deguin, B.; Hamel, C.; Fleury, M.-B.; Largeron, M. *Collect. Czech. Chem. Commun.* **2003**, *68*, 1515−1530. (e) Chaves, M. H.; Roque, N. F. *Phytochemistry* **1997**, *46*, 879−881.

(24) (a) Clarkson, C.; Stærk, D.; Hansen, S. H.; Smith, P. J.; Jaroszewski, J. W. *J. Nat. Prod.* **2006**, *69*, 1280−1288. (b). Jaroszewski, J. W. *Planta Med.* **2005**, *71*, 795−802. (c) Jaroszewski, J. W. *Planta Med.* **2005**, *71*, 691−700. (d) Clarkson, C.; Stærk, D.; Hansen, S. H.; Jaroszewski, J. W. *Anal. Chem.* **2005**, *77*, 3547−3553.

(25) (a) Jansma, A.; Chuan, T.; Albrecht, R. W.; Olson, D. L.; Peck, T. L.; Geierstanger, B. H. *Anal. Chem.* **2005**, *77*, 6509−6515. (b) Yoo, H. D.; Cremin, P. A.; Zeng, L.; Garo, E.; Williams, C. T.; Lee, C. M.; Goering, M. G.; O'Neil-Johnson, M.; Eldridge, G. R.; Hu, J. F. *J. Nat. Prod.* **2005**, *68*, 122−124. (c) Gronquist, M.; Meinwald, J.; Eisner, T.; Schroeder, F. C. *J. Am. Chem. Soc.* **2005**, *127*, 10810−10811.