

# Competitive Hydrogen Bonds and Conformational Equilibria in 2,6-Disubstituted Phenols Containing two Different Carbonyl Substituents

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**Summary.** Rotational isomers of ten 2,6-disubstituted phenols containing two different carbonyl substituents (COOH, COOCH<sub>3</sub>, CHO, COCH<sub>3</sub>, CONH<sub>2</sub>) have been investigated theoretically with the aid of DFT methods (B3LYP/6-31G(d,p)). The relative stabilities of four to five conformers of each compound were determined by full geometry optimizations for the free molecules and, in order to simulate solvent effects, also for molecules in reaction fields with dielectric constants up to  $\epsilon = 37.5$ . Comparison with available experimental IR spectroscopic data revealed excellent agreement with the theoretically predicted stability sequences and conformational equilibria. The two determinative energy contributions, that of the attractive intramolecular hydrogen bond interactions and that of the (mostly repulsive) interactions between the phenolic oxygen atoms and the other non-hydrogen-bonded carbonyl substituents, were separately calculated from isodesmic reactions (benzoyl compound + phenol  $\rightleftharpoons$  2-hydroxybenzoyl compound + benzene). The stability sequences of the conformers, as obtained from the sum of each two energy contributions, almost exactly comply with the sequences obtained from the full geometry optimizations. With all compounds the conformation of the most stable isomer is determined by the energetically most favourable non-bonded O $\cdots$ R-C interaction and not by the more favourable one of the two possible O-H $\cdots$ O=C H-bond interactions.

**Keywords.** DFT calculations; Conformational equilibria; 2,6-Disubstituted phenols; Hydrogen bonding; IR spectra; Isodesmic reactions.

## Konkurrierende Wasserstoffbrückenbindungen und Konformationsgleichgewichte in 2,6-disubstituierten Phenolen mit zwei unterschiedlichen Carbonylsubstituenten

**Zusammenfassung.** Die strukturellen, energetischen und spektroskopischen Eigenschaften der Rotationsisomeren von zehn unsymmetrisch substituierten 2,6-Dicarbonylphenolen (COOH, COOCH<sub>3</sub>, CHO, COCH<sub>3</sub>, CONH<sub>2</sub>) wurden mit DFT-Methoden (B3LYP/6-31G(d,p)) untersucht. Die relativen Stabilitäten von vier bis fünf Konformeren jeder Verbindung wurden durch Geometrieoptimierungen einerseits der freien Moleküle und andererseits, um auch Lösungsmittelleffekte zu berücksichtigen, in Reaktionsfeldern mit Dielektrizitätskonstanten bis zu  $\epsilon = 37.5$  bestimmt. Vergleiche mit experimentellen IR-spektroskopischen Daten zeigen eine vortreffliche

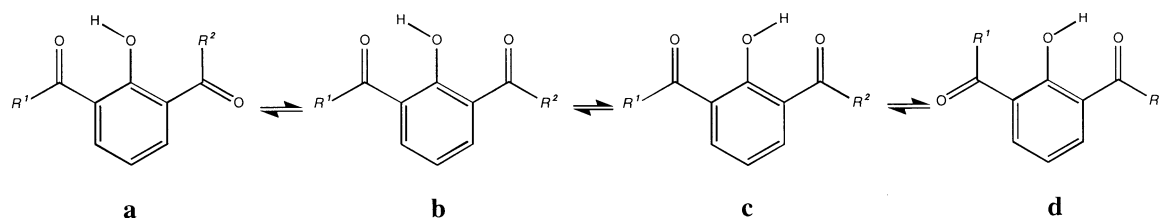
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Übereinstimmung mit den theoretisch vorhergesagten Stabilitätssequenzen und Konformationsgleichgewichten. Die beiden entscheidenden Energiebeiträge, jene der Wasserstoffbrückenbindungen und jene der (zumeist abstoßenden) Wechselwirkungen zwischen den phenolischen Sauerstoffatomen und den nicht wasserstoffbrückengebundenen Carbonylsubstituenten, wurden mit Hilfe von isodesmischen Reaktionen berechnet (Benzoyl-Verbindung + Phenol  $\rightleftharpoons$  2-Hydroxy-benzoyl-Verbindung + Benzol). Die aus den Summen der beiden Beiträge ermittelten Stabilitätssequenzen stimmen nahezu exakt mit jenen überein, die bei den vollständigen Geometrieoptimierungen erhalten wurden. In allen Fällen wird die Konformation des stabilsten Isomers durch die energetisch günstigste O...R-C-Wechselwirkung bestimmt und nicht durch die günstigere der beiden möglichen O-H...O=C-Wasserstoffbrückenbindungen.

## Introduction

In the course of theoretical and experimental studies on intramolecular hydrogen bonding in small organic model compounds we have investigated a series of 2,6-disubstituted phenols containing two carbonyl substituents. Compounds of this type are found as substructural units of various natural substances like phloroglucinoles [1–4], depsides [5–7], euglobins [8], ochratoxins [9], and of synthetic derivatives with physiological activity [10–11]. Whereas 2,6-disubstituted phenols with two equal carbonyl substituents have been the subject of several investigations [12–17], studies about phenols containing two different carbonyl substituents are very scarce [18, 19]. With respect to intramolecular hydrogen bonding it is, however, just the latter family that offers some particularly challenging questions. Above all, these compounds are capable of forming two (competitive) kinds of intramolecular O–H...O=C hydrogen bonds (H-bonds) between the phenolic OH group and the two different carbonyl oxygen atoms. Additionally, for both H-bonded species there exist two rotational isomers with the non-H-bonded carbonyl group being either *syn* or *anti* with respect to the phenolic C–O group. Hence, with any such compound we have to deal with (at least) four different conformers (Fig. 1), and an understanding of the structural and/or spectroscopic properties of a given compound requires knowledge of the factors that govern the stability sequences (*i.e.* the energies or at least the energy differences) of the conformers. Basically, to a first approximation there are two contributions to the total energy of a given conformer that have to be taken into account: (i) the attractive H-bond interaction between the phenolic OH group and one of the two carbonyl oxygen atoms and (ii) the (mostly repulsive) interaction between the phenolic oxygen atom and the second non-H-bonded carbonyl substituent.

The present study includes ten different 2,6-disubstituted phenols that result from the combinations of each two of five different carbonyl substituents: COOH,



**Fig. 1.** The four basic conformers of 2,6-disubstituted phenols containing two different carbonyl substituent

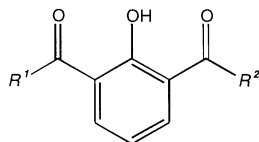
COOCH<sub>3</sub>, CHO, COCH<sub>3</sub>, and CONH<sub>2</sub>. From theoretical and experimental structural and spectroscopic data (H-bond energies, bond distances, vibrational frequencies, NMR shifts, ...) of 2-hydroxybenzoyl compounds [20, 21] it has been safely established that the H-bond strengths increase within the series COOH ≤ COOCH<sub>3</sub> < CHO < COCH<sub>3</sub> < CONH<sub>2</sub>. This is the starting point of our concerns, since naively one might expect that the H-bond strength should be the main factor in governing the stabilities of the conformers of a given compound. In the following sections, after some experimental and computational details, we firstly focus on theoretical stability sequences as obtained from full geometry optimizations. Data are reported not only for free molecules, but we also account for solvent effects using the *Onsager* reaction field method [22]. Secondly, we confront the theoretical results with experimental IR spectroscopic data in order to assess the reliability of the calculations. Thirdly, we deal with isodesmic reactions, which can be used to evaluate independently the energy contributions of the various kinds of H-bonded and non-bonded interactions. For any given conformer a total interaction energy can be calculated from the sum of two such contributions, and it turns out that the stability sequences obtained in that way almost perfectly agree with the sequences obtained from the full geometry optimizations. Finally, we discuss some pertinent points that emerge from exploring these isodesmic reactions, and we show that this approach can clearly contribute toward the understanding of the conformational stability sequences and, hence, toward the understanding of the intrinsic properties of the title compounds.

## Materials and Methods

The compounds included in this study are listed in Table 1 along with the subsequently used compound numbering. IR spectra of CCl<sub>4</sub> and CDCl<sub>3</sub> solutions were measured with a Perkin-Elmer Spectrum 2000 FTIR spectrometer. 3-Formyl-2-hydroxy-benzoic acid (**2**) was commercially

**Table 1.** Compounds and compound numberings

	<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>
<b>1</b>	-OH	-OCH <sub>3</sub>
<b>2</b>	-OH	-H
<b>3</b>	-OH	-CH <sub>3</sub>
<b>4</b>	-OH	-NH <sub>2</sub>
<b>5</b>	-OCH <sub>3</sub>	-H
<b>6</b>	-OCH <sub>3</sub>	-CH <sub>3</sub>
<b>7</b>	-OCH <sub>3</sub>	-NH <sub>2</sub>
<b>8</b>	-H	-CH <sub>3</sub>
<b>9</b>	-H	-NH <sub>2</sub>
<b>10</b>	-CH <sub>3</sub>	-NH <sub>2</sub>



available from Lancaster. 3-Formyl-2-hydroxy-methylbenzoate (**5**) has been prepared from **2** by standard methods.

The quantum chemical calculations were performed with the Gaussian92 [23] and Gaussian94 [24] programs. Geometric, energetic, and vibrational spectroscopic data of the title compounds and of the components of the isodesmic reactions were computed at the density functional B3LYP level of theory [25, 26] using the 6-31G(d,p) basis set [27]. If not otherwise stated, the optimized geometries were calculated without any constraints. For the simulation of solvent effects, we used the self-consistent *Onsager* reaction field method [22] as implemented in the Gaussian program packages. Within the *Onsager* approach the electrostatic effect of a solvent is represented in terms of the interaction between the molecular dipole moment and a reaction field which is defined by  $(2(\epsilon - 1)/2\epsilon + 1) \cdot a_0^{-3} \cdot \mu$ . Calculations were performed for dielectric constants  $\epsilon = 2.2, 4.8,$  and  $37.5$ , corresponding to  $\text{CCl}_4, \text{CDCl}_3,$  and  $\text{CD}_3\text{CN}$  solutions, respectively [28]. The radii of the spherical cavities occupied by the molecules,  $a_0$ , were calculated from the volumes of the optimized structures of the free molecules and increased by 50 pm in order to account for the *van der Waals* radii of the surrounding solvent molecules.

## Results and Discussion

The theoretical energy differences relative to the most stable conformer of a given compound for a total of 44 different conformers are summarized in Table 2. Each first line contains data of free molecules, each second line data of molecules in a

**Table 2.** Theoretical<sup>a</sup> energy differences ( $\text{kJ} \cdot \text{mol}^{-1}$ ) between the rotational isomers<sup>b</sup>, as obtained from full geometry optimizations ( $\Delta E_{\text{tot}}$ ) and from isodesmic reactions ( $\Delta E_{\text{int}}$ , in parentheses) for free molecules (each first line) and for  $\epsilon = 37.5$  (each second line)

	<b>a</b>	<b>b</b>	<b>c</b>	<b>d<sub>(E)</sub><sup>c</sup></b>	<b>d<sub>(Z)</sub><sup>c</sup></b>
<b>1</b>	10(4)	15(7)	14(6)	0(0)	10(3)
	32(22)	34(27)	30(24)	0(0)	27(19)
<b>2</b>	0(0)	15(11)	15(12)	3(6)	10(9)
	1(6)	15(21)	18(24)	0(0)	19(19)
<b>3</b>	3(0)	24(16)	15(7)	0(2)	10(5)
	16(12)	35(32)	26(23)	0(0)	25(19)
<b>4</b>	0(0)	32(26)	28(22)	11(16)	24(19)
	14(0)	45(31)	36(23)	0(0)	35(19)
<b>5</b>	0(0)	15(11)	16(13)	11(10)	
	0(0)	15(15)	22(21)	3(16)	
<b>6</b>	0(0)	22(16)	14(9)	8(6)	
	0(0)	21(20)	15(14)	15(9)	
<b>7</b>	0(0)	32(26)	30(23)	25(20)	
	0(0)	33(31)	29(26)	27(22)	
<b>8</b>	3(4)	25(20)	16(12)	0(0)	
	12(6)	23(26)	10(14)	0(0)	
<b>9</b>	0(0)	33(26)	29(21)	13(9)	
	3(0)	27(31)	13(20)	0(6)	
<b>10</b>	0(0)	34(27)	40(30)	17(14)	
	0(0)	28(31)	28(32)	10(13)	

<sup>a</sup> B3LYP/6-31G(d,p) level of theory; <sup>b</sup> relative to the most stable conformer; <sup>c</sup> (E)- and (Z)-conformations of non-bonded carboxyl groups (see also Table 5)

reaction field with a dielectric constant of  $\varepsilon = 37.5$  corresponding to a solution in  $\text{CD}_3\text{CN}$ . Each first number refers to the relative energy difference between the total energies,  $\Delta E_{\text{tot}}$ , as obtained from full geometry optimizations, each second number (in parentheses) to the relative differences between the interaction energies,  $\Delta E_{\text{int}}$ , as obtained from isodesmic reactions. For the *anti*-conformers of non-bonded carboxyl groups (**1d–4d**) we additionally distinguish between the (*E*)- and the (*Z*)-conformation of the COOH group ( $\mathbf{d}_{(E)}$  and  $\mathbf{d}_{(Z)}$ , see also Table 5), the latter being commonly the more stable conformation of carboxylic acids. As should be noted at this point, in order to distinguish between the intrinsic  $\text{O–H} \cdots \text{O}=\text{C}$  H-bond and the non-bonded  $\text{O} \cdots \text{O}=\text{C}$  or  $\text{O} \cdots \text{R–C}$  interactions, we use the term “non-bonded” also in those few cases where the  $\text{O} \cdots \text{R–C}$  interaction is actually also a weak H-bond.

### Full geometry optimizations

If we firstly confine to the data obtained from full geometry optimizations, even a quick inspection of Table 2 reveals some general points, three of which should be noted. (1) Referring to the sequence of proton acceptor capabilities noted in the introduction, in only three out of the ten compounds the most stable conformer of the free molecule displays the stronger one of the two possible  $\text{O–H} \cdots \text{O}=\text{C}$  H-bonds (conformers **d** of **1**, **3**, **8**), whereas in seven cases just the opposite is true (conformers **a** of **2**, **4–7**, **9**, **10**). Obviously, the naive expectation that the strength of the characteristic intramolecular  $\text{O–H} \cdots \text{O}=\text{C}$  H-bond should be mainly determinative for the stability sequence of the rotameric isomers of a given compound does not apply and, consequently, the interaction between the phenolic oxygen and the non-H-bonded carbonyl substituent must play an important or even decisive role in determining that stability sequence. (2) As to the non-bonded interactions, in all instances the most stable conformer is an *anti*-conformer (**a** or **d**) and, moreover, the second stable conformer is also an *anti*-conformer, *i.e.* that with the other  $\text{O–H} \cdots \text{O}=\text{C}$  H-bond. Hence, it can be concluded that any of the  $\text{O} \cdots \text{R–C}$  interactions of the *anti*-conformations **a** and **d** is always more favourable than the  $\text{O} \cdots \text{O}=\text{C}$  interactions of the corresponding *syn*-conformations **b** or **c**. (3) Concerning the environmental effects, as calculated with the *Onsager* reaction field approach, going from the gas phase to polar solvents results in a more or less distinct stabilization of all conformers. In Table 3, the stabilization energies for  $\varepsilon = 37.5$ , as defined by the differences between the total energies  $E(\varepsilon = 37.5) - E(\varepsilon = 1)$ , are given along with the dipole moments of the free species. As should only be noted, for  $\varepsilon = 2.2$  ( $\text{CCl}_4$  solutions) and  $\varepsilon = 4.8$  ( $\text{CDCl}_3$  solutions) the stabilization energies amount to 39( $\pm 2$ ) and 69( $\pm 2$ )% respectively, of the values at  $\varepsilon = 37.5$  which almost exactly matches the theoretical relations of the *Onsager* model. Moreover, from the data given in Table 3 we obtain an excellent correlation between the stabilization energies and the squares of the dipole moments (linear correlation coefficient:  $r = 0.989$ ) which, because the molecular volumes of the considered compounds are very similar, also complies with the presumptions of the *Onsager* approach. Besides these relations, Table 3 clearly shows that the stabilization energies of the conformers of the single compounds are partly significantly different. Consequently, on going from the gas phase to polar solvents

**Table 3.** Theoretical<sup>a</sup> stabilization energies ( $\text{kJ} \cdot \text{mol}^{-1}$ ) for  $\varepsilon = 37.5^{\text{b}}$  (each first line), as obtained from full geometry optimizations and dipole moments ( $D$ ) of free isomers (each second line)

	<b>a</b>	<b>b</b>	<b>c</b>	$d_{(E)}^{\text{c}}$	$d_{(Z)}^{\text{c}}$
<b>1</b>	2.7	5.0	7.4	24.0	6.5
	2.6	3.6	4.3	7.5	3.9
<b>2</b>	10.6	12.5	8.8	15.0	3.0
	4.6	5.2	4.4	5.6	2.6
<b>3</b>	7.2	9.2	9.3	20.4	5.1
	4.0	4.8	4.8	6.9	3.5
<b>4</b>	7.4	9.3	13.9	33.0	10.3
	4.0	4.7	5.7	8.3	4.7
<b>5</b>	13.3	13.7	7.8	1.5	
	5.5	5.8	4.5	1.9	
<b>6</b>	9.5	10.1	7.8	3.2	
	4.9	5.2	4.7	2.9	
<b>7</b>	10.1	9.5	11.6	7.5	
	4.9	5.1	5.7	4.2	
<b>8</b>	4.1	12.4	15.7	11.2	
	3.1	5.4	6.1	5.0	
<b>9</b>	3.5	12.8	23.6	19.6	
	2.7	5.4	7.1	6.3	
<b>10</b>	6.7	12.3	18.2	13.6	
	3.9	5.6	6.5	5.5	

<sup>a</sup> B3LYP/6-31G(d,p) level of theory; <sup>b</sup> $E(\varepsilon = 37.5) - E(\varepsilon = 1)$ ; <sup>c</sup> $(E)$ - and  $(Z)$ -conformations of non-bonded carboxyl groups (see also Table 5)

we find more or less distinct changes of the energy differences  $\Delta E_{\text{tot}}$  between the rotational isomers (Table 2) and, hence, corresponding changes of the conformational equilibrium distributions. The most prominent example is compound **4**: whereas **4a** is by far the most stable conformer at  $\varepsilon = 1$  ( $11 \text{ kJ} \cdot \text{mol}^{-1}$  below  $\mathbf{4d}_{(E)}$ ),  $\mathbf{4d}_{(E)}$  becomes the most stable conformer at  $\varepsilon = 37.5$  ( $14 \text{ kJ} \cdot \text{mol}^{-1}$  below **4a**).

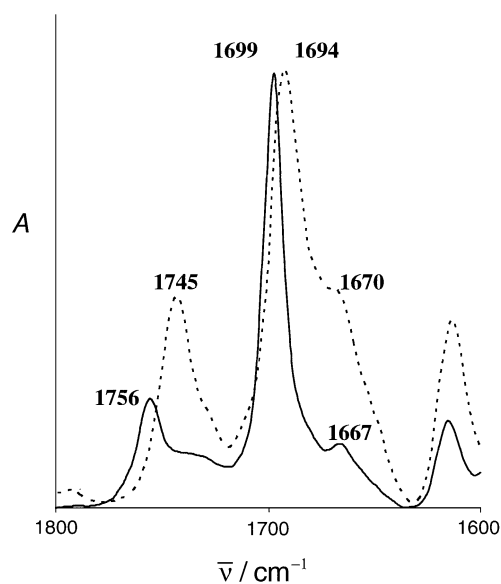
#### *Comparison between theoretical and experimental data*

In order to check the reliability of the above calculations we briefly confront the theoretical data as obtained from the full geometry optimizations with some available experimental results. In particular, the IR carbonyl stretching frequency region seems to be well suited to distinguish between different conformers. Some relevant theoretical and experimental data are compiled in Table 4. For an assignment of experimentally observed carbonyl stretching frequencies one may either refer to the corresponding DFT calculated frequencies or to experimental frequencies of eligible reference compounds, *i.e.* 2-hydroxy-benzoyl compounds for H-bonded carbonyl groups and benzoyl compounds for non-H-bonded carbonyl groups. From experiment as well as from theory it turns out that the non-bonded carbonyl frequencies of the *syn*-conformers are always distinctly higher than those of the reference benzoyl compounds, whereas the non-bonded carbonyl frequencies

**Table 4.** Theoretical (first figure)<sup>a</sup> and experimental (second figure)<sup>b</sup> carbonyl stretching frequencies ( $\text{cm}^{-1}$ ) of selected compounds and conformers

	(CO)-CH <sub>3</sub>	(CO)-H	(CO)-OCH <sub>3</sub>	(CO)-OH
Benzoyl compound	1776/1692	1796/1709	1799/1729	1818/1743
Salicyl compound	1713/1646	1733/1668	1736/1683	1755/1696
<b>2a</b>		1782/1699		1755/1699
<b>2d</b> <sub>(E)</sub>		1725/1667		1840/1756
<b>2d</b> <sub>(Z)</sub>		1732/(1667)		1801/(1730)
<b>5a</b>		1781/1698	1738/1681	
<b>5d</b>		1732/	1781/	
<b>6a</b>	1765/1683		1734/1683	
<b>6d</b>	1710/1647		1777/1710	
<b>6c</b>	1710/1647		1816/1735	

<sup>a</sup> B3LYP/6-31G(d,p) level of theory; <sup>b</sup> CCl<sub>4</sub> solutions

**Fig. 2.** IR spectra of 3-formyl-2-hydroxy-benzoic acid in CCl<sub>4</sub> (solid line) and in CDCl<sub>3</sub> (dashed line) solutions

of the *anti*-conformers are distinctly lower, with the exception of the *anti*-(*E*) conformers of COOH groups (Table 4).

In Fig. 2, the carbonyl stretching frequency region of CCl<sub>4</sub> and CDCl<sub>3</sub> solution IR spectra of 3-formyl-2-hydroxy-benzoic acid (**2**) are shown. According to the theoretical stability sequence (Table 2) one must expect an equilibrium between two energetically largely similar conformers **2a** and **2d**<sub>(E)</sub>, which excellently complies with the experimental findings: the high frequency band at 1756  $\text{cm}^{-1}$  (in CCl<sub>4</sub>) can reasonably well be assigned to the non-bonded carboxyl group of conformer **2d**<sub>(E)</sub>, the medium frequency band at 1699  $\text{cm}^{-1}$  arises from a superposition of the H-bonded carboxyl and the non-bonded formyl groups of

conformer **2a**, and the low frequency band at  $1667\text{ cm}^{-1}$  should be due to the H-bonded formyl group of conformer **2d<sub>(E)</sub>**. As should be noted, the presence of the two conformers is also confirmed by two corresponding  $\nu(\text{OH})$  bands, one at  $3525\text{ cm}^{-1}$  for **2a** and the other at  $3395\text{ cm}^{-1}$  for **2d<sub>(E)</sub>**. What is more, according to Table 2 the equilibrium  $\mathbf{2a} \rightleftharpoons \mathbf{2d}_{(E)}$  should become shifted towards isomer **2d<sub>(E)</sub>** upon increasing the solvent polarity, and indeed we find that, besides some small frequency shifts, the relative intensities of the carbonyl bands of conformer **2d<sub>(E)</sub>** distinctly increase when going from  $\text{CCl}_4$  to  $\text{CDCl}_3$  solutions.

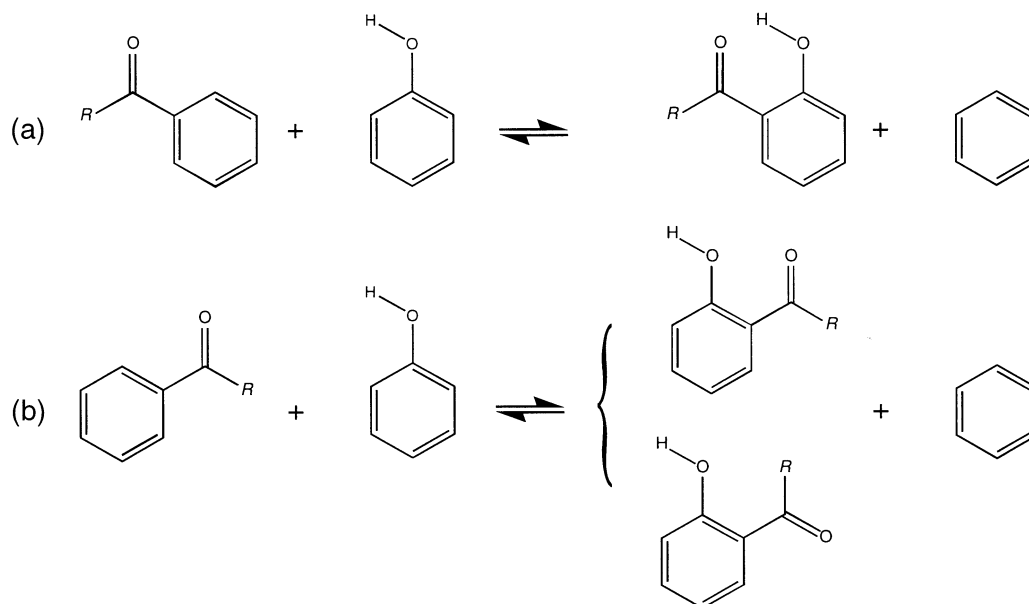
For another example, according to Table 2 conformer **5a** should be the most stable rotational isomer of 3-formyl-2-hydroxy-methylbenzoate (**5**), and its stability relative to the next stable conformer **5d<sub>(E)</sub>** increases on increasing solvent polarity. Consistently, we observe a lower frequency band at  $1681\text{ cm}^{-1}$  that can be assigned to the H-bonded carboxylate group and a higher frequency band due to the non-H-bonded formyl group at  $1698\text{ cm}^{-1}$ . Moreover, no distinct changes occur on going from  $\text{CCl}_4$  to  $\text{CDCl}_3$  solution. We note, however, that, although the experimental data agree well with the theoretical prediction, in this special case they do not actually confirm that prediction, since the carbonyl frequencies of the second stable conformer **5d** should be almost the same as those of **5a** (see Table 4).

Finally, we refer to a literature IR spectrum ( $\text{CCl}_4$  solution) of 3-acetyl-2-hydroxy-benzoic acid methyl ester (**6**) [19]. In the reported spectrum the carbonyl frequency region is dominated by a strong band at  $1683\text{ cm}^{-1}$  which is obviously due to a superposition of the H-bonded carboxylate group and the non-H-bonded acetyl group of the most stable conformer **6a**. Additionally, the spectrum shows three weak features that can reasonably well be assigned to the two next stable but energetically distinctly less favourable conformers: a band at  $1647\text{ cm}^{-1}$  due to the H-bonded acetyl group of both **6d** and **6c**, a shoulder at  $1710\text{ cm}^{-1}$  due to the non-bonded ester group of the anti-conformer **6d**, and a band at  $1735\text{ cm}^{-1}$  due to the non-H-bonded ester group of the *syn*-conformer **6c**. In summary, for all three compounds the observed spectral features excellently comply with those predicted from the calculated energies and stability sequences of the conformers, which gives strong evidence for the reliability of the calculations.

#### *Interaction energies from isodesmic reactions*

As already noted in the introduction, to a first approximation the energy differences between the conformers of a given compound should be governed by two energy contributions: the attractive  $\text{O}-\text{H} \cdots \text{O}=\text{C}$  H-bond interaction and the (mostly repulsive) interaction between the phenolic oxygen atom and the second non-H-bonded carbonyl substituent. For a more detailed understanding of the stability sequences it would be desirable to quantitatively evaluate these energy contributions independently from each other. Here we run into the problem that, other than with intermolecular interactions, the definition and evaluation of intramolecular interaction energies is by far not obvious, because the natural reference systems (i.e. the free molecules) do not exist. With more simple cases, such as *ortho*-substituted phenols, intramolecular H-bond energies are most commonly assessed from the energy differences between the H-bonded species and the conformer with the OH group rotated by  $180^\circ$  around the C–O single bond, either



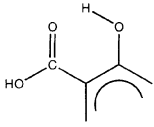
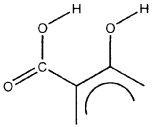
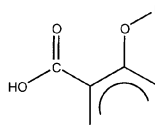
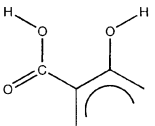
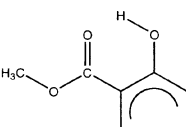
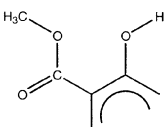
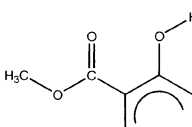
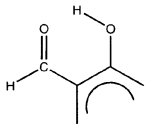
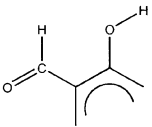
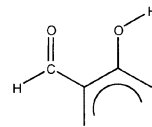
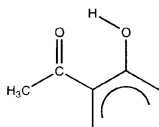
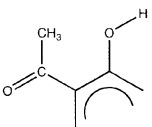
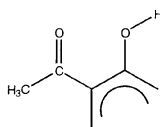
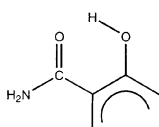
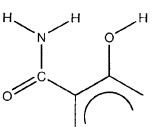
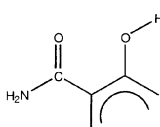


**Fig. 3.** Isodesmic reactions describing the formation (a) of the intramolecular O–H···O=C H-bonds and (b) of the non-bonded O···O=C or O···R–C interactions

with or without subsequent geometry optimization. For the title compounds, because of the second carbonyl substituent, these possibilities are of course immediately ruled out and, moreover, they are basically not at all applicable for evaluating non-H-bonded interaction energies.

Isodesmic reactions [29] provide an alternate tool for calculating intramolecular interaction energies. The underlying idea is that an intramolecular interaction may formally be built up by a fictitious chemical reaction, and the energy of this interaction-building reaction should be representative of the interaction energy. The isodesmic reactions that should appropriately describe the formation of the intramolecular O–H···O=C H-bonds and the formation of the non-bonded O···O=C or O···R–C interactions are shown in Figs. 3a and 3b, respectively. The theoretical energies that were calculated from the total energies of the four components of the corresponding reaction ( $E(2\text{-hydroxy-benzoyl}) + E(\text{benzol}) - E(\text{benzoyl}) - E(\text{phenol})$ ) are compiled in Table 5. Within our approach, the sum of the two energy contributions of a given conformer  $E_{\text{int}} = E_{\text{Hb}} + E_{\text{nb}}$  ( $E_{\text{Hb}}$  for the formation of the H-bond and  $E_{\text{nb}}$  for the formation of the non-bonded interaction) should be representative of the entire interaction energy. The respective energy differences  $\Delta E_{\text{int}}$  (relative to the most stable conformer of a given compound) have already been presented in Table 2 along with the corresponding energy differences as obtained from full geometry optimizations. As can easily be seen, although there are partly some quantitative differences, the stability sequences of the conformers of any given compound as obtained from the two energy scales almost perfectly agree with each other. For the free molecules, in only one out of ten cases (*i.e.* with compound **3**) we find an interchange between the two most stable conformers:  $E_{\text{tot}}$  prefers **d** by  $2 \text{ kJ} \cdot \text{mol}^{-1}$ , whereas  $E_{\text{int}}$  prefers **a** by  $3 \text{ kJ} \cdot \text{mol}^{-1}$ . Hence, it may

**Table 5.** Theoretical<sup>a</sup> interaction energies  $E_{\text{Hb}}$  and  $E_{\text{nb}}$  ( $\text{kJ}\cdot\text{mol}^{-1}$ ) as obtained from isodesmic reactions (see text) for free molecules (each first line) and for  $\epsilon = 37.5$  (each second line) and dipole moments ( $D$ ) of the free molecules (each third line)

$E_{\text{Hb}}$ (O-H $\cdots$ O=C)		$E_{\text{nb}}$ (O $\cdots$ R-C)		$E_{\text{nb}}$ (O $\cdots$ O=C)	
	-33 -32 2.1		12 -6 6.5		18 17 2.7
			15 13 3.3		
	-33 -33 2.5		16 14 3.2		19 19 2.3
	-38 -36 3.0		2 -3 4.7		13 11 4.2
	-39 -38 3.2		5 0 4.5		21 20 3.6
	-38 -39 4.2		-8 -13 4.9		18 18 3.8

<sup>a</sup> B3LYP/6-31G(d,p) level of theory

certainly be claimed that the stability sequences are well predicted within our isodesmic reaction approach and consequently, this approach should provide a valuable means for a thorough understanding and interpretation of these sequences.

Coming back to the three general points noted above, first of all Table 5 reveals that the energy contributions of the H-bond interactions  $E_{\text{Hb}}$  are rather similar throughout with a maximum energy difference of only  $6\text{ kJ}\cdot\text{mol}^{-1}$  between the different carbonyl groups, whereas the contributions of the non-bonded interactions  $E_{\text{nb}}$  cover a distinctly larger range of about  $25\text{ kJ}\cdot\text{mol}^{-1}$ . From this finding it

is immediately understandable that the conformational stability sequences are primarily governed by the non-bonded and not by the H-bond interactions (*i.e.* the more favourable non-bonded interaction wins over the stronger H-bond interaction). Table 5 indicates that the energies of the non-bonded interactions increase within the series  $\text{CONH}_2 < \text{COH} < \text{COCH}_3 < \text{COOH} < \text{COOCH}_3$ , and indeed we find that with almost all compounds the most stable conformer is that with the most favourable non-bonded interaction (the only exception again concerns the two energetically largely similar conformers **a** and **d** of compound **3**).

Secondly, among the non-bonded interactions we can clearly distinguish between the energetically more favourable *anti*-conformations and the less favourable *syn*-conformations, which makes it understandable that the most stable as well as the second most stable conformer of all compounds display an *anti*-conformation. The energy difference between each of the two corresponding *anti*- and *syn*-conformations ranges from 3 to 26  $\text{kJ} \cdot \text{mol}^{-1}$  for the free molecules and up to 31  $\text{kJ} \cdot \text{mol}^{-1}$  for the most polar environment considered here. Expectedly, the largest difference concerns the amide group, where the *syn*-conformation is associated with a weak but clearly attractive  $\text{O} \cdots \text{H}-\text{N}$  H-bond, whereas the smallest difference concerns the ester group where both conformations are associated with a highly unfavourable, strongly repulsive  $\text{O} \cdots \text{O}$  interaction. As a consequence we find that with the most stable conformers of compounds, which contain amide or/and ester groups, the amide group is always engaged in a non-bonded interaction, despite it is the strongest proton acceptor within our series, whereas the ester group almost always acts as proton acceptor, despite it forms rather weak H-bonds.

Thirdly, concerning the solvent effects, as simulated by the *Onsager* reaction field method, on going from the gas phase to  $\text{CD}_3\text{CN}$  solutions Table 5 shows minute or even negligible effects ( $\leq 2 \text{ kJ} \cdot \text{mol}^{-1}$ ) for all H-bonded species as well as for all *syn*-conformers and for two *anti*-conformers of the non-H-bonded species. Noticeable effects ( $\sim 5 \text{ kJ} \cdot \text{mol}^{-1}$ ) are observed with the *anti*-conformers of amide, acetyl, and formyl groups, whereas the only outstanding case concerns the *anti*-(*E*)-conformation of the carboxyl group, which becomes stabilized by as much as 18  $\text{kJ} \cdot \text{mol}^{-1}$ . The latter prominent effect agrees well with a common and well known characteristic of carboxylic acids; *e.g.* calculations of benzoic acid at the B3LYP/6-31G(d,p) level of theory reveal that in the gas phase the (*Z*)-isomer is more stable by about 30  $\text{kJ} \cdot \text{mol}^{-1}$ , whereas the energy difference becomes significantly reduced in polar environments (down to 20  $\text{kJ/mol}$  for  $\epsilon = 37.5$ ). If we now compare the environmental effects predicted from isodesmic reactions with those obtained from full geometry optimizations (Table 2), we find that the former yield correct trends, whereas the quantitative agreement is less satisfying. The latter drawback is, however, inherently associated with the *Onsager* model: on the one hand, within this approach the electrostatic interaction is directly proportional to the square of the dipole moment of a molecule under consideration, whereas, on the other hand, the dipole moments of the title compounds **1–10** are, of course, not simply sums of the dipole moments of the basic compounds of Table 5.

From the above discussion it may certainly be claimed that the isodesmic reactions are not only remarkably successful in reproducing the conformational stability sequences. In particular, they provide a basis for a quantitative (or at least

semiquantitative) understanding of the factors that govern these stability sequences. For the carbonyl groups considered here, a main key is that the sequence of increasing attractive H-bond strengths, as noted in the introduction ( $\text{COOH} \leq \text{COOCH}_3 < \text{CHO} < \text{COCH}_3 < \text{CONH}_2$ ), and the sequence of decreasing repulsive non-bonded interactions,  $\text{COOCH}_3 > \text{COOH} > \text{COCH}_3 > \text{CHO} > \text{CONH}_2$  (Table 5), are largely similar. Hence, in most cases we are dealing with a rather subtle interplay between two possible H-bond interactions that favour one isomer, and two non-bonded interactions that favour just the other isomer, but the isodesmic reactions can reasonably well help us learn why the stabilities and the stability sequences are as they are.

With respect to further applications, we have recently started to use the isodesmic reaction approach for the prediction of conformational stability sequences of more complex compounds, and preliminary results for some phloroglucin derivatives revealed rather promising results. As examples we notice 3-acetyl-2,4,6-trihydroxy-benzaldehyde, which is a biologically active synthetic analog of grandinol [3], and 2,4-dihydroxy-6-methoxy-3-formylacetophenone. For both compounds, full geometry optimizations and isodesmic reactions yield almost identical results with respect to the conformational stability sequences. In the first case, the energies of the two most stable conformers are largely similar,  $\Delta E_{\text{tot}} = 2 \text{ kJ} \cdot \text{mol}^{-1}$  and  $\Delta E_{\text{int}} = 0 \text{ kJ} \cdot \text{mol}^{-1}$ , whereas in the latter case one conformer is distinctly more stable than the other three conformers:  $\Delta E_{\text{tot}} > 70 \text{ kJ} \cdot \text{mol}^{-1}$  and  $\Delta E_{\text{int}} > 50 \text{ kJ} \cdot \text{mol}^{-1}$ . This gives first strong evidence that, even for more complex compounds, the single energy contributions obtained from isodesmic reactions might actually be used for predictive purposes. Work concerning these issues (the applicability and the limitations) is currently under progress.

### Conclusions

A total of 44 rotational isomers of ten 2,6-disubstituted phenols containing two different carbonyl substituents ((C=O)-R, R=OH, OCH<sub>3</sub>, H, CH<sub>3</sub>, NH<sub>2</sub>) have been investigated theoretically at the B3LYP/6-31G(d,p) level of theory. Calculations were performed for free molecules as well as for reaction fields with  $\epsilon = 2.2, 4.8,$  and  $37.5$ . Comparison with available IR spectroscopic data revealed excellent agreement between experiment and theory and confirms the reliability of the calculations. The following are our conclusions:

- (a) The energies (and the stability sequence) of the conformers of a given compound are governed by a subtle interplay of an attractive hydrogen bond interaction  $\text{O}-\text{H} \cdots \text{O}=\text{C}$  between the phenolic OH group and one of the two carbonyl groups, and a (mostly repulsive) interaction  $\text{O} \cdots \text{R}-\text{C}$  or  $\text{O} \cdots \text{O}=\text{C}$  between the phenolic oxygen atom and the other non-hydrogen-bonded carbonyl substituent.
- (b) The energy contributions of the two single interactions can be separately determined from the energies of corresponding interaction-forming isodesmic reactions (benzoyl compound + phenol  $\rightleftharpoons$  2-hydroxybenzoyl compound + benzene). For any conformer, a total interaction energy can be evaluated from the sum of each two contributions, and it appeared that the stability sequences obtained in

this way almost perfectly agree with those obtained from full geometry optimizations.

(c) In particular, it turned out that the conformation of the most stable isomer of a given compound is not determined by the more favourable one of the two possible O–H ··· O=C H-bond interactions, but it is always determined by the most favourable non-bonded O ··· R–C interaction. The isodesmic reactions have proved remarkably successful in reproducing and predicting the conformational stability sequences. They provide a valuable means for a thorough understanding of the conformational equilibria and of the structural and spectroscopic properties of the compounds.

(d) Finally, evidence is given that the single energy contributions obtained from isodesmic reactions might be also used to predict conformational stabilities of distinctly more complex compounds.

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