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Competitive Hydrogen Bonds and Conformational Equilibria in Polysubstituted 3-Formyl-2-hydroxy-benzoyl Compounds

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Summary. Stability sequences of rotational isomers were investigated for a series of polysubstituted 3-formyl-2-hydroxy-benzoyl compounds (acylresorcinols and acylphloroglucinols) at the B3LYP/6-31G(d,p) level of theory. Comparison with IR spectroscopically determined data revealed excellent agreement between theoretical prediction and experiment. The theoretical stability sequences were obtained by full geometry optimizations and, additionally, by an isodesmic reaction approach. In the latter case, the total interaction energy between the various substituents is determined from the sum of single interaction energies between each two adjacent substituents, which are calculated from corresponding interaction-forming reactions. It is shown that the isodesmic reaction approach provides a quick and easy, but nevertheless reliable means for estimating relative stabilization energies from a simple increment system. It also provides a valuable tool for a discussion of the importance of the single contributions. Expectedly, the number and kind of hydrogen bonds is clearly the first and most decisive factor that governs the conformational stabilities.

Keywords. Acylresorcinols; Acylphloroglucinols; Conformational equilibria; Density functional calculations; Hydrogen bonds; Rotational isomers.

Introduction

In a previous study on competitive hydrogen bonds, the stability sequences of the rotational isomers of ten 2,6-disubstituted phenols containing two different carbonyl substituents –(C=O)–*R* (–*R* = –OH, $-OCH_3$, –H, $-CH_3$, $-NH_2$) have been investigated [1, 2]. These compounds are able to form two different intramolecular –O–H···O=C< hydrogen bonds [3, 4] with the two different carbonyl oxygen atoms ('competitive hydrogen bonds'). Furthermore, for both possible hydrogen-bonded species there exist two rotational isomers with the remaining non-bonded

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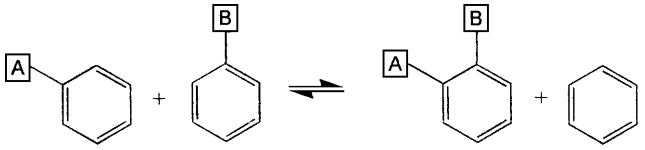


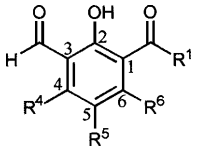
Scheme 1. Isodesmic reaction for calculating the intramolecular $A \cdots B$ interaction energy

carbonyl C=O group being either *syn* or *anti* with respect to the phenolic C–O bond. Hence, at least four conformers have to be considered for each compound to account for possible conformational equilibria. Comparison of stability sequences obtained from full geometry optimizations with available IR spectroscopic data revealed excellent agreement between theory and experiment and confirmed the reliability of the performed calculations.

Expectedly, it turned out that the total energies of the various conformers, and hence the stability sequence of the conformers of a given compound, are mainly governed by a subtle interplay of the attractive hydrogen bond interaction between the phenolic O–H group and one of the two carbonyl groups and the (mostly repulsive) interaction between the phenolic oxygen atom and the other non-hydrogen-bonded carbonyl substituent. To a first approximation, the energy contributions of these single interactions can be approximately determined from the energies of corresponding interaction-forming isodesmic reactions (Scheme 1): benzoyl compound + phenol → 2-hydroxybenzoyl compound + benzene [1, 2, 5]. From the sum of the two energy contributions, a relative stabilization energy can be estimated for any given conformer. It is shown that the conformational stability sequences of the considered compounds obtained by this 'isodesmic reaction approach' excellently comply with those obtained from full geometry optimizations.

In the present paper we extend the above investigations to a series of related, but distinctly more complex compounds (Table 1): two 4,6-di- and two 4,5,6-trisubstituted 3-formyl-2-hydroxy-acetophenones (**1**–**4**), two 4,6-disubstituted 3-formyl-2-hydroxy-benzoic acid esters (**5**–**6**), and one 4,6-disubstituted 3-formyl-2-hydroxy-benzoic acid (**7**). As a main characteristic, besides the parent substructural unit of the previously studied 2,6-disubstituted phenols [1], the compounds considered here contain one or two additional O–H groups in 3- or/and 5-position, which gives rise to a variety of possible hydrogen bond patterns and rotational isomers. There are good reasons for believing that rotational conformation and hydrogen bond pattern play an important role for the well-known biological activity of the title compounds and related substances [6–26]. 3-Formyl-2,6-dihydroxy-4-methoxy-acetophenone (**1**) is the phloroglucinol moiety of some euglobals [15–21] (inhibitors of *Epstein-Barr* virus activation) that have been isolated from the leaves of different species of *Eucalyptus*. 3-Formyl-2,4-dihydroxy-6-methoxy-acetophenone (**2**) has been isolated from the roots of *Euphorbia kansui* [7], which is widely distributed in north-western China; the plant is applied as anti tumour drug. Compound **2** has also been isolated from the bark of the plant *Cedrelopsis grevei* Baillon which is domiciled in Madagascar [13, 14]. The natives use the bark for therapeutical purposes. 3-Formyl-2,4-dihydroxy-5-methyl-6-methoxy-acetophenone ('Kosin 16', **3**) has been isolated from *Hagenia abyssinica* [8, 9] which grows in East Africa. The female flowers are used by the Abyssinians to

Table 1. Compounds, numbering, and labeling



	R^1	R^4	R^5	R^6
1	$-CH_3$	$-OCH_3$	–H	–OH
2	$-CH_3$	–OH	–H	$-OCH_3$
3	$-CH_3$	–OH	$-CH_3$	$-OCH_3$
4	$-CH_3$	–OH	$-CH_3$	–OH
5	$-OCH_3$	–OH	–H	–OH
6	$-OCH_3$	$-OCH_3$	–H	–OH
7	–OH	–OH	–H	$-CH_3$

expel tapeworms. 3-Formyl-2,4,6-trihydroxy-5-methyl-(3-methylbutyrophenone) ('Grandinol'), which is a homologue of compound **4**, has been isolated from *Eucalyptus grandis*, and its structure has been determined by *Crow et al*. [12]. This compound is a strong inhibitor of seed germination [10, 11]. 3-Formyl-2-hydroxybenzoic acid derivatives are found as intermediates in the synthesis of natural compounds [8–9] or as common compounds of lichen dimeric esters [22–26]. 3-Formyl-2,4-dihydroxy-6-methyl-benzoic acid ('Haematommic acid', **7**) [22] is a common compound of the lichen dimeric ester atranorin [23–25].

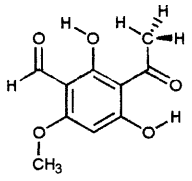
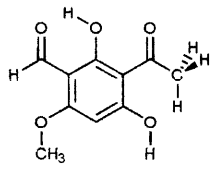
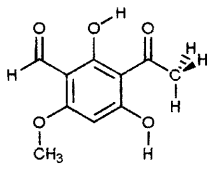
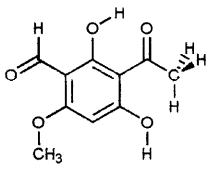
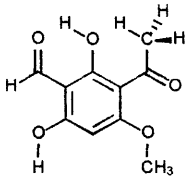
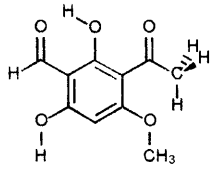
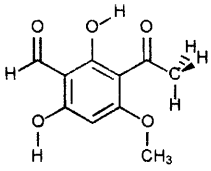
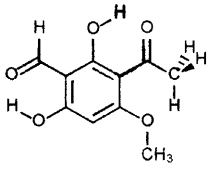
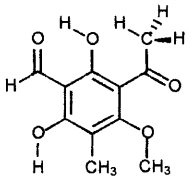
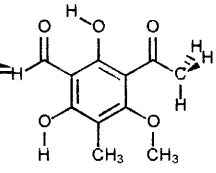
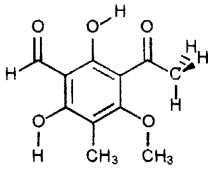
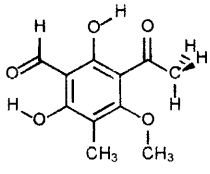
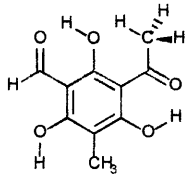
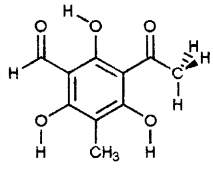
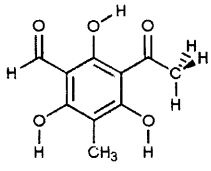
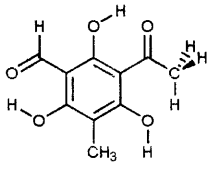
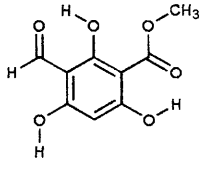
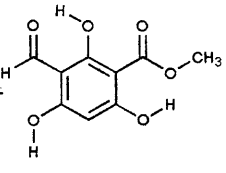
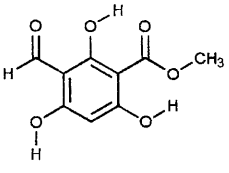
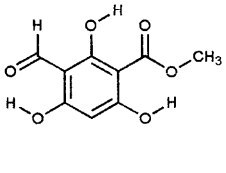
In this contribution we firstly report the theoretical stability sequences as obtained from full geometry optimizations. Secondly, in order to assess the reliability of the calculations, the theoretical results are confronted with experimental IR spectroscopic data. Thirdly, we apply the above described 'isodesmic reaction approach' for the prediction of conformational stabilities and compare the results with those obtained from full geometry optimizations. Advantages as well as limitations and deficiencies of that method are discussed. Finally, we show that this approach is not only a proper vehicle for estimating the stability sequence of the conformers of a given compound from a simple increment system, but also a valuable tool for analyzing and understanding the contributions of the various bonded and non-bonded interactions that govern the relative stabilities.

Results and Discussion

Stability sequences from full geometry optimizations

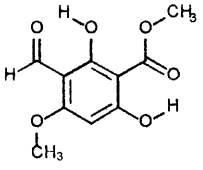
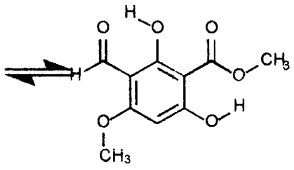
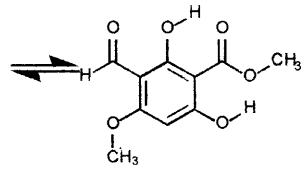
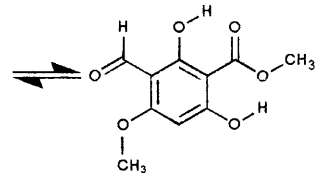
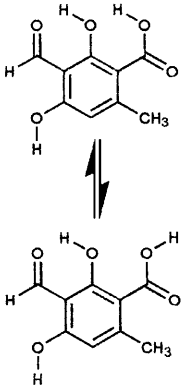
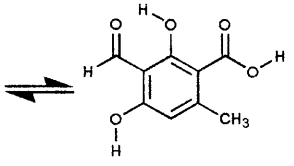
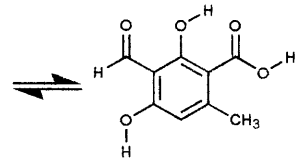
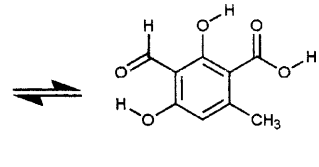
In Table 2, the rotational isomers of compounds **1**–**7** considered in the calculations are shown. Also given are the energy differences relative to the most stable conformer of each compound, ΔE_{FGO}, as obtained from full geometry optimizations at the B3LYP/6-31G(d,p) level of theory. The denotation is that of Ref. [1]: **a**, **b** denote the *anti* and *syn* conformers of the 2-OH$\cdots$3-formyl hydrogen-bonded

Table 2. Rotational isomers and calculated energy differences, ΔE_{FGO} (kJ · mol^{-1}), as obtained from full geometry optimizations at the B3LYP/6-31G(d,p) level of theory

	a	b	c	d
1				
ΔE_{FGO}	0	82	79	72
2				
ΔE_{FGO}	72	79	75	0
3				
ΔE_{FGO}	57	78	73	0
4				
ΔE_{FGO}	0	89	87	3
5				
ΔE_{FGO}	26	52	66	0

(*continued*)

Table 2 (*continued*)

	a	**b**	**c**	**d**
6				
ΔE_{FGO}	0	26	41	37
7				
ΔE_{FGO}	45 (*anti*) 55 (*syn*)	62	67	0

species, and **c**, **d** the *syn* and *anti* conformers of the 2-OH···1-acyl hydrogen-bonded species, respectively. With compound **7a**, we additionally distinguish between *anti*- and *syn*-conformers with respect to the 1-carboxyl group.

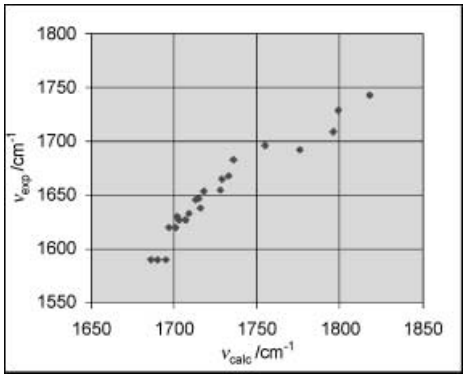
The factors governing the conformational stabilities will be discussed below in more detail. At this point, only some obvious and possibly even trivial points should be noted: (*i*) the energetically most favourable rotational isomers of all title compounds contain two –O–H···O=C< hydrogen bonds, which is the maximum possible number; (*ii*) with compound **4** there exist two energetically largely similar rotational isomers (**4a** and **4d**) with both carbonyl groups being involved in hydrogen bonding; (*iii*) all remaining rotational isomers containing only one –O–H···O=C< hydrogen bond are less stable by at least 25 kJ · mol^{-1} than the ground state conformers.

Vibrational spectra

Calculated ν(C=O) carbonyl frequencies obtained at the B3LYP/6-31G(d,p) level of theory are compiled in Table 3 for simple benzoyl and salicoyl compounds

Table 3. Theoretical (B3LYP/6-31G(d,p) level of theory) and experimental (CCl_4 solution IR spectra) carbonyl frequencies (cm^{-1}) of benzoyl and salicoyl compounds and of rotational isomers of the title compounds; the insert shows the correlation between theoretical and experimental frequencies

	–(CO)–H		–(CO)–CH_3		–(CO)–OCH_3		–(CO)–OH	
	calcd.	exp.	calcd.	exp.	calcd.	exp.	calcd.	exp.
Benzoyl	1796	1709	1776	1692	1799	1729	1818	1743
Salicoyl	1733	1668	1713	1646	1736	1683	1755	1696
1a	1701	1620	1697	1620				
1b	1708		1791					
1c	1792		1690					
1d	1782		1691					
2a	1708		1780					
2b	1712		1791					
2c	1793		1686					
2d	1711		1689					
3a	1705		1755					
3b	1714		1799					
3c	1795		1688					
3d	1709	1633	1686	1590				
4a	1703	1627	1695	1590				
4b	1711		1809					
4c	1793		1689					
4d	1707	1627	1690	1590				
5a	1706				1720			
5b	1708				1829			
5c	1793				1735			
5d	1715	1647			1729	1665		
6a	1702	1630			1718	1654		
6b	1704				1828			
6c	1790				1734			
6d	1782				1731			
7a$_{(anti)}$	1706						1820	
7a$_{(syn)}$	1716						1797	
7b	1716						1834	
7c	1796						1732	
7d	1716	1638					1728	1655



and for the rotational isomers of the seven title compounds. Additionally, corresponding experimental IR data are given as far as available. In two instances the experimental data refer to homologues of the theoretically treated compounds (Euglobal-G9 [16] instead of **1** and Grandinol [12] instead of **4**) which should, however, not seriously affect the results. Comparison between calculated and experimental vibrational data provides a valuable means to check the reliability of theoretical calculations. We note that carbonyl frequencies are known to be slightly but systematically overestimated at the B3LYP/6-31G(d,p) level of theory. Compared to CCl_4 solution spectra, the differences amount to about 4% [3].

Carbonyl vibrational frequencies are well suited for a characterization of hydrogen bond patterns involving carbonyl groups because they undergo characteristic

low frequency shifts upon hydrogen bonding; the experimentally observed differences between corresponding benzoyl and salicoyl compounds amount to about $50\,cm^{-1}$ (Table 3). For the title compounds this means that energetically favourable conformers with two –O–H···O=C< hydrogen bonds should give rise to two lower frequency carbonyl bands. On the other hand, distinctly less stable conformers with only one –O–H···O=C< hydrogen bond, which can be neglected at ambient temperatures, always should give rise to one higher frequency carbonyl band that corresponds to the non-hydrogen-bonded carbonyl group. Table 3 shows that, in agreement with the theoretical predictions, high frequency carbonyl bands are missing in all of the experimentally observed spectra. The good agreement between theory and experiment becomes also apparent from a numerical comparison between the corresponding calculated and observed frequency values (Table 3, insert). A second order polynomial fit yields a standard deviation of less than $10\,cm^{-1}$, which is certainly very satisfying and confirms the reliability of the computations.

For compound **4**, theory predicts two energetically almost equivalent conformers **4a** and **4d** (Table 2), from which a conformational equilibrium close to 50:50 should result at ambient temperatures. Theory also predicts two low-frequency ν(C=O) carbonyl frequencies for both conformers with almost negligible differences between **4a** ($1703 + 1695\,cm^{-1}$) and **4d** ($1707 + 1690\,cm^{-1}$). Experimentally, we observe two low-frequency bands ($1627 + 1590\,cm^{-1}$) which, according to the theoretical prediction, can consistently be assigned to two overlapping ν(C=O) carbonyl frequencies of the two conformers. On the other hand, from experiment alone one could only guess whether the two observed bands result from overlapping bands of two energetically almost equivalent conformers or if they are predominantly due to only one (and which?) conformer. This example clearly shows how theoretical predictions may help to settle questions that remain open from experimental data.

Conformational stabilities and the isodesmic reaction approach

Basically, there exists no unequivocal and commonly accepted method (neither an experimental nor a theoretical one) to uniquely determine energies of intramolecular interactions. The use of isodesmic reactions is a proper approach to this problem out of several theoretical approaches. Here, the interaction energy between two adjacent substituents on an aromatic ring is defined by the reaction energy of a fictitious interaction building reaction (Scheme 1) which is calculated from the total energies of the four involved species. The isodesmic reaction approach has been proved to be particularly useful for evaluating bond strengths sequences of intramolecular hydrogen bonds [3, 5]. As noted in the introduction, more recently the isodesmic reaction approach has also successfully been applied to the calculation of stability sequences of rotational isomers of 2,6-disubstituted phenols containing two different carbonyl substituents [2] which are something like parent compounds of the title compounds. The basic idea was that the relative stabilities of the isomers should mainly be governed by the total interaction energies between the three substituents, and that to a first approximation the total interaction energy should be equal to the sum of the two single interaction energies between each two substituents. Actually, it turned out that the conformational stability sequences

obtained in this way excellently comply with those obtained from full geometry optimizations. With the title compounds, the situation is of course distinctly more complex, since we are dealing not only with two but with up to six single interactions. When applying the isodemic reaction approach for the prediction of conformational stabilities of the title compounds one must therefore be prepared for less reliable results and for larger deviations from results of full geometry optimizations.

The single interaction energies, $E_{x\cdots y}$, between substituents in *x*- and *y*- positions as obtained from isodesmic reactions are compiled in Table 4 for the rotational isomers of compounds **1**–**7**. Also given are the total interaction energies, $E_{\mathrm{IRA}} = \Sigma E_{x\cdots y}$, resulting therefrom as well as the stabilization energies, ΔE_{IRA}, relative to the most stable conformer. For convenience, the relative stabilization

Table 4. Theoretical (B3LYP/6-31G(d,p) level of theory) single interaction energies $E_{x\cdots y}$, total interaction energies E_{IRA}, and relative stabilities ΔE_{IRA} as obtained from isodesmic reactions (see text), and relative total energies ΔE_{FGO} as obtained from full geometry optimizations ($\mathrm{kJ \cdot mol^{-1}}$)

	$E_{1\cdots 2}$	$E_{2\cdots 3}$	$E_{3\cdots 4}$	$E_{4\cdots 5}$	$E_{5\cdots 6}$	$E_{6\cdots 1}$	E_{IRA}	ΔE_{IRA}	ΔE_{FGO}
1a	4.6	−37.6	2.3	–	–	−38.7	−69.4	0	0
1b	20.9	−37.6	2.3	–	–	4.6	−9.8	60	82
1c	−38.7	13.3	2.3	–	–	4.6	−18.5	51	79
1d	−38.7	1.6	13.8	–	–	4.6	−18.7	51	72
2a	4.6	−37.6	1.6	–	–	23.2	−8.2	60	72
2b	20.9	−37.6	1.6	–	–	7.0	−8.1	60	79
2c	−38.7	13.3	1.6	–	–	7.0	−16.8	51	75
2d	−38.7	1.6	−37.6	–	–	7.0	−67.7	0	0
3a	4.6	−37.6	1.6	0.6	15.3	23.2	7.7	62	57
3b	20.9	−37.6	1.6	0.6	15.3	7.0	7.8	62	78
3c	−38.7	13.3	1.6	0.6	15.3	7.0	−0.9	53	73
3d	−38.7	1.6	−37.6	−1.7	15.3	7.0	−54.1	0	0
4a	4.6	−37.6	1.6	0.6	−1.7	−38.7	−71.2	0	0
4b	20.9	−37.6	1.6	0.6	0.6	4.6	−9.3	62	89
4c	−38.7	13.3	1.6	0.6	0.6	4.6	18.0	53	87
4d	−38.7	1.6	−37.6	−1.7	0.6	4.6	−71.2	0	3
5a	16.3	−37.6	1.6	–	–	−33.0	−52.7	33	26
5b	19.2	−37.6	1.6	–	–	−16.8	−33.6	52	52
5c	−33.0	13.3	1.6	–	–	−16.8	−34.9	51	66
5d	−33.0	1.6	−37.6	–	–	−16.8	−85.8	0	0
6a	16.3	−37.6	2.3	–	–	−33.0	−52.0	0	0
6b	19.2	−37.6	2.3	–	–	−16.8	−32.9	19	26
6c	−33.0	13.3	2.3	–	–	−16.8	−34.2	18	41
6d	−33.0	1.6	13.8	–	–	−16.8	−34.4	18	37
7a$_{(anti)}$	12.2	−37.6	1.6	–	–	7.0	−16.8	41	45
7a$_{(syn)}$	15.4	−37.6	1.6	–	–	7.0	−13.6	44	55
7b	18.2	−37.6	1.6	–	–	11.2	−6.6	51	62
7c	−32.9	13.3	1.6	–	–	11.2	−6.8	51	67
7d	−32.9	1.6	−37.6	–	–	11.2	−57.7	0	0

energies, ΔE_{FGO}, as obtained from the full geometry optimizations (Table 2), are also included.

From the last two columns of Table 4, two points can immediately be assessed. Firstly, the relative stabilization energies obtained from the isodesmic reaction approach, ΔE_{IRA}, are throughout somewhat lower than the energy differences obtained from full geometry optimizations, ΔE_{FGO}. Hence, the isodesmic reaction approach seems to systematically underestimate or level the differences between favourable and non-favourable conformers. Secondly, although the differences between the stability sequences based on ΔE_{IRA} and ΔE_{FGO} are expectedly more frequent and more significant with the title compounds than with the more simple parent 2,6-disubstituted phenols [1], notable differences are only observed for non-favourable high energy rotational isomers. The ground states as well as additional low-energy conformers, which may considerably contribute to conformational equilibria, are correctly predicted throughout.

For a first inspection of the factors governing the conformational stabilities, let us divide the single interactions that build up the total interaction energies into three classes: (1) hydrogen bonds, which establish the only strongly attractive interactions with interaction energies of -39 to $-33\,kJ\cdot mol^{-1}$ for –O–H···O=C< type bonds and $-17\,kJ\cdot mol^{-1}$ for –O–H···O< type bonds, (2) weak (mainly repulsive) non-bonded interactions with interaction energies between -2 and $7\,kJ\cdot mol^{-1}$, and (3) strongly repulsive interactions with interaction energies between 11 and $23\,kJ\cdot mol^{-1}$; these are mainly O···O type interactions, but there also exist some few (outstanding) strongly repulsive contacts other than O···O type (such as $E_{5\cdots6}$ in **3a–d**, $E_{1\cdots2}$ in **7a**$_{(anti)}$ or $E_{6\cdots1}$ in **7b–d**).

As already noted at the beginning of this section, the number of hydrogen bonds (class (1) interactions) is clearly the first and most decisive factor that governs the conformational stabilities. Table 4 as well as Table 2 show that this is not only due to the loss of a strongly attractive interaction upon breaking a hydrogen bond, but also and moreover because breaking a hydrogen bond is always accompanied by the appearance of a strongly repulsive class-(3) interaction. From the isodesmic reaction approach one can roughly estimate a general loss of stabilization energy of about $50\,kJ\cdot mol^{-1}$ for breaking a –O–H···O=C< type bond and $30\,kJ\cdot mol^{-1}$ for breaking a –O–H···O< type bond, where the difference reflects the different hydrogen bond strengths of –O–H···O=C< and –O–H···O< type bonds. Compared to the dominating role of class (1) and (3) interactions in determining the conformational stabilities, the weak class-(2) interactions play only a minor role.

These guiding principles become clearly evident from Tables 2 and 4. To a first approach, the stabilities of the conformers can simply be ranked according to number and kind of the hydrogen bonds. The most simple situation is encountered for the 3-formyl-2-hydroxy-acetophenones **1–3**. With compounds **1–3**, each conformer contains two –O–H···O=C< type hydrogen bonds, whereas the remaining three conformers contain only one. The former (**1a**, **2d**, **3d**) establish the ground state conformers, whereas the latter (**1b–d**, **2a–c**, **3a–c**) are less stable by $57–82\,kJ\cdot mol^{-1}$ (as measured by ΔE_{FGO}). With compound **4**, both *anti*-conformers **4a** and **4d** contain two –O–H···O=C< type hydrogen bonds, whereas the two *syn*-conformers **4b** and **4c** contain only one. Conformers **4a** and **4d** are

energetically largely similar (or even equivalent within the isodesmic reaction approach), whereas conformers **4b** and **4c** are less stable by 87–89 kJ · mol^{-1}. The situation is more complex for the 3-formyl-2-hydroxy-benzoic acid esters **5** and **6** because of the additional possibility of the formation of –O–H···O< type hydrogen bonds that involve the ester methoxy oxygens. The most stable conformer of compound **5**, **5d**, contains two –O–H···O=C< type and one –O–H···O< type hydrogen bond. The second stable conformer, **5a** ($\Delta E_{FGO} = 26$ kJ · mol^{-1}), contains two –O–H···O=C< type hydrogen bonds, whereas **5b** and **5c** ($\Delta E_{FGO} = 36$–52 kJ · mol^{-1}) contain only one –O–H···O=C< type and one –O–H···O< type hydrogen bond. Similarly, the most stable conformer of compound **6**, **6a**, contains two –O–H···O=C< type hydrogen bonds, whereas **6b–d** ($\Delta E_{FGO} = 26$–41 kJ · mol^{-1}) contain one –O–H···O=C< type and one –O–H···O< type hydrogen bond. As to the 3-formyl-2-hydroxy-benzoic acid **7**, the most stable conformer, **7d**, also contains two –O–H···O=C< type hydrogen bonds, whereas the remaining conformers **7a–c** ($\Delta E_{FGO} = 45 - 66$ kJ · mol^{-1}) contain only one.

This first order classification, which is based on number and kind of hydrogen bonds, excellently complies with both ΔE_{IRA} and ΔE_{FGO} stability sequences. Some notable differences between ΔE_{IRA} and ΔE_{FGO} stability sequences we find, however, within the classes. If we assume that the relative stability energies ΔE_{FGO} are 'real and correct', the differences show up the limitations of the isodesmic reaction approach. This approach relies on the basic assumption that the single interaction energies between two given *ortho*-substituents are just the same for the basic disubstituted parent compounds and for complex polysubstitued compounds. Unfortunately, it is not possible to directly determine these single interaction energies within the complex title compounds and hence, to directly determine possible differences. However, instead of energies one may compare representative contact distances as obtained from full geometry optimizations that are known to correlate well with the interaction energies. Let us for example inspect the O···O distances within the 3-formyl-2-hydroxy moieties, which are a common feature of all title compounds. In the basic disubstituted compound, salicylaldehyde, which provides the basis of the isodesmic approach, the O···O distances are 2.62 Å and 2.77 Å for the intramolecularly hydrogen bonded ground state conformer and for the non-bonded rotamer with the O–H group being rotated by 180°. In the title compounds, the O···O distances are distinctly shorter throughout: 2.54 ± 0.03 Å for the hydrogen-bonded conformers (**a** and **b**) and 2.72 ± 0.01 Å for the non-bonded contacts (**c**). Hence, the hydrogen bond interactions are slightly stronger (by about 5–10 kJ · mol^{-1}), and the non-bonding interactions are more repulsive in the title compounds than in salicylaldehyde.

As to the various 2-hydroxy-1-acyl moieties, in the majority of instances we also find similar systematically decreased O···O distances (-0.05 to -0.10 Å) for both the hydrogen-bonded and the non-bonded species. There are, however, two cases, which show just the opposite behaviour: in conformers **1b–4b** the non-bonded >O···O=C (acetyl) distances measure 2.86 ± 0.02 Å compared to only 2.65 Å for the corresponding non-hydrogen-bonded 2-hydroxy-acetophenone rotamer, and in conformer **7b** the non-bonded >O···O=C (carboxyl) distance amounts to 2.88 Å compared to only 2.70 Å for the corresponding non-hydrogen-bonded salicylic

acid rotamer. Expectedly, it turns out that the question of decreasing or increasing O···O distances is directly related to the planarity of the compounds, where planarity refers to the plane of the phenyl rings. In the outstanding cases **1b**–**4b** and **7b**, the acetyl and carboxyl groups are largely twisted out of the plane. The C_{ar}–C_{ar}–C=O torsion angles measure about 40° to 60°, which is the dominating reason for the observed significant increase of the O···O distances when compared to those of the basic (nearly) planar disubstituted compounds. In all other instances, the acyl moieties are planar or at least nearly planar, the corresponding C_{ar}–C_{ar}–C=O torsion angles being less than 10°.

The examples just discussed clearly show that the predictive accuracy of the isodesmic reaction approach is of course limited because of possible mutual interactions between substituents and/or because of steric effects like changes of torsion angles, as it also applies to various other increment systems. Nevertheless, it can be claimed that the isodesmic reaction approach provides the possibility for a quick and easy and at least rough estimation of relative conformational stabilities by a simple increment system.

Conclusions

Relative stabilities of each four to five rotational isomers were investigated for seven polysubstituted 3-formyl-2-hydroxy-benzoyl compounds (acylresorcinols and acylphloroglucinols) at the B3LYP/6-31G(d,p) level of theory. The stability sequences were determined by full geometry optimizations. The reliability of the calculations were confirmed by a comparison between theoretical and experimental IR spectroscopic data.

Additionally, the stability sequences were assessed by using an isodesmic reaction approach, where the total interaction energy between the substituents was estimated from the sum of single interaction energies between each two adjacent substituents. The latter were calculated from interaction-forming reactions for the corresponding *ortho*-disubstituted benzene compounds. It was shown that the isodemic reaction approach not only provides a quick and easy means for approximately estimating relative stabilization energies from a simple increment system, but also provides a valuable tool for discussing the importance of the single contributions to the total interaction energies. The number and kind of hydrogen bonds is clearly the first and most decisive factor that governs the conformational stabilities. This is not only due to the loss of a strongly attractive interaction upon breaking a hydrogen bond, but also because breaking a hydrogen bond is always accompanied by the appearance of a strongly repulsive interaction. Whereas rotational isomers that contain the same number and kind of hydrogen bonds are energetically largely similar, breaking a –O–H···O=C< type bond results in a loss of stabilization energy of about $50\,kJ \cdot mol^{-1}$; breaking a –O–H···O< type bond results in a loss of stabilization energy of about $30\,kJ \cdot mol^{-1}$.

Materials and Methods

The compounds included in the calculations are listed in Table 1, along with the subsequently used compound and atom numberings. IR solution spectra (in CCl_4) were measured with a Perkin-Elmer

Spectrum 2000 FTIR spectrometer. All spectra were checked for intermolecular association effects by appropriate dilution series. Spectra were measured of the following samples/compounds: Euglobal-G9 [16], which contains compound **1** as the basic substructural unit, and Grandinol [12], which is a homologue of compound **4** ($R^1 = CH_2CH(CH_3)_2$ instead of CH_3) (supplied by Prof. *H. Etoh*, Shizuoka, Japan); Kosin 16 [8] (**3**) and synthetic samples of the esters **5** and **6** [8, 9] (supplied by Prof. *G. P. Schiemenz*, Kiel, Germany); and acid **7** [22] (supplied by Prof. *R. Tabacchi*, Neuchatel, Switzerland).

Theoretical calculations of energetic, geometric, and vibrational spectroscopic data were performed for each four to five rotational isomers of the compounds of Table 1 as well as for various components of the isodesmic reactions. All calculations were performed at the B3LYP/6-31G(d,p) level of theory [27–29] using the GAUSSIAN 98 program suite [30]. The optimized geometries were calculated without constraints, and each structure was characterized by a harmonic frequency analysis.

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References

[1] Simperler A, Mikenda W (1999) Monatsh Chem **130**: 1003
[2] Reichl G (1996) Thesis, University of Vienna
[3] Lampert H, Mikenda W, Karpfen A (1996) J Phys Chem **100**: 7418
[4] Steinwender E, Mikenda W (1994) Monatsh Chem **125**: 695
[5] George P, Bock CW, Trachtman M (1985) J Mol Struct (Theochem) **133**: 11
[6] Delle Monache F, Menichini F, Cuca Suarez LE (1996) Gazz Chim Ital **126**: 275
[7] Ding YL, Jia ZJ (1992) Phytochemistry **31**: 1435
[8] Schiemenz GP, Schröder JM (1985) Z Naturforsch B: Chem Sci **40**: 669
[9] Schiemenz GP, Behrens H, Ebert CP, Maienschein K, Schröder JM (1985) Z Naturforsch B: Chem Sci **40**: 681
[10] Bolte ML, Crow WD, Takahashi N, Sakurai A, Uji-Je M, Yoshida S (1985) Agric Biol Chem **49**: 761
[11] Bolte ML, Bowers J, Crow WD, Paton DM, Sakurai A, Takahashi N, Uji-Je M, Yoshida S (1984) Agric Biol Chem **48**: 373
[12] Crow WD, Osawa T, Paton DM, Willing RR (1977) Tetrahedron Lett **12**: 1073
[13] Schulte KE, Rücker G, Klewe U (1973) Arch Pharm **306**: 857
[14] Klewe U (1971) Thesis, Univ Münster, Germany
[15] Singh IP, Umehara K, Asai T, Etoh H, Takasaki M, Konoshima T (1998) Phytochemistry **49**: 1699
[16] Umehara K, Singh IP, Etoh H, Takasaki M, Konoshima T (1998) Phytochemistry **47**: 1157
[17] Chiba K, Arakawa T, Tada M (1998) J Chem Soc Perkin Trans 1, 2939
[18] Chiba K, Arakawa T, Tada M (1996) Chem Commun 1763
[19] Takasaki M, Konoshima T, Fujitani K, Yoshida S, Nishimura H, Tokuda H, Nishino H, Iwashima A, Kozuka M (1990) Chem Pharm Bull **38**: 2737
[20] Takasaki M, Konoshima T, Shingu T, Tokuda H, Nishino H, Iwashima A, Kozuka M (1990) Chem Pharm Bull **38**: 1444

[21] Kozuka M, Sawada T, Kasahara F, Mizuta E, Amano T, Komiya T, Goto M (1982) Chem Pharm Bull **30**: 1952
[22] Stepanenko LS, Krivoshchekova OE, Mishchenko NP (1984) Phytochemistry **24**: 354
[23] Elix JA, Wardlaw JH (1996) Aust J Chem **49**: 536
[24] Elix JA, Chester DO, Gaul KL, Parker JL, Wardlaw JH (1989) Aust J Chem **42**: 1191
[25] Pulgarin C, Tabacchi R (1989) Helv Chim Acta **72**: 1061
[26] Elix JA, Norfolk S (1975) Aust J Chem **28**: 1113
[27] Becke AD (1993) J Chem Phys **98**: 5648
[28] Lee C, Yang W, Parr RG (1988) Phys Rev B **37**: 785
[29] Hehre WJ, Ditchfield R, Pople JA (1972) J Chem Phys **56**: 2257
[30] Frisch MJ et al (1998) Gaussian 98, Rev A1, Gaussian Inc, Pittsburgh, PA