

Intra- and Intermolecular C(sp²)-H...O Hydrogen Bonds in a Series of Isobenzofuranone Derivatives: Manifestation and Energetics

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Derivatives 2–6 were prepared as models for studying intra- and intermolecular C(sp²)-H...O hydrogen bonding. Their X-ray structures confirm the presence of intramolecular hydrogen bonds in derivatives of the “a” series: the corresponding C...O distances vary between 2.91 and 2.97 Å. The corresponding ¹³C-¹H coupling constants are increased by about 7.5 Hz, and the ¹H chemical shifts in CDCl₃ are 9.1–10.7 ppm. No intramolecular hydrogen bonds can form in derivatives of the isomeric “b” series. In this series, the chemical shifts of the corresponding aromatic protons exhibit strong solvent dependency; in particular, they are as sensitive as the proton in chloroform to the presence of DMSO. The vinylic protons activated by the electron-accepting COOR groups behave similarly. Quantum mechanical calculations in the gas phase and in DMSO reproduce the experi-

mental observations. Energies of the intramolecular hydrogen bonds evaluated by two independent approaches vary between 3.7 and 4.4 kcal mol⁻¹ in the gas phase and still amount to at least 2.5 kcal mol⁻¹ in 2a in DMSO. These estimates are practically independent of the computational method (HF, MP2, and DFT B3LYP were employed for derivatives 2). We conclude that the behavior of both activated aromatic and vinylic C(sp²)-H atoms in the studied derivatives is qualitatively and quantitatively similar to the behavior of the C(sp³)-H atom in chloroform. The existence of hydrogen bonds involving these atoms can easily be detected by NMR spectroscopy.

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Introduction

Phenomena relating to hydrogen bonds (HBs) are the focus of a huge number of studies, owing to their importance in chemistry, physics, and biology.^[1] Whereas the roles of “conventional” O-H...O HBs in determining the structure and properties of water and functions of biomolecules have been recognized for more than 50 years, C-H...O interactions were categorized as true HBs only later, after sufficient experimental data (IR, Raman, NMR spectra, gas-phase and solid structures, and theoretical results) had been accumulated.^[2] The interaction energy of CH₄ and H₂O was calculated to be rather small: between 0.3 and 0.7 kcal mol⁻¹, depending on the computational methods.^[3] This energy increases considerably when electronegative substituents are attached to the C atom: the BSSE-corrected MP2/6-31+G(d,p) values are 0.29 and 3.7 kcal mol⁻¹ for CH₃H...OH₂ and CF₃H...OH₂, respectively.^[4] The latter

value is more than 80% of the energy (4.51 kcal mol⁻¹) calculated for the HOH...OH₂ dimer at the same level of theory.^[4] Further examples can be found in a recent review.^[5]

IR spectroscopic data imply that proton-donating ability increases in the series C(sp³)-H < C(sp²)-H < C(sp)-H,^[2a] which is corroborated by quantum mechanical calculations. Thus, C-H...O binding energies for benzene as proton donor were reported to amount to 1.1–1.7 kcal mol⁻¹, depending on the level of calculation and the proton acceptor.^[6] These energies are considerably increased in polyfluorinated benzenes. However, relatively few examples of vinylic or aromatic C-H groups involved in strong, easily detectable HBs are known. Experimentally, formation of complexes between 1,2,4,5-tetrafluorobenzene as proton donor and various proton acceptors in the gas phase have been observed by fluorescence-detected IR spectroscopy.^[7] Aromatic C-H...N and C-H...O HB formation was evidenced by low-frequency shifts and intensity enhancement of the aromatic C-H stretching vibration. The stabilization energy of the complex with dimethyl ether was calculated to amount to 5.39 kcal mol⁻¹ [MP2/6-31+G(d), without BSSE correction], or to 4.27 and 3.16 kcal mol⁻¹ with 50% and 100% BSSE correction, respectively.^[7b] Similarly, supersonic-jet spectroscopy showed that fluorinated benzenes form H-bonded dimers with 2-pyridone.^[8] The C-H...O=C

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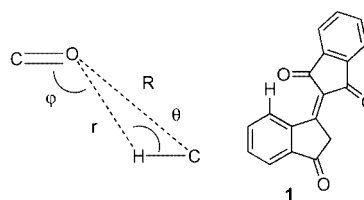
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HB strengths were calculated as 2.8 kcal mol⁻¹ for fluorobenzene and 4.0 kcal mol⁻¹ for tetrafluorobenzenes at the PW91/6-311++G(d,p) level.^[8b]

Several theoretical investigations have been carried out on model compounds to estimate possible HBs in solids, especially those in proteins.^[6c,9] C–H···O HBs, although weaker than conventional O–H···O HBs, are certainly one of the factors predetermining the structures of solids – structures of proteins in particular. Calculations on *N*-methylmaleimide complexes with acetone and water, in which the both vinylic H atoms were involved in HBs, yielded 1.4–1.7 kcal mol⁻¹ per bond.^[9c] The contribution of the C–H···O interaction to stabilization of the adenine–uracil pair has been estimated to reach 6% of the total interaction energy.^[9d] It is difficult to extract an estimation of the HB energy from the total interaction energy either in this case or from the results of other recently reviewed studies relating to nucleic acid dimers.^[10] C–H···O bonding has been observed in several transition metal poly(azoly)borato complexes.^[11a] Statistical analysis of the C–H···O interaction in the doubly H-bonded C=CH–C=O dimer using data available in the Cambridge Structural Database showed that this pattern occurs frequently in crystals.^[11b] The total binding energy within fragments approximating to H-bonded 1,4-benzoquinone dimers was calculated as 4.3 kcal mol⁻¹, of which about 1.4 kcal mol⁻¹ was partitioned for each C–H···O HB (MP2, EZPPB basis set). The interaction energy in a two-dimensional slab of a 1,4-benzoquinone crystal was calculated to reach 5.3 kcal mol⁻¹ [HF/6-31 G(d,p), BSSE-corrected].^[12]

C–H···O HBs with energies lower than 1.5 kcal mol⁻¹ can indeed be an important factor influencing crystal lattice structures, but would hardly be expected to be observed at room temperature in solution, as calculations predict that HBs of this type weaken considerably with growing dielectric constant.^[9a] On the other hand, aromatic C–H···O interactions can exceed 4 kcal mol⁻¹ and in this case can be studied in solution by conventional spectroscopic techniques, of which NMR is one of the most informative. It has thus been found that a pyridylurea–tetraazaanthracenedione complex involving three HBs is more stable than an analogous complex with four HBs.^[13] The X-ray structures of the tetraazaanthracenedione dimer and the complex revealed the presence of two N···H HBs and two C–H···O contacts (2.941 Å) in the former and three N···H HBs and one C–H···O contact (2.520 Å) in the latter. Monitoring of the dimerization process by ¹H NMR showed that the corresponding C–H signal is shifted by about 0.1 ppm. The complexation process, which gave rise to the formation of the intramolecular C–H···O contact (2.520 Å), was accompanied by a 1.73 ppm downfield shift. The C–H···O short contacts were classified as “putative HBs” as they indeed might be forced by the N···H HBs, and the observed downfield shifts may stem from the C–H groups’ proximity to the C=O anisotropic deshielding cones.^[13] Recently, we demonstrated that unusually large low-field chemical shifts of one of the aromatic protons in the ¹H NMR spectra of bindone (**1**) and other products of indan-1,3-dione self-

condensation are a feature of HBs.^[14] Indeed, the accepted geometric criteria of the existence of the HB as derived from crystallographic data^[15] involve distances *R* and *r*, together with angles *θ* and *φ*



where the relevant ranges are *R* = 3.0–4.0 Å, *r* = 2.0–2.8 Å, *θ* = 110–180°, and *φ* = 120–140°.

According to the X-ray structure, derivative **1** fits these criteria, with *R* = 2.955 Å, *θ* = 138°, and *φ* = 117°. We showed that of the 1.8 ppm low-field shift of the aromatic H-7, only about 1.2 ppm can be explained by the magnetic anisotropy of the carbonyl group, oxygen steric influence, and electric field effect. The remaining 0.6 ppm can be regarded as a reasonable measure of the influence of the intramolecular HB.^[14] However, the rigid structure of derivative **1**, involving two cyclic moieties connected by the double bond, makes estimation of the HB energy also problematic in this case.

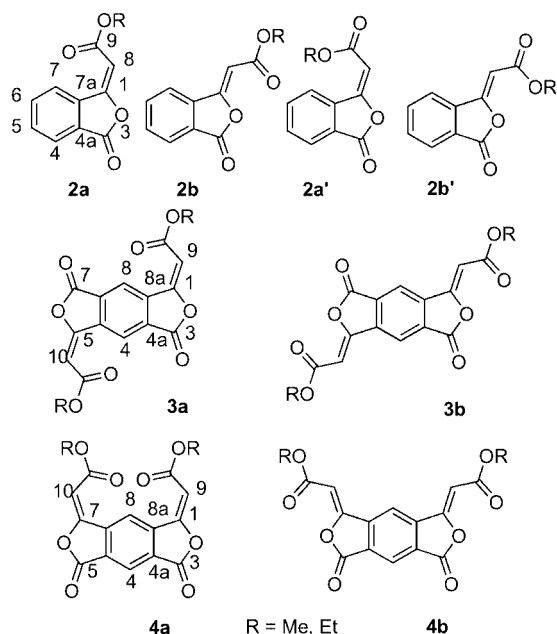
Here we report on our investigation of a series of 2-[3-oxoisobenzofuran-1(3*H*)-ylidene]acetate derivatives **2–6**. The **a** series (*E* isomers) possesses a fragment isostructural to bindone (**1**) in the vicinity of the ester carbonyl group and exhibits similar ¹H NMR features: the signals of the protons potentially involved in intramolecular H-bonding are strongly shifted to low field (9.1–10.7 ppm in CDCl₃). Unlike **1**, however, derivatives **2** can also exist as *Z* isomers (**b** series) and also, possibly, as **a'** and **b'** series. Whereas no intramolecular HB can form either in the **b** or in the **b'** series, the activated H atoms are free to participate in intermolecular HBs with the solvent molecules. Therefore, these compounds might serve as very useful models for study of HB-related phenomena. Indeed, quantum mechanical calculations reproduce the observed ¹H NMR features and provide estimates of the HB energies.

Results and Discussion

Synthesis

Derivatives **2** and their analogues are well known precursors for synthesis of natural and bioactive compounds, and several synthetic approaches have been elaborated. They have been prepared by esterification of the acid,^[16] treatment of *o*-iodobenzoic acid with ethyl propiolate in the presence of cuprous iodide in DMF,^[17] Baylis–Hillman reactions between *o*-carboxybenzaldehydes and acrylates,^[18] palladium-catalyzed carbonylative cyclizations of Baylis–Hillman adducts,^[19] and through Wittig reactions between phthalic anhydrides and [(alkoxycarbonyl)methylene]triphenylphosphoranes.^[20]

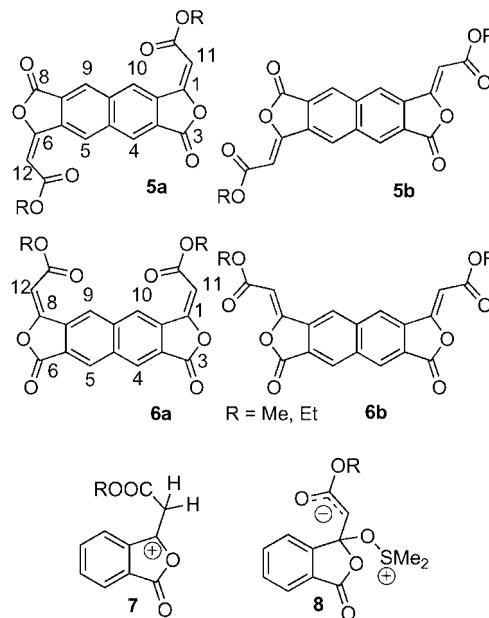
Except in the cases of the first two methods, which afforded pure *Z* isomers, *E* isomers – characterized by unusually large chemical shifts of 7-H (8.5–9 ppm) – were the sole or predominant products. Thus, Wittig reactions yielded exclusively *E* isomers, in 60% yield when the reaction was carried out without a solvent^[20a] or in 87% yield after 18 h in chloroform at reflux.^[20b] Later, during a mechanistic study of this reaction, it was found that in chloroform at room temperature the *E* isomer was formed in 52% yield along with a 13% yield of the *Z* isomer.^[20c] Non-cyclic anhydrides are known to react with stabilized phosphoranes to afford the acylation products, diketo phosphoranes,^[21] and the occurrence of the normal Wittig reaction and the exclusive or predominant formation of the *E* isomers with phthalic anhydride were explained in terms of formation of a π - π complex between the C=O group of the phosphorane and the electron-deficient benzenic ring of phthalic anhydride.^[20a,20c,20d] In the process of this investigation, when we realized that 3,6-H atoms of phthalic anhydride and its analogues can form relatively strong HBs, we assumed that the H-bonded complexes with the phosphorane can precede the Wittig reaction, and that chloroform, which is itself capable of H-bonding, is therefore not the best choice as a solvent. Indeed, the reaction in dry toluene afforded a mixture of *E* and *Z* isomers **2a** and **2b** (R = Et) in 84% and 12% yields, respectively. Formation of **2b** could either be explained by the presence of acidic impurities in the commercial ethoxycarbonylmethylenephosphorane or might result from intermolecular reaction of the non-complexed components.



We found that all derivatives of the **a** series are indeed sensitive to acids and partially isomerize into the *Z* isomers when heated in toluene in the presence of a catalytic amount of methanesulfonic acid. Isomerization of **2a** into **2b** had previously been observed to occur only on UV irradiation.^[20a] In all probability, isomerization proceeds through intermediates of type **7**, in which intramolecular

H-bonding cannot occur for steric reasons. Preparatively, the *Z* isomers can be isolated by dissolving the *E* isomers in warm sulfuric acid and pouring onto ice.

Derivatives **3–6** were previously unknown and were prepared from commercially available pyromellitic anhydride and the bis-anhydride of naphthalene-2,3,6,7-tetracarboxylic acid.^[22]



It is worth noting that, although pyromellitic anhydride is the strongest electron acceptor of the three anhydrides employed here, the yield of the mixture of isomers in this case was just 53%, whereas the mixture of isomers **5** and **6** was isolated in 95% yield. At the same time, the activated aromatic C–H atoms are the most shielded (by the four carbonyl groups) in pyromellitic anhydride, which speaks more in favor of the H-bonded complex intermediates than those of the π - π complex. The full synthesis and isolation procedures are given in the Supporting Information.

X-ray Structures and Geometry Optimization

The NMR spectra of derivatives **2–6** (R = Et) showed that each isolated pair of isomers is the *E* and *Z* isomer with regard to one of two possible conformations of the C=C–C=O fragment, but could not unequivocally distinguish between the *cis* and *trans* conformers **a/a'** and **b/b'**. All signals are sharp, and no temperature dependence of their shape and position was observed (in toluene between 20 and 100 °C, for instance), which excludes the possibility of **a**→**a'** and **b**→**b'** interconversion in solution.

X-ray structure determinations were carried out for derivatives **2a**, **2b**, **3a**, **4a**, and **5a** (R = Et), confirming the structural assignment. Single crystals of each compound were selected from batches of crystals of identical shape, the NMR spectra of which were identical to the spectra of the compounds isolated from the reaction mixtures. All non-hydrogen atoms and the aromatic and vinylic hydrogen atoms lie in one plane (within 1°), except for the carbonyls

of the ester groups, which form dihedral angles of 3.5–6.4° (7.9° for **2b**) with this plane. All derivatives of the **a** series exhibit short C–H...O=C contacts: *R* varies between 2.91 Å (**3a**) and 2.97 Å (**4a**), θ between 133° (**3a**) and 135° (**5a**), and ϕ between 120° (**5a**) and 122° (**3a**) (see Figures 1, 2, 3, and 4). The geometries of the C–H...O=C fragments in these derivatives are very close to that in bindon (**1**) and also perfectly fit the criteria for HBs. It is noteworthy that of two *R* distances in **4a**, one is one of the shortest (2.928 Å) and another one the longest (2.965 Å) within the series.

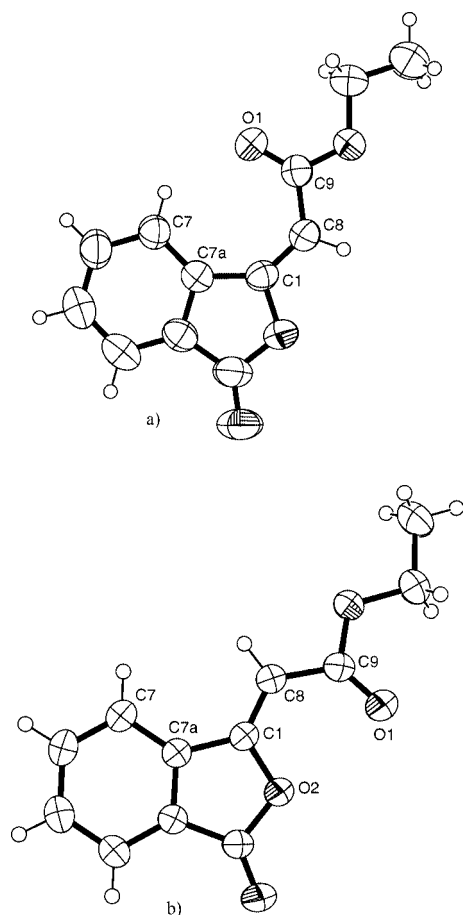


Figure 1. Selected experimentally determined and *calculated* (printed in *italics*) [B3LYP 6-31G(d,p)] distances [Å]. a) Compound **2a**: C7–C7a 1.393(3) (1.40), C7a–C1 1.464(3) (1.47), C1–C8 1.329(3) (1.35), C8–C9 1.460(3) (1.47), C9–O1 1.196(3) (1.22), O1...C7 2.957 (2.98); b) Compound **2b**: C7–C7a 1.393(2) (1.40), C7a–C1 1.458(2) (1.47), C1–C8 1.333(2) (1.35), C8–C9 1.460(3) (1.47), C9–O1 1.207(2) (1.21), O1...O2 2.825 (2.869).

Since part of our later argument is based on the results of quantum mechanical calculations, it is instructive at this point to analyze how well the experimental geometries are reproduced with different model chemistries.^[23] Geometry optimizations for **2–6** (*R* = Me) starting from nonplanar molecules without symmetry constraints rapidly converged to the planar systems in all cases (except for the crowded **4a'**), which indicates the lack of appreciable steric hindrance. The experimentally determined *R* values for **2a** are overestimated by about 0.02 Å by both HF/6-31G(d) and

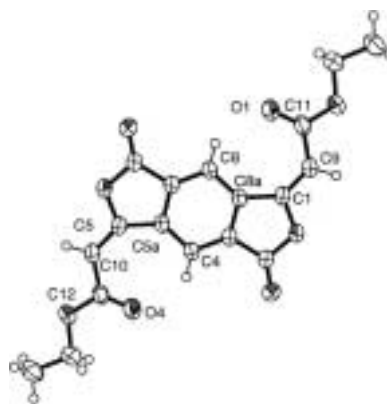


Figure 2. Selected experimentally determined and *calculated* (printed in *italics*) [B3LYP 6-31G(d,p)] distances [Å]. Compound **3a**: C4–C4a, C8–C8a 1.388(2) (1.40); C8a–C1, C5a–C5 1.472(2) (1.47); C1–C9, C5–C10 1.335(3) (1.35); C9–C11, C10–C12 1.467(3) (1.47); C11–O1, C12–O4 1.206(2) (1.22); O1...C8, O4...C4 2.913 (2.94).

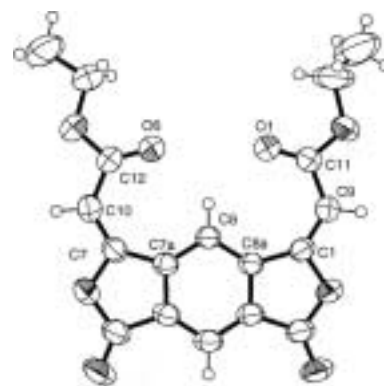


Figure 3. Selected experimentally determined and *calculated* (printed in *italics*) [B3LYP 6-31G(d,p)] distances [Å]. Compound **4a**: C8–C8a 1.390(3) (1.40), C8–C7a 1.394(3), C8a–C1 1.471(3) (1.48), C7a–C7 1.469(3), C1–C9 1.332(3) (1.35), C7–C10 1.328(3), C9–C11 1.463(3) (1.47), C10–C12 1.462(3).

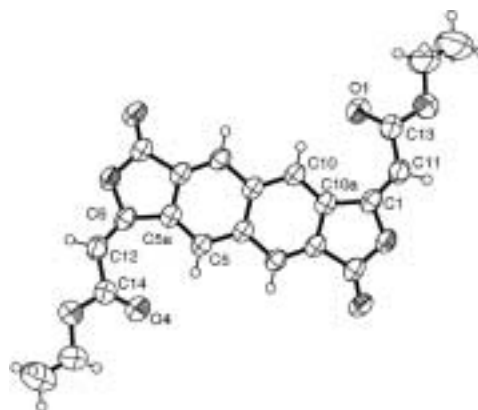


Figure 4. Selected experimentally determined and *calculated* (printed in *italics*) [B3LYP 6-31G(d,p)] distances [Å]. Compound **5a**: C5–C5a, C10–C10a 1.372(3) (1.38); C5a–C6, C10a–C1 1.468(3) (1.47); C1–C11, C6–C12 1.329(3) (1.35); C11–C13, C12–C14 1.460(3) (1.47); C13–O1, C14–O4 1.191(3) (1.22); O1...C10, O4...C5 2.934 (2.96).

B3LYP/6-31G(d,p),^[24] by 0.03 Å by B3LYP/6-31+G(d,p), by 0.01 Å by MP2/6-31G(d), and by 0.01 Å by MP2/6-31+G(d,p) levels. The experimentally determined O1...O2 distance in **2b** (2.83 Å) is reproduced on the MP2/6-31G(d) level, but overestimated by 0.03, 0.04, 0.06, and 0.02 Å by the HF/6-31G(d), B3LYP/6-31G(d,p), B3LYP/6-31+G(d,p), and MP2/6-31+G(d,p) levels, respectively. On the whole, for both derivatives **2a** and **2b**, the HF/6-31G(d) model chemistry yielded the smallest mean deviation (about 0.005 Å), whereas the B3LYP and MP2 methods gave very similar results with mean deviations of about -0.011 Å, both somewhat biased toward overestimation of the bond lengths. Addition of diffuse functions only increases the bias with regard to the aromatic C-C and exocyclic C=C bonds. Further calculations were therefore carried out with the HF/6-31G(d) and B3LYP/6-31G(d,p) model chemistries as a reasonable compromise. These two methods, applied to derivatives **3a–5a**, gave mean deviations of 0.009 and -0.007 Å, respectively, which is close to the experimentally determined 3σ values. The details on the experimentally determined and calculated geometries and statistical analysis of the results are given in the Supporting Information.

Geometry optimizations and energy comparisons in the following sections were performed without taking the basis set superposition error (BSSE) into account, leading to overestimation of the interaction energy, since the usual procedure of counterpoise correction^[25] cannot be used for single molecules. However, with the relatively small basis set employed in this study, the incomplete recovery of the correlation energy giving rise to underestimation of the interaction energy (i.e., acting in the opposite direction) is also pronounced, and the BSSE correction is known to underestimate the energies in many cases even at higher levels of theory.^[26] Only comparison of computational results with available experimental data can answer the question of whether the two opposite factors cancel at the selected level of theory. It is shown in the following sections that canceling errors indeed occur to a considerable degree at the B3LYP/6-31G(d,p) level.

Energetics of Intramolecular HBs

The calculated relative energies of the major possible isomers of derivatives **2–6** are given in Table 1.

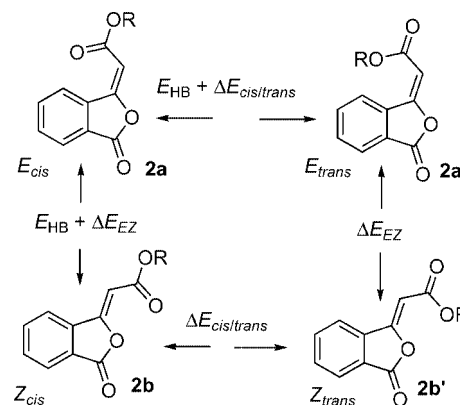
In the gas phase, the derivatives of the **a** series are the most stable in all cases and those of the **a'** series are the least stable. Derivatives of the **b** and **b'** series have approximately the same stability. As an initial approximation, we can assume that through-space interaction (namely, the HB) exists only in the **a** series, as shown in Scheme 1 for derivatives **2**. In such case, $\Delta E_{cis/trans} = -0.1$ kcal mol⁻¹ (0 kcal mol⁻¹ ZPE-corrected) and the energy of the HB in **2a** is $E_{2a} - \Delta E_{cis/trans} = 4.1$ (3.9) kcal mol⁻¹. The energy differences in terms of enthalpies [$\Delta H^\circ(298\text{ K})$] are very close. Of course, derivatives of the **a'** series may also involve non-negligible stabilizing C-H...O-bonding (weakened by the unfavorable planar conformation and electron-ac-

Table 1. Relative energies (kcal mol⁻¹) of the major isomers of derivatives **2–6** calculated by the B3LYP/6-31G(d,p)/B3LYP/6-31G(d,p) method (ZPE-corrected values given in parentheses).

	ΔE [kcal mol ⁻¹]		ΔE [kcal mol ⁻¹]
2a	0 (0); 0 (0) ^[a]	4a'	7.5 (7.5)
2b	3.5 (3.2); -0.3 (-0.6) ^[a]	4b'	5.0 (4.8)
2a'	4.0 (3.9); 2.5 (2.4) ^[a]	5a	0 (0)
2b'	3.4 (3.2); 0.8 (0.5) ^[a]	5b	8.3 (7.8)
3a	0 (0)	5a'	8.5 (8.3)
3b	6.8 (6.5)	5b'	8.2 (7.8)
3a'	6.8 (6.8)	6a	0 (0)
3b'	7.0 (6.7)	6b	8.0 (7.6)
4a	0 (0)	6a'	8.7 (8.5)
4b	5.1 (4.8)	6b'	7.8 (7.5)

[a] Calculated in DMSO.

cepting effect of the neighboring carbonyl group). This possibility makes our estimation the minimum at the selected level of calculations. Analogous considerations applied for the other derivatives of the **a** series (except for **4a**, as **4a'** is nonplanar as a result of steric hindrance) yield 3.3 (3.3), 4.3 (4.2), and 4.5 (4.3) kcal mol⁻¹ per HB for **3a**, **5a**, and **6a**, respectively. Interestingly, according to this estimation, the HB strength increases in the series **3a** < **2a** < **5a** < **6a**, although the aromatic protons in **3a** are the most activated by the accepting substituents.



Scheme 1. Relative energies of derivative **2** isomers.

An alternative estimation of HB energies can be achieved if we consider the transition state energies for, for example, the conversions **2a** → **2a'** and **2b** → **2b'**. The relaxed potential energy scans for rotation over the CH-COOR bonds are instructive and are shown in Figure 5. Unexpectedly large barriers to rotation (about 5 kcal mol⁻¹ for conversions **2a'** → **2a** and **2b** → **2b'**) show that interconversion between these species, at least in nonpolar solvents, is hardly possible. Apparently, the conjugation between the alkoxy-carbonyl group and the phthalide moiety contributes considerably to stabilization of each species. The *Z* isomer **2b'** is more stable than the *E* isomer **2a'** with the same *trans* configuration by $\Delta E_2 = 0.6$ kcal mol⁻¹. The difference in energies between the transition states ΔE_3 , when both the conjugation and possible through-space interactions between the two moieties are “switched off”, is about 0.3 kcal mol⁻¹,

also in favor of the *Z* isomers. Both ΔE_2 and ΔE_3 are of the same order of magnitude, and the difference between them might originate either from destabilization of **2a'** or from stabilization of **2b'** by 0.3 kcal mol⁻¹. Therefore, in the absence of the HB in **2a**, that isomer should be less stable than **2b** by the same 0.3 kcal mol⁻¹ (ΔE_3), since both are in the same *cis* configuration. This provides us with another independent estimation of the HB energy in **2a**: $E_{2b} + \Delta E_3 = 3.5 + 0.3 = 3.8$ kcal mol⁻¹. This value is close to the previous estimation from ΔE_1 (4.1 kcal mol⁻¹) and is also the minimum value, as we assumed that there are no additional stabilizing effects in **2b**, such as through-space $-O\cdots O=$ interaction. The correction of 0.3 kcal mol⁻¹ should be larger if such an interaction is present. Interestingly, this estimation involving the energies of the transition states is almost independent of the calculation method: we obtained 3.8 and 3.7 kcal mol⁻¹ from the analogous calculations on the HF/6-31G(d) and MP2/6-31(d) levels, respectively.

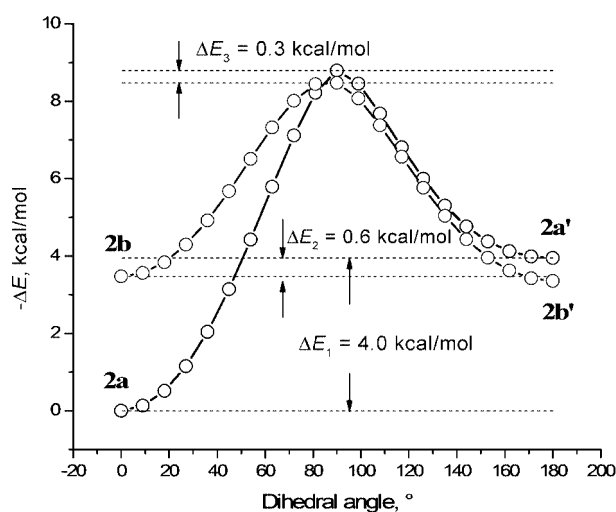


Figure 5. Relaxed potential energy scans for conversions **2a** → **2a'** and **2b** → **2b'** calculated by B3LYP/6-31G(d,p) method in the gas phase. The dihedral angle H–C–C=O was varied between 0° and 180°.

The transition state energies were also calculated at the same level of theory for derivatives **3** and **5**. These derivatives each involve two CH–COOR bonds, so two transition states corresponding to consecutive rotation over each bond were found. A scheme used for estimation of HB energies and the energies of the corresponding isomers is given in the Supporting Information. Breaking the first HB in **3a** produced 3.7 kcal mol⁻¹ as the minimum estimation of the HB energy at the B3LYP/6-31G(d,p) level, and the same value was calculated for the second step. The HF/6-31G(d) method yielded 3.7 and 3.8 kcal mol⁻¹ for the first and the second steps, respectively. The same method applied for **5a** gave an estimation of 4.4 kcal mol⁻¹ for each HB in this molecule, which is close to the 4.3 kcal mol⁻¹ estimated from the energy difference between **5a** and **5a'**. The approach involving transition state energies can be applied to **4a**, as the energy of the sterically crowded **4a'** is not involved. The corresponding calculations afforded only 0.8 kcal mol⁻¹ for

the first step and 3.7 kcal mol⁻¹ for the second. This is a very reasonable result showing that the ability of the aromatic H atom to form the HB is almost (but not fully) exhausted by one HB. It is also in qualitative agreement with the experimental findings (see discussion in the next section).

Analogous calculations performed for the pairs **2a** → **2a'** and **2b** → **2b'** with the IEF-PCM model in DMSO ($\epsilon = 46.7$) revealed a different picture (Figure 6). In this case, the most stable isomer is **2b**, which is more stable than **2a** by 0.3 kcal mol⁻¹. The reason for such considerable stabilization of **2b** is the increase in the $-O\cdots O= \leftrightarrow -O^+\cdots -O-$ through-space interaction induced by the reaction field of the polar solvent. Indeed, whereas the optimized geometries of **2b'** in the gas phase and DMSO are similar and the $-O\cdots O-$ distance remains practically the same, the $-O\cdots O=$ distance in **2b** in DMSO is shortened by 0.021 Å. At the same time, the H $\cdots$ O distance in **2a** in DMSO is 0.04 Å longer than in the gas phase. As above, we can estimate the HB energy by comparing the energies of **2a** and **2a'** [i.e., as ΔE_1 , which is 2.5 (2.4) kcal mol⁻¹]. If it is taken into account that in the gas phase **2b** was less stable than **2b'** by 0.1 kcal mol⁻¹, the extra stabilization of **2b** in DMSO can be estimated as 1.1 kcal mol⁻¹. The difference in energies between **2a'** and **2b'** (ΔE_2) is close to the difference in energies of the two excited states (ΔE_3), as was the case in the gas phase. Therefore, another independent estimation of the HB energy is 1.1 + 1.4 = 2.5 kcal mol⁻¹ (i.e., the same value as above).

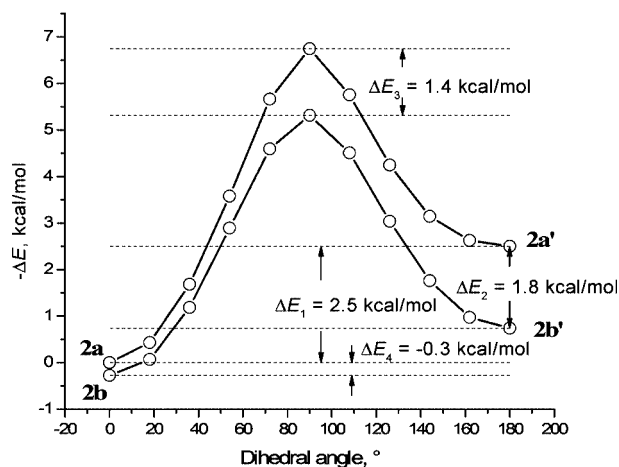


Figure 6. Relaxed potential energy scans for conversions **2a** → **2a'** and **2b** → **2b'** in DMSO, calculated by the B3LYP/6-31G(d,p) method. The dihedral angle H–C–C=O was varied between 0° and 180°.

It is noteworthy that the barriers for the conversions **2a'** → **2a** and **2b** → **2b'** calculated in DMSO, although lower than those calculated in the gas phase, still exceed 4 kcal mol⁻¹. All energy differences computed in DMSO are practically the same in terms of $\Delta H^\circ(298\text{ K})$ as in the case of the gas-phase calculations. Calculated ZPE-corrected energies, enthalpies, and free energies of all isomers and transition states are given in the Supporting Information.

NMR Spectra of Derivatives 2–6 and Intermolecular H-Bonding

The ¹H signals (δ) of all aromatic and vinylic protons (except for H-5 in **2**) in derivatives **2–6** undergo unusually large solvent shifts ($\Delta\delta$). The corresponding experimentally determined chemical shifts and those calculated by the GIAO method^[27] are given in Table 2. The calculated values agree reasonably well with the experimentally determined shifts observed in chloroform. However, the chemical shifts of the protons participating in the HBs are overestimated as in the case of derivative **1**,^[14] for possible reasons discussed below. The most solvent-sensitive protons in derivatives **2** are those most activated by the electron-accepting substituents. In both compounds, the δ value of the vinylic H-8 gradually shifts towards lower field when moving from toluene (neither a proton donor nor acceptor) to chloroform (a proton donor), acetone (a proton acceptor), and DMSO (both a proton donor and acceptor). The overall $\Delta\delta$ of this proton in **2b** is 0.82 ppm and is almost four times larger than in **2a**. The overall solvent shift of aromatic H-4 is about 0.5 ppm in both compounds, reaching its maximum in acetone. These large shifts can only partially be explained by the known Aromatic Solvent Induced Shifts (ASISs), as the $\Delta\delta$ values are still unusually large for the chloroform→DMSO solvent pair. The most remarkable from this point of view is the behavior of H-7. Whereas $\Delta\delta$ in **2b** amounts to 1.64 ppm (toluene→DMSO), the trend observed in **2a** is the opposite, and $\Delta\delta$ is –0.31 ppm. The aromatic H-4 and H-8 in **3a** and **3b** show the same pattern: $\Delta\delta$ (CDCl₃→DMSO) is –0.36 and 0.60 ppm, respectively. Although the NMR spectra calculations in solvent give generally good results (see^[28] and refs. therein), our attempts to reproduce the chemical shifts of **2a** and **2b** by calculations using the IEF-PCM model in DMSO did not yield even qualitative agreement with the experiment.

In general, these experimental observations and the failure of the computational approach to predict the chemical shifts of the H-bonded protons reasonably without taking specific interactions into account can be explained as follows. With regard to the relaxed potential scan results (see Figures 5 and 6), we can see that at room temperature (about 0.6 kcal mol^{–1}) the dihedral angle in the H–C–C=O fragment can reach 20°, opening room for the solvent to form an intermolecular HB in addition to the intramolecular one. No intermolecular HB form with toluene is possible, and the observed δ value for **2a** is lower than that calculated as the result of ASIS. Acetone can form a weaker HB with H-7 in addition to the existing intramolecular bond, only slightly lowering the overall effect, whereas chloroform will partially bind the C=O group, weakening the existing intramolecular HB more noticeably. The variations of $\Delta\delta$ (CDCl₃→DMSO) and the different signs for the **2a**, **3a** and the **2b**, **3b** couples are more difficult to interpret. They are considerably larger than usually observed for polar aprotic compounds (± 0.1 ppm)^[29] and comparable to the shifts of dichloromethane and chloroform (0.49 and 1.06 ppm, respectively), explained by formation of HBs with DMSO.^[29]

Table 2. Experimentally determined and calculated [GIAO B3LYP/6-31G(2d,p)] ¹H chemical shifts (ppm) for derivatives **2–6**.

	[D ₈]Toluene	CDCl ₃	[D ₆]Acetone	[D ₆]DMSO	Calculated
2a H-4	7.62	8.01	8.16	8.12	8.05
H-6	7.29	7.86	8.12	8.07	7.88 (8.19) ^[a]
H-7	9.29	9.09	9.19	8.94	9.97 (9.49) ^[a]
H-8	6.12	6.19	6.28	6.33	5.95
2b H-4	7.54	8.01	8.17	8.11	8.08
H-6	7.01	7.82	8.10	8.02	7.74
H-7	6.90	7.79	8.33	8.34	7.77 (8.42) ^[a]
H-8	5.69	5.92	6.32	6.51	5.67 (6.46) ^[a]
3a H-4,8	–	9.70	–	9.34	9.93
H-9,10	–	6.35	–	6.50	5.72
3b H-4,8	–	8.32	–	8.92	7.93
H-9,10	–	6.08	–	6.71	5.52
4a H-4	–	8.55	–	8.55	8.23
H-8	–	10.71	–	10.15	11.28
H-9,10	–	6.39	–	6.50	5.79
5a H-4,9	–	8.83	–	8.92	8.84
H-5,10	–	9.95	–	9.58	10.81
H-11,12	–	6.32	–	6.30	6.13
6a H-4,5	–	8.77	–	9.11	8.70
H-9,10	–	10.00	–	9.74	10.93
H-11,12	–	6.34	–	6.41	6.13

[a] Calculated for 1:1 complexes with DMSO for the protons involved in H-bonding.

The ¹H NMR spectra of **2a** and **2b** in CDCl₃/DMSO mixtures were also measured, with different molar ratios of these solvents and constant concentration (4.6×10^{-2} M) of the solutes. The changes in the chemical shifts of the most sensitive protons of **2a** and **2b**, along with those of chloroform, are shown in Figure 7. The initial rapid changes become smaller, but increase again after the molar ratio of CDCl₃/DMSO becomes approximately 1:1. An additional sharp shift to lower field was observed when the 5:95% mixture was replaced by pure DMSO. Although the initial changes of the chloroform proton shift were more pronounced, qualitatively the behavior of all protons, except for H-7 of **2a**, is the same, so a more detailed consideration of the HB in Cl₃C–H...O=SMe₂ may be helpful here.

The formation of 2:1 and 1:1 chloroform/DMSO complexes has been a subject of several experimental investigations, including NMR and thermodynamic data analysis.^[30] The H-bonding natures of these complexes have been demonstrated by Raman and IR spectra measurements of their mixtures.^[31] The reported enthalpy of 1:1 complex formation was determined to be about –2.6,^[30c] –2.7,^[30d] and –3.3^[30a] kcal mol^{–1}. Neat DMSO is known to exist associated in oligomers and dimers.^[30d,32] Assuming that all DMSO molecules are dimerized, we calculated ΔH° (298 K) for the reaction (DMSO)₂ + CHCl₃ + CHCl₃ → 2(CHCl₃/DMSO). The HF method yielded –2.2 kcal mol^{–1}, whereas the B3LYP method gave –2.6 kcal mol^{–1} as a minimum estimation, in good agreement with the experimentally measured values. As discussed above, no BSSE corrections were carried out either for geometry optimization or in the final frequency calculations. Using the counterpoise correction procedure yielded an unreasonably large ΔH° (298 K) value of –4.9 kcal mol^{–1} with the B3LYP method.^[33] The calculated C–H stretching frequency of 2964 cm^{–1} for the com-

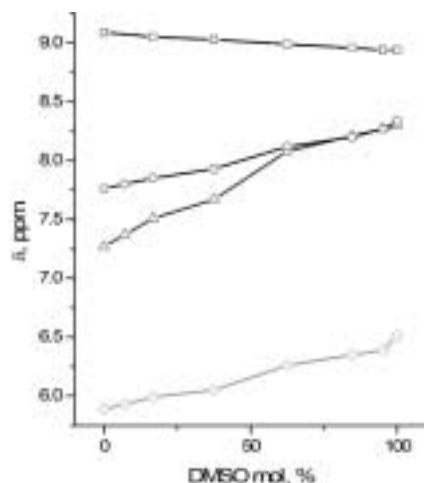


Figure 7. ^1H chemical shifts vs. molar ratio of $[\text{D}_6]\text{DMSO}$ in $\text{CDCl}_3/[\text{D}_6]\text{DMSO}$ mixtures. Triangles: protons of residual CHCl_3 , circles: H-8 (**2b**), rhombs: H-8 (**2b**), squares: H-7 (**2a**).

plex (scale factor 0.961) is also in good agreement with the experimentally measured value of 2977 cm^{-1} .^[31] The HB energy, which corresponds to the electronic energy difference between the complex ($\text{CHCl}_3/\text{DMSO}$) and the free components, was 6.5 (HF) and 7.4 kcal mol^{-1} (B3LYP) (ZPE-corrected).

Analogous calculations for 1:1 complexes **2a**/DMSO and **2b**/DMSO were also performed with the B3LYP method. Whereas the $\Delta H^\circ(298\text{ K})$ value for the first complex was only $-0.4\text{ kcal mol}^{-1}$, for the second one it amounted to $-6.3\text{ kcal mol}^{-1}$. The optimized structures of both complexes involve several shortened $\text{O}\cdots\text{H}$ distances characteristic of HBs, as shown in Figure 8. In the **2a**/DMSO complex, the carbonyl group interacts not only with the aromatic H7 hydrogen atom, but also with both of the Me groups in DMSO. As a result, the aromatic $\text{C}-\text{H}\cdots\text{O}=\text{C}$ becomes $0.072\text{ \AA}$ longer than in **2a**, accounting for the high-field shift observed in the NMR spectrum in DMSO. Both aromatic and vinylic H atoms interact with the O atom of DMSO in **2b**; these protons are indeed the most sensitive to the presence of DMSO. The above qualitative conclusions are also supported quantitatively: the calculated chemical shifts for the protons involved in H-bonding in complexes **2a**/DMSO and **2b**/DMSO given in Table 2 are in better agreement with the experimentally determined values. Apparently, calculations should be carried out for complexes involving two or even three molecules of DMSO to reproduce the chemical shifts of all protons.

Thus, in addition to stabilization of **2b** in the reaction field of the polar solvent (DMSO) and the corresponding weakening of the intramolecular HB in **2a**, the specific interaction with this solvent increases these effects and gives rise to the characteristic ^1H NMR spectral changes. This conclusion is also confirmed experimentally. We found that although heating of **2a** and **5a** in dry DMSO at $100\text{ }^\circ\text{C}$ for more than 20 h did not affect their NMR spectra, the appearance of **2b** and the isomer of **5b** involving only one HB was observed at $140\text{ }^\circ\text{C}$. The ratio of isomers became about

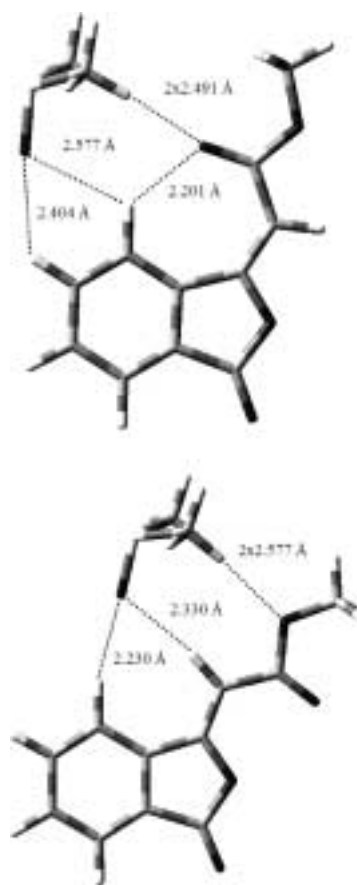


Figure 8. The equilibrium geometries of **2a**/DMSO and **2b**/DMSO complexes.

1:1 after 16 h of heating. Derivative **3a** is more reactive and had already isomerized at $100\text{ }^\circ\text{C}$, in agreement with the weaker HBs predicted by calculations. Derivative **4a** had already undergone isomerization upon warming of its DMSO solution, in agreement with the weakest first HB energy predicted by calculations. In DMSO it may proceed via intermediates of type **8** resulting from the nucleophilic attack of the DMSO oxygen atom on the positively polarized C-1 atoms of **2a–6a**. Delocalization of the negative charge within the $\text{C}-\text{COOR}$ moiety prevents rotation about the $\text{C}-\text{C}$ bond so that after the intramolecular HB is broken, neither **2a'** nor **2b'** can form.

The isomerization of derivatives of the **a** series into the **b** series, stabilized in the solvents of high dielectric constants, can thus proceed both by electrophilic (sulfuric acid, $\epsilon = 100$) and by nucleophilic (DMSO, $\epsilon = 46.7$) pathways. However, the NMR spectra of the crude reaction mixtures did not reveal the presence of derivatives of the **a'** and **b'** series, which can be regarded as true isomers owing to the high isomerization barriers.

The ^{13}C chemical shifts, along with the $^{13}\text{C}-^1\text{H}$ coupling constants for **2a**, **2b**, **3a**, and **4a**, are collated in Tables 3 and 4. The example of chloroform is also helpful for analysis of these data. It is well known that not only are the ^1H and ^{13}C chemical shifts of chloroform changed in the solvents capable of forming the HB, but the $^{13}\text{C}-^1\text{H}$ coupling con-

Table 3. ¹³C Chemical shifts [ppm] and ¹J(¹³C-¹H) [Hz] for **2a** and **2b**.

	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-4a	C-7a
2a ^[a]	157.79	165.68	125.31 (167.0)	132.44 (165.1)	135.23 (163.1)	128.18 (172.7)	102.43 (163.1)	165.61	126.52	136.10
2a ^[b]	157.28	165.18	125.44	133.18 (167.0)	135.68 (165.1)	127.32 (172.7)	101.83 (165.1)	164.09	126.08	135.30
2b ^[a]	154.04	165.57	125.98 (167.0)	132.27 (165.1)	135.00 (165.1)	121.16 (165.1)	96.00 (163.1)	163.61	124.75	138.96
2b ^[b]	154.07	165.82	125.49 (167.0)	132.74 (165.1)	135.54 (165.1)	122.52 (167.0)	95.86 (167.0)	163.09	124.01	138.64

[a] In CDCl₃, [b] In [D₆]DMSO.Table 4. ¹³C Chemical shifts [ppm] and ¹J(¹³C-¹H) [Hz] of **3a** and **4a** in CDCl₃.

	C-1	C-3	C-4	C-5	C-7	C-8	C-9	C-4a	C-8a
3a	155.75	163.71	126.05 (178.5)	155.75	163.71	126.05 (178.5)	105.35 (163.1)	138.65	132.13
4a	155.78	163.35	122.76 (174.8)	163.35	155.78	128.26 (182.3)	106.10 (163.1)	129.71	141.40

stant also increases considerably.^[34] Thus, the value of ¹J(¹³C-¹H) increases by 8.2 Hz for chloroform solution in DMSO.^[34b]

For **2a** and **2b** in chloroform, the major variation is seen in C-7, directly attached to the hydrogen atom involved in the HB in **2a**. Both the chemical shift and the one-bond coupling constant of C-7 are larger – by 7 ppm and 7.6 Hz, respectively – in **2a** than in **2b**. Similar, albeit smaller, variations can be seen in the spectra of **3a** and **4a**. The difference in the one-bond coupling constant of C-8 and C-4 in **4a** is still about the same, at 7.5 Hz. The observed changes in the one-bond coupling constants are close to those detected for derivative **1** and its analogues.^[14] In DMSO, the variations of the one-bond coupling constants are smaller, but nevertheless instructive. Whereas all coupling constants, except for C-7, are increased by about 2 Hz in **2a**, only those of C-7 and C-8 are increased – by 2 and 5 Hz, respectively – in **2b**, in agreement with the proposed model.

Conclusions

The X-ray structure determinations, selective formation, high thermal stability in solution, and the NMR spectral features demonstrate the presence of relatively strong intramolecular HBs in derivatives of the **a** series. We used two independent approaches to evaluate the HB energies in these compounds: one based on the assumption that there are no through-space stabilizing interactions in derivatives of the **a'** series and the second involving the differences in energies of the transition states. The two approaches yielded similar gas-phase energy estimations, which vary between 3.5 and 4.4 kcal mol⁻¹. The only exception was derivative **4a**, in which the aromatic H atom is bonded with two oxygen atoms and the energy corresponding to breaking the first of two HBs is only 0.8 kcal mol⁻¹, showing that the H-bonding capability of the H atom is already almost fully saturated by one HB, the energy of which is the same as in derivative **3a** (3.7 kcal mol⁻¹). The HB energy estimations

are strikingly insensitive to the calculation methods and, if our assumptions are wrong, will only increase. B3LYP/6-31G(d,p) not only appeared to be optimal for describing the geometries, but also fortunately makes the BSSE correction unnecessary. The estimated HB energy in **2a** is diminished by about 35% in DMSO solution, because of the solvent reaction field, but still amounts to 2.5 kcal mol⁻¹ in this solvent. Moreover, specific interactions with DMSO giving rise to the formation of H-bonded complexes, are especially evident in the ¹H NMR spectra of the derivatives of the **b** series, in which the activated H atom, locked in the **a** series, can now form intermolecular HBs with the solvent.

Experimental Section

Experimental Procedures: Toluene was dried by azeotropic distillation and 1,4-dioxane by heating at reflux over sodium and distillation under argon. Commercially available phthalic anhydride and pyromellitic dianhydride were both purified by crystallization in acetic anhydride.

Melting points were recorded on a Büchi 510 capillary melting point apparatus. IR spectra were measured on a Nicolet Avatar 320 FT-IR spectrometer. NMR spectra were recorded on a Bruker 250 MHz spectrometer. The NMR parameters (δ in ppm, J in Hz) were determined by simulation and subsequent optimization by use of the gNMR 5.0 program (P. H. M. Budzelaar, ©1995–2006 Ivory-Soft).

Reaction between Phthalic Anhydride and Ethyl (Triphenylphosphoranylidene)acetate: Ethyl (triphenylphosphoranylidene)acetate (1.18 g, 3.38 mmol) was added in portions over 30 min at room temperature to a solution of phthalic dianhydride (0.5 g, 3.38 mmol) in toluene (5 mL). After stirring for 3 h at room temperature and heating at 85 °C for 15 min, the reaction mixture was concentrated under reduced pressure. The crude pink solid obtained was purified by chromatography on silica gel (Et₂O/cyclohexane, 3:7). The major isomer **2a** was eluted first (0.61 g, 84%), followed by the minor isomer **2b** (0.09 g, 12%). The overall yield 96%.

Ethyl [(E)-3-Oxo-1,3-dihydroisobenzofuran-1-ylidene]acetate (2a**):** Colorless crystals, m.p. 71.0–72.0 °C. ¹H NMR (CDCl₃): δ = 9.09

(m, $^3J_{6,7} = 8.0$, $^4J_{5,7} = 0.9$, $^5J_{4,7} = 0.8$ Hz, 1 H, H-7), 8.01 (m, $^3J_{4,5} = 7.6$, $^4J_{4,6} = 1.2$ Hz, 1 H, H-4), 7.86 (m, $^3J_{5,6} = 7.5$ Hz, 1 H, H-6), 7.74 (m, 1 H, H-5), 6.19 (br., $^5J_{7,8} = 0.3$, $^6J_{6,8} = 0.1$ Hz, 1 H, H-8), 4.26 (q, 2 H, $^3J = 7.1$ Hz, CH₂), 1.33 (t, 3 H, $^3J = 7.1$, CH₃) ppm. ^{13}C NMR (CDCl₃): $\delta = 165.68$ (C-3), 165.61 (C-9), 157.79 (C-1), 136.10 (C-7a), 135.23 (C-6), 132.44 (C-5), 128.18 (C-7), 126.52 (C-4a), 125.31 (C-4), 102.43 (C-8) ppm. IR (Nujol): $\tilde{\nu}_{\text{max}} = 1805$, 1787 (C=O phthalide), 1710 (C=O ester), 1652 (C=C) cm⁻¹.

Ethyl [(Z)-3-Oxo-1,3-dihydroisobenzofuran-1-ylidene]acetate (2b): Colorless crystals, m.p. 133.0–134.0 °C. ^1H NMR (CDCl₃): $\delta = 8.01$ (m, $^3J_{4,5} = 7.7$, $^4J_{4,6} = 0.8$, $^5J_{4,7} = 1$ Hz, 1 H, H-4), 7.82 (m, $^3J_{5,6} = 7.5$, $^3J_{6,7} = 7.9$ Hz, 1 H, H-6), 5.88 (br., $^5J_{7,8} = 0.4$, $^6J_{6,8} = 0.2$ Hz, 1 H, H-8), 4.30 (q, $^3J = 7.1$ Hz, 2 H, CH₂), 1.35 (t, $^3J = 7.1$ Hz, CH₃) ppm. ^{13}C NMR (CDCl₃): $\delta = 165.57$ (C-3), 163.61 (C-9), 154.04 (C-1), 138.96 (C-7a), 135.00 (C-6), 132.27 (C-5), 125.98 (C-4), 124.75 (C-4a), 121.16 (C-7), 96.00 (C-8) ppm. IR (Nujol): $\tilde{\nu}_{\text{max}} = 1805$ (sh), 1792 (C=O phthalide), 1718 (C=O ester), 1676 (C=C) cm⁻¹.

Isomerization of Derivatives from the a-Series into the b-Series: A derivative from the a-series (0.10 g) was dissolved in concentrated sulfuric acid (1 mL). After stirring for 20 h at room temperature, the reaction mixture was poured into ice. The precipitate was filtered and washed with water. The crude esters were purified by crystallization to remove the admixture of the corresponding acid.

Compound 3b: This compound was obtained in 60% yield as a colorless powder, m.p. > 250 °C. ^1H NMR (CDCl₃): $\delta = 8.37$ (s, 2 H, H-4,8), 6.13 (s, 2 H, H-8,10), 4.38 (q, $^3J = 7.1$ Hz, 4 H, CH₂), 1.42 (t, $^3J = 7.1$ Hz, 6 H, CH₃) ppm. ^{13}C NMR (CDCl₃): $\delta = 163.34$ (C-3,7), 162.70 (C-10,11), 151.94 (C-1,5), 141.53 (C-4a,7a), 130.46 (C-5a,8a), 119.32 (C-4,8), 99.22 (C-9,10), 61.47 (2 × CH₂), 14.21 (2 × CH₃) ppm. IR (Nujol): $\tilde{\nu}_{\text{max}} = 1813$ (C=O phthalide), 1697 (br., C=O ester + C=C) cm⁻¹.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, NMR spectroscopic data, Cartesian coordinates and energies for computed structures, X-ray structure experimental details.

Acknowledgments

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