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Experimental and Computational Thermochemistry of 1,4-Benzodioxan and its 6-R Derivatives

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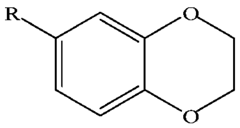
The derivatives of 1,4-benzodioxan are found widely spread in nature and have great biomedical importance. The present work reports an experimental and computational study on the thermochemistry of 1,4-benzodioxan and several of its 6-R derivatives in the gaseous phase, at $T = 298.15$ K. Our current results were obtained from measurements of combustion energies, at $T = 298.15$ K, using a static bomb calorimeter. The standard molar enthalpies of vaporization/sublimation were measured by Calvet microcalorimetry and corrected to $T = 298.15$ K. Additionally, estimates were performed of the enthalpies of formation of all the studied compounds in the gas phase, using DFT and other more accurate correlated calculations, together with appropriate isodesmic or homodesmic reactions. There is a reasonable agreement between computational and experimental results.

1. Introduction

The derivatives of 1,4-benzodioxan (I) are very important and are found widely spread in nature. Some of them are antipsychotic agents and others are used by some living species in their chemical communication systems.[1]1,4-Benzodioxan derivatives are vasodilatator drugs that can selectively dilate the cerebral and coronary vessels and reduce the aggregation of thrombocytes caused by adrenaline and ADP; they are also found to increase the resistance of the organisms against hypoxic and radiation influences. The main mechanisms of action of the selected derivatives of 1,4-benzodioxan are selective blocking of the reactions mediated by vascular α_2-adrenoceptors; inhibition of the entrance of calcium ions into the cell and suppression of the biosynthesis of the products of lipoxygenase transformation of arachidonic acid.[2]

Previously we have studied the thermochemistry of some of 1,3-benzodioxole derivatives (II).[3,4] Many of these compounds play important roles in several areas of industry, in medicine and in chemistry as well.

Structurally, the molecules of these two families of compounds are similar in that both have a benzenic ring fused to a ring containing two atoms of oxygen.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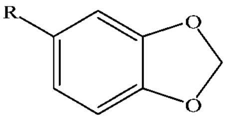
II

The standard molar enthalpy of combustion of 1,4-benzodioxan was determined by Cass et al. in 1958,[5] but no energetic corrections for the standard state were considered in the calculations. The same authors derived, from vapor pressure, a value for the enthalpy of vaporization, and calculated for the standard molar enthalpy of formation of gaseous 1,4-benzodioxan the value of −204 kJ·mol^{-1}. For 1,4-benzodioxan derivatives there are no thermochemical values in literature.

In the present work we report the standard molar enthalpies of formation of several derivatives of 1,4-benzodioxan in the gaseous phase, at $T = 298.15$ K. Our current results were obtained from measurements of combustion energies, at $T = 298.15$ K, using a static bomb calorimeter. The standard molar enthalpies of vaporization/sublimation were measured by Calvet microcalorimetry, at $T = 298.15$ K.

In addition to the experimental thermochemical work, we present estimates of the enthalpies of formation of all the studied compounds in gas phase, using DFT and also other more accurate composite correlated calculations together with appropriate isodesmic or homodesmic reactions. The good agreement between theoretical and experimental results gives support to estimates based on computational thermochemistry of the enthalpies of formation of other 1,4-benzodioxan derivatives whose experimental study has not been done.

The present work is an additional contribution to the understanding of the energetic effect of substitutions in the benzenic ring of heterocycles. So, we focus our attention on the relative enthalpic effects due to the different substitutents R both in 1,4-benzodioxan (I) and in 1,3-benzodioxole (II).

2. Experimental Section

2.1. Materials and DSC. All the compounds are commercial products from Aldrich Chemical Co., 1,4-benzodioxan [CAS 493-09-4] 1,4-benzodioxan-6-nitro [CAS 16498-20-7], 1,4-benzodioxan-6-carboxaldehyde [CAS 29668-44-8], 1,4-benzodioxan-6-yl methyl ketone [CAS 2879-20-1] [CAS Registry Numbers supplied by the author]. All the samples were purified by repeated distillation or sublimation under reduced pressure before the experimental studies. For the solid compounds, the impurity mass fractions (Table 1) were derived from DSC (Setaram DSC 141) analysis by a fractional fusion technique.[6] The samples, hermetically sealed in stainless steel crucibles, were heated at 1.67×10^{-2} K·s^{-1}. The temperature scale of the calorimeter was calibrated by measuring the melting

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TABLE 1: Temperatures of Fusion, T_{fus}, Enthalpies of Fusion, $\Delta_{cr}^{l}H_m^0(T_{fus})$, and the Purity, %, of the Studied Benzodioxan Derivatives

	T_{fus}/K	$\Delta_{cr}^{l}H_m^0(T_{fus})$/kJ·mol^{-1}	purity, %
1,4-benzodioxan-6-nitro	394.02 ± 0.08	24.27 ± 0.11	100.06
1,4-benzodioxan-6-carboxaldehyde	324.42 ± 0.11	19.44 ± 0.16	99.89
1,4-benzodioxan-6-yl methyl ketone	356.04 ± 0.10	23.49 ± 0.14	99.90

TABLE 2: Typical Combustion Experiments, at T = 298.15 K

	1,4-benzodioxan	1,4-benzodioxan-6-nitro	1,4-benzodioxan-6-carboxaldehyde	1,4-benzodioxan-6-yl methyl ketone
$m(CO_2$, total)/g	1.87716	1.17338	1.52471	1.62039
m(cpd)/g	0.68388	0.60149	0.63017	0.65456
m'(fuse)/g	0.00278	0.00267	0.00261	0.00275
m'(Melinex)/g	0.04550			
ΔT_{ad}/K	1.3365	0.8001	1.0282	1.1288
ϵ_f/J·K^{-1}	16.11	15.22	15.68	16.09
$\Delta m(H_2O)$/g	0.0	0.0	0.0	−0.1
$-\Delta U$(IBP)/J	21410.78	12816.44	16471.11	18082.94
ΔU(fuse)/J	45.15	43.36	42.39	44.66
ΔU(Melinex)/J	1041.95			
$\Delta U(HNO_3)$/J	1.04	24.28	0.63	9.37
ΔU(ign)/J	1.17	1.18	1.15	0.97
ΔU_Σ/J	13.64	10.86	11.58	11.82
$-\Delta_c u^0$/J·g^{-1}	29696.73	21177.31	26050.92	27525.50

temperature of three high purity reference materials (naphthalene, benzoic acid and indium)[7] and its power scale was calibrated with high-purity indium (mass fraction > 0.99999). The recorded thermograms did not show any phase transition between 298 K and the melting temperature of the studied compounds.

The purity of the liquid compound, 1,4-benzodioxan, was evaluated as 99.85% by gas−liquid chromatography (Agilent 4890 D cromatograph).

The purity of the samples was also confirmed through the carbon dioxide gravimetry results. The average ratios, together with the standard deviation of the mean, of the mass of carbon dioxide recovered after each combustion experiment to that calculated from the mass of sample were: 1,4-benzodioxan (1.0000 ± 0.0002), 1,4-benzodioxan-6-nitro (1.0003 ± 0.0004), 1,4-benzodioxan-6-carboxaldehyde (0.9996 ± 0.0001), 1,4-benzodioxan-6-yl methyl ketone (0.9994 ± 0.0001). The densities of the samples were estimated, from the mass and the dimensions of pellets of the crystalline compounds, as 1,4-benzodioxan-6-nitro (1.06 g·cm^{-3}), 1,4-benzodioxan-6-carboxaldehyde (1.12 g·cm^{-3}), 1,4-benzodioxan-6-yl methyl ketone (1.09 g·cm^{-3}) for the solids and 1.14 g·cm^{-3} for the liquid compound.

2.2. Combustion Calorimetry. The combustion experiments were performed with a static bomb calorimeter, using a twin valve bomb, type 1108 of Parr Instrument Company. The apparatus and technique have been described previously,[8,9] so only a brief description is made here. Benzoic acid (Bureau of Analyzed Samples, Thermochemical Standard, BCS-CRM-190 p) was used for calibration of the bomb. Its massic energy of combustion is $\Delta_c u = -26435.1 \pm 3.5$ J·g^{-1}, under certificate conditions. The calibration results were corrected to give the energy equivalent ϵ_{cal} corresponding to the average mass of water added to the calorimeter, 3119.6 g. From six independent calibration experiments performed $\epsilon_{cal} = 16004.8 \pm 1.6$ J·K^{-1}, where the uncertainty quoted is the standard deviation of the mean.

The crystalline compounds were burnt in pellet form. The liquid, 1,4-benzodioxan, was enclosed in polyester bags made of Melinex, using the technique described by Skinner and Snelson[10] who determined the specific energy of combustion of dry Melinex as $\Delta_c u^0 = -22902 \pm 5$ J·g^{-1}. This value was confirmed in our laboratory. The mass of Melinex used in each experiment was corrected for the mass fraction of water (0.0032) and the mass of carbon dioxide produced from it was calculated using the factor previously reported.[10]

Combustion experiments were made in oxygen at p = 3.04 MPa, with 1.00 cm^3 of water added to the bomb. The electrical energy for ignition, ΔU(ign), was determined from the change in potential difference across a capacitor when discharged through the platinum ignition wire. As samples were ignited at T = 298.15 K,

$$U(\text{IBP}) = \{\varepsilon_{cal} + \Delta m(H_2O)c_p(H_2O,l) + \varepsilon_f\}\Delta T_{ad} + \Delta U_{ign} \quad (1)$$

where ΔU(IBP) is the energy associated to the isothermal bomb process, ϵ_f is the energy of the bomb contents after ignition, and ΔT_{ad} is the adiabatic temperature raise calculated using the program LABTERMO.[11] For the cotton-thread fuse, empirical formula $CH_{1.686}O_{0.843}$, the value of -16250 J·g^{-1}[12] was taken for the massic energy of combustion, $\Delta_c u^0$ (the value has been confirmed in our laboratory). The corrections for nitric acid formation $\Delta U(HNO_3)$ were based on -59.7 kJ·mol^{-1},[13] for the molar energy of formation of 0.1 mol·dm^{-3} HNO_3(aq) from N_2, O_2, and H_2O(l). The mass of compound, m(compound), used in each experiment was determined from the total mass of carbon dioxide, $m(CO_2$,total), produced after allowance for that formed from the cotton thread fuse and Melinex.

An estimated pressure coefficient of specific energy: $(\partial/\partial p)_T = -0.2$ J·g^{-1} MPa^{-1} at T = 298.15 K, a typical value for most organic compounds, was assumed.[14] For each compound, the corrections to the standard state, ΔU_Σ, to derive the standard massic energy of combustion, $\Delta_c u^0$, were made by the procedure given by Hubbard et al.[15] The atomic weights of the elements were those recommended by the IUPAC commission in 2005.[16]

2.3. Microcalorimetry Calvet. The standard molar enthalpies of sublimation or vaporization were measured using the "vacuum sublimation" drop microcalorimetric method.[17] The microcalorimeter was calibrated in situ for these measurements using the reported enthalpy of sublimation of naphthalene[18] and of vaporization of n-decane.[19]

Samples, of about 3−5 mg of the crystalline compounds and of 7−10 mg of the liquid compound, contained in a thin glass

TABLE 3: Individual Values of the Massic Energy of Combustion, at $T = 298.15$ K

1,4-benzodioxan	1,4-benzodioxan-6-nitro	1,4-benzodioxan-6-carboxaldehyde	1,4-benzodioxan-6-yl methyl ketone
		$-\Delta_c u^0$, J·g^{-1}	
29683.54	21200.39	26042.94	27525.50
29686.18	21164.80	26057.90	27500.71
29712.74	21176.00	26046.00	27529.56
29699.02	21163.65	26055.23	27508.83
29701.03	21187.12	26045.14	27544.73
29702.49	21172.43	26046.62	27539.58
29696.73	21182.92	26056.56	27535.55
29695.79	21189.90	26064.85	27519.11
29679.51	21177.31	26053.85	
29711.89		26050.92	
		$-\langle\Delta_c u^0\rangle$/J·g^{-1}	
29696.9 ± 3.5	21179.4 ± 4.0	26052.0 ± 2.2	27525.4 ± 5.4

capillary tube sealed at one end, were dropped, at room temperature, into the hot reaction vessel, in a high temperature Calvet microcalorimeter (SETARAM HT 1000D) held at $T =$ 366 K for 1,4-benzodioxan and 1,4-benzodioxan-6-carboxaldehyde, at $T = 390$ K for 1,4-benzodioxan-6-nitro and at $T =$ 375 K for 1,4-benzodioxan-6-yl methyl ketone, and then removed from the hot zone by vacuum evaporation. The thermal corrections for the glass capillary tubes were determined in separate experiments and were minimized, as far as possible, by dropping tubes of nearly equal mass into each of the twin calorimeter cells. From six independent experiments for each compound a mean value was obtained for the observed standard molar enthalpy of sublimation/vaporization, $\Delta^{\mathrm{g},T}_{\mathrm{cr,l}\ 298.15\mathrm{K}}H^0_\mathrm{m}$, which was then corrected to $T = 298.15$ K, $\Delta^{T}_{298.15\mathrm{K}}H^0_\mathrm{m}(\mathrm{g})$, using the equation:

$$\Delta^{T}_{298.15\mathrm{K}}H^0_\mathrm{m}(\mathrm{g}) = \int_{298.15\mathrm{K}}^{T} C^0_{p,\mathrm{m}}(\mathrm{g})\,\mathrm{d}T \tag{2}$$

where T is the temperature of the hot reaction vessel, $C^0_{p,\mathrm{m}}(\mathrm{g})$ is the molar heat capacity of the compound in the gas phase and was obtained from statistical thermodynamics using the vibrational frequencies obtained from the DFT calculations with the B3LYP functional and the 6-31G* basis set:

1,4-benzodioxan

$$C^0_{p,\mathrm{m}}(\mathrm{g})/\mathrm{J\cdot mol^{-1}\cdot K^{-1}} = -0.000339(T/\mathrm{K})^2 + 0.693(T/\mathrm{K}) - 46.285 \tag{3}$$

1,4-benzodioxan-6-nitro

$$C^0_{p,\mathrm{m}}(\mathrm{g})/\mathrm{J\cdot mol^{-1}\cdot K^{-1}} = -0.000400(T/\mathrm{K})^2 + 0.781(T/\mathrm{K}) - 30.873 \tag{4}$$

1,4-benzodioxan-6-carboxaldehyde

$$C^0_{p,\mathrm{m}}(\mathrm{g})/\mathrm{J\cdot mol^{-1}\cdot K^{-1}} = -0.000354(T/\mathrm{K})^2 + 0.738(T/\mathrm{K}) - 29.838 \tag{5}$$

1,4-benzodioxan-6-yl methyl ketone

$$C^0_{p,\mathrm{m}}(\mathrm{g})/\mathrm{J\cdot mol^{-1}\cdot K^{-1}} = -0.000393(T/\mathrm{K})^2 + 0.829(T/\mathrm{K}) - 28.788 \tag{6}$$

3. Computational Details

The geometries of all molecules have been fully optimized using density functional theory (DFT) with the Becke 3-parameter hybrid exchange[20] and the Lee−Yang−Parr[21] correlation density functionals (B3LYP) and the Pople's split-valence 6-31G* extended basis set.[22] The optimum structures so obtained where further certified as true minima by constructing and diagonalizing the corresponding Cartesian Hessian matrix, this procedure providing also the harmonic vibrational frequencies which, after properly scaled by the recommended scaling factor 0.9614[23] allow reliable calculations of the thermal corrections to the molecular energy. We have further refined the optimum structures by reoptimizing them using the same methodology with the Pople's split-valence 6-311G** extended basis set.[24] These final optimized structures where then used to perform single point DFT calculations with the cc-pVTZ basis set[25] and also energy calculations based on more accurate correlated computational techniques of the MCCM/3 suite[26,27] which will be described later.

All the geometry optimizations vibrational analysis and single point calculations have been performed using the UK version of program GAMESS.[28,29] The Nucleus Independent Chemical Shifts (NICS) values were calculated using B3LYP/6-311G** wavefunctions at the B3LYP/6-311G** geometries. The methodology used was developed by Schleyer and his co-workers as a mean of providing useful aromaticity indices.[30] Two different values were calculated for each ring and each molecule: one at the geometrical center of the ring (i.e., the point whose coordinates are the nonweighted mean of the homologous coordinates of the heavy atoms of the rings) denoted NICS(0) and 1.0 Å above the center of the ring, denoted NICS(1.0). The calculation of NICS values has been performed with the Gaussian 03 series of programs[31] and all NBO analyses were made with the program NBO 5.0.[32]

4. Experimental Results

4.1. Enthalpies of Fusion. The temperatures of fusion of the crystalline compounds were measured using a differential scanning calorimeter. The results (observed in each case at the onset temperature of the calorimetric peak), T_{fus}, are presented in Table 1 together with the enthalpies of fusion, at the temperatures of fusion, $\Delta^{\mathrm{l}}_{\mathrm{cr}}H^0_\mathrm{m}(T_{\mathrm{fus}})$, and the mass fraction of impurities, x, of the purified samples. Those values represent the mean values of six independent experiments on fresh samples and the uncertainties are twice the standard deviation of the mean.

4.2. Combustion Calorimetry Results. Results for a typical combustion experiment of each compound are given in Table 2. The individual results of all combustion experiments, together with the mean value and its standard deviation, are given for each compound in Table 3. The derived standard molar energies, $\Delta_c U^0_\mathrm{m}(\mathrm{cr,l})$, enthalpies of combustion, $\Delta_c H^0_\mathrm{m}(\mathrm{cr,l})$, and the standard molar enthalpies of formation, $\Delta_f H^0_\mathrm{m}(\mathrm{cr,l})$, of the studied compounds are in Table 4.

TABLE 4: Derived Standard ($p° = 0.1$ MPa) Molar Values, at $T = 298.15$ K

compound	$-\Delta_c U_m^0$/kJ·mol^{-1}	$-\Delta_c H_m^0$/kJ·mol^{-1}	$-\Delta_f H_m^0$(cr,l)/kJ·mol^{-1}
1,4-benzodioxan	4043.2 ± 1.6	4045.7 ± 1.6	245.7 ± 1.9
1,4-benzodioxan-6-nitro	3836.6 ± 1.7	3834.7 ± 1.7	313.8 ± 2.0
1,4-benzodioxan-6-carboxaldehyde	4276.7 ± 1.3	4277.9 ± 1.3	407.0 ± 1.8
1,4-benzodioxan-6-yl methyl ketone	4904.7 ± 2.3	4907.2 ± 2.3	457.0 ± 2.7

TABLE 5: Derived Standard ($p° = 0.1$ MPa) Molar Enthalpies of Formation at $T = 298.15$ K

compound	$-\Delta_f H_m^0$(cr,l)/kJ·mol^{-1}	$\Delta_{cr,l}^{g} H_m^0$/kJ·mol^{-1}	$-\Delta_f H_m^0$(g)/kJ·mol^{-1}
1,4-benzodioxan	245.7 ± 1.9	67.4 ± 1.7	178.3 ± 2.5
1,4-benzodioxan-6-nitro	313.8 ± 2.0	100.6 ± 1.2	213.2 ± 2.3
1,4-benzodioxan-6-carboxaldehyde	407.0 ± 1.8	98.2 ± 1.4	308.8 ± 2.3
1,4-benzodioxan-6-yl methyl ketone	457.0 ± 2.7	102.5 ± 1.1	354.5 ± 2.9

TABLE 6: Calculated Electronic Energies and Thermal Corrections to $T = 298.15$ K[a]

compound	$E_{\mathrm{B3LYP/6\text{-}311G^{**}}}$	$E_{\mathrm{B3LYP/cc\text{-}pVTZ}}$	$E_{\mathrm{MC\text{-}UT/3}}$	$\mathrm{TCE}_{\mathrm{B3LYP/6\text{-}31G^*}}$[b]
1,4-benzodioxan	−460.218270	−460.268935	−459.499477	0.148055
1,4-benzodioxan-6-nitro	−664.778755	−664.851317	−663.798317	0.153222
1,4-benzodioxan-6-carboxaldehyde	−573.576230	−573.638259	−572.699438	0.159128
1,4-benzodioxan-6-yl methyl ketone	−612.909142	−612.974683	−611.966506	0.187801
1,4-benzodioxan-6-carboxylic acid	−648.852965	−648.922664	−647.888598	0.165431
1,4-benzodioxan-6-ethanoic acid	−688.171161	−688.245078	−687.142952	0.194252
1,4-benzodioxan-6-hydroxyde	−535.460084	−535.519729	−534.654534	0.153126
1,4-benzodioxan-6-hydroxymethyl	−574.776286	−574.840037	−573.906771	0.182234
1,4-benzodioxan-6-cyano	−552.485741	−552.545356	−551.625371	0.148621
1,4-benzodioxan-6-methyl	−499.545850	−499.600270	−498.760296	0.176489

[a] All energies are in au (1 $E_H = 2625.50184$ kJ·mol^{-1}). [b] $\mathrm{TCE}_{\mathrm{B3LYP/6\text{-}31G^*}} = E_{\mathrm{trans}} + E_{\mathrm{rot}} + E_{\mathrm{zp}} + \Delta_{0\,K}^{298.15\mathrm{K}} E_{\mathrm{vib}}$.

In accordance with customary thermochemical practice,[33] the uncertainty assigned to the standard molar enthalpy of combustion, is twice the overall standard deviation of the mean and includes the uncertainty in calibration. To derive $\Delta_f H_m^0$(cr,l) from $\Delta_c H_m^0$(cr,l), the standard molar enthalpies of formation of H_2O(l) and CO_2(g), at $T = 298.15$ K, -285.830 ± 0.042 kJ·mol^{-1} [34] and -393.51 ± 0.13 kJ·mol^{-1},[34] respectively, were used.

4.3. Microcalorimetric Results. The standard molar enthalpies of sublimation or vaporization, $\Delta_{cr,l}^{g} H_m^0$(298.15 K), were determined from six independent experiments (the uncertainty is twice the standard deviation of the mean). To obtain the standard molar enthalpies of sublimation, at $T = 298.15$ K, the observed enthalpies in each experiment, at T, were corrected using eqs 2–6.

4.4. Enthalpies of Formation. Combining the values of the standard molar enthalpies of sublimation or vaporization and the standard molar enthalpies of formation in the condensed phase leads to the values of the standard enthalpies of formation in the gaseous phase, at $T = 298.15$ K. The values are listed in Table 5.

5. Computational Results and Discussion

5.1. Optimized Geometries. All studied molecules were found to consist of a completely planar benzenic ring and a dioxan moiety where the two oxygen atoms and the carbons directly attached to them are found to define structures clearly distorted from planarity. The loss of planarity can be ascribed mainly to steric repulsions between the two contiguous CH_2 groups. Indeed, we observed that the degree of nonplanarity, as measured by the torsional dihedral angle 6−9−7−8 (see Figure 1 for atom numbering) is very uniform and does not depend on the substituent attached to the benzenic ring, thus indicating a major influence of the steric repulsions between the hydrogen atoms of those $-CH_2$ fragments. This contrasts with what is observed with respect to the nonplanarity of the heterocyclic ring of 1,3-benzodioxole and its derivatives.[3,4] In this case, the nonplanarity arises as a consequence of hyperconjugative (anomeric) interactions involving the π-lone electronic pairs of the two oxygen atoms. As such, the electronic nature (donor or acceptor) of the substituents is a major factor to consider and the deviations from the planarity depend crucially on the substituent which is attached to the benzenic ring.

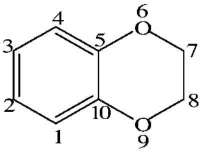
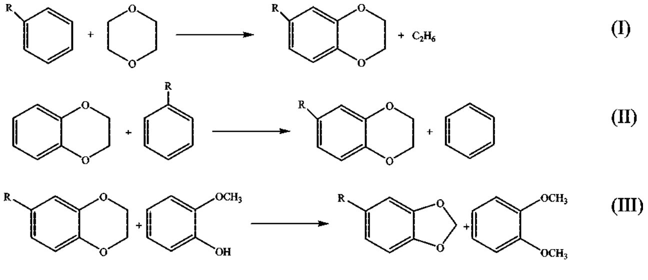


Figure 1. Atom numbering scheme for the geometric results of the 1,4-benzodioxan.

5.2. Calculated Enthalpies of Formation. To estimate the enthalpies of formation of the systems from the calculated energies, we used the following set of reactions involving auxiliary systems whose thermochemical properties are well established experimentally.[35]



(R= -H, -NO$_2$, -CHO, -COCH$_3$, -COOH, -CH$_2$COOH, -OH, -CH$_2$OH, -CN, -CH$_3$)

Total energies, identified by the subscripts B3LYP/6-311G** and B3LYP/cc-pVTZ, and thermal corrections, $\mathrm{TCE}_{\mathrm{B3LYP/6\text{-}31G^*}}$

TABLE 7: Theoretical Estimates of the Standard Enthalpies of Formation in the Gas Phase at $T = 298.15$ K of 1,4-Benzodioxans

		$-\Delta_f H_m^0(g)$/kJ·mol^{-1}			
compound	R	6-311G**	cc-pVTZ	MC-UT/3	experimental
1,4-benzodioxan	I	198.7	196.7	190.0	178.3 ± 2.5
	III	171.3	172.8	167.0	
1,4-benzodioxan-6-yl methyl ketone	I	372.5	370.7	362.4	354.5 ± 2.9
	II	352.0	352.3	350.7	
	III	349.9	351.8	346.2	
1,4-benzodioxan-6-carboxaldehyde	I	323.6	322.1	312.9	308.8 ± 2.3
	II	303.2	303.6	301.2	
	III	297.0	298.3	292.7	
1,4-benzodioxan-6-nitro	I	218.4	217.0	207.5	213.2 ± 2.3
	II	198.0	198.6	195.8	
	III	207.1	208.6	203.3	
1,4-benzodioxan-6-carboxylic acid	I	579.3	577.6	569.4	
	II	558.9	559.2	557.8	
	III	558.6	559.9	554.7	
1,4-benzodioxan-6-hydroxymethyl	I	380.4	378.1	371.8	
	II	360.0	359.7	360.1	
	III	357.7	359.0	353.5	
1,4-benzodioxan-6-hydroxyde	I	371.7	369.4	362.8	
	II	351.3	351.0	351.2	
	III	355.7	357.2	350.8	
1,4-benzodioxan-6-ethanoic acid	I				
	II				
	III	574.1	575.7	355.1	
1,4-benzodioxan-6-methyl	I	229.3	227.0	220.1	
	II	208.9	208.5	208.4	
	III	214.2	215.6	209.7	
1,4-benzodioxan-6-cyano	I	69.1	67.4	53.	
	II	48.7	49.0	41.7	
	III	71.0	55.8	44.5	

are reported in Table 6 for the 1,4-benzodioxan derivatives studied. The optimum geometries, the energies and the thermal corrections for all the auxiliary molecules have also been obtained using the same procedures as described above (Supporting Information).

The resulting estimates of the enthalpies of formation, at the B3LYP/6-311G** and B3LYP/cc-pVTZ levels of calculation, are provided in Table 7, for all reactions used.

Because we are using approximate energies (i.e., energies calculated with a deficient electron correlation treatment) the particular choice of the reactions is of outmost importance. In fact, even if we used always reactions of the same formal type, i.e., isodesmic, homodesmic, hyper-homodesmic, etc., the differences in the electron correlation account between the molecules would manifest themselves in different results obtained for different systems. Of course the situation is even worse when we compare results from different reaction types. This is clearly the case with our results, and we can observe that different reaction types are described with different accuracy by the calculations: reactions of type III are the better described ones, with small absolute deviations, the only exception being 1,4-benzodioxan-6-carboxaldehyde, where an error of about 12 kJ·mol^{-1} can be observed for both basis sets used. Reaction type II, which is of the homodesmotic type, is also well described for all systems, with the exception of 1,4-benzodioxan-6-nitro, for which errors of about 15 kJ·mol^{-1} are observed for both basis sets. Finally, reactions of type I, being only of the isodesmic type, provide the worst results for the studied compounds, with errors of about 12−20 kJ·mol^{-1}, with the exception of 1,4-benzodioxan-6-nitro. This lack of consistency in the description of the energetics of reactions is, we believe, a manifestation of the inefficient electron correlation treatment by our B3LYP calculations. The usual ways of dealing with the electron correlation problem involve very computationally costing procedures, which, as such, can only be applied to a very limited set of moderately sized systems. Accurate methods involving the combination of results from different levels of electronic structure theory and/or different one-electron basis sets, usually with empirical parameters and trying to extrapolate to a more accurate result than the most accurate component calculation, have been proposed,[36–40] providing generally results with almost chemical accuracy, i.e., ±1 kcal·mol^{-1}. These multilevel methods, constitute a very powerful alternative to single-level methods but, unfortunately the computational cost of most of them formally still scales as N^7, N being the number of atoms, and are thus not usable for moderately sized systems. More recently a series of multilevel methods using both correlated wave function methods and density functional methods have been proposed.[26,27] These methods, called multicoefficient correlation methods (MC-CM's), have the enormous advantage of scaling as N^6 or even as N^5, while essentially maintainig a high level of accuracy. In this work we decided to test one of the methods of the MCCM/3[26] suite, namely the MC-UT/3 (a method scaling as N^6). All the calculations have been performed using the MLGAUSS program, version 2.0,[41] which relies in the Gaussian 03 series of programs.[31] The results of these calculations are also tabulated in Table 7. We can observe from the table that even though for reactions of type II and III the new calculations provide slightly worse estimates than the older ones, for reactions of type I a considerable amelioration is obtained. Thus, even though using an approximate method of accounting for electronic correlation, the MC-UT/3 method seems to provide generally better results, even for reactions which are only of the isodesmic type, and this, at a cost not much higher than the single-level methods we generally use.

5.3. Enthalpic Increments and Correlations. The standard molar enthalpy of combustion of 1,4-benzodioxan was determined by Cass et al. in 1958.[5] These authors did not do any energetic corrections for the standard state, and the obtained value $\Delta_c H_m^0(l) = -4036.7 \pm 1.3$ kJ·mol^{-1} is 10 kJ·mol^{-1} apart from the value obtained in this work, $\Delta_c H_m^0(l) = -4045.7 \pm 1.4$ kJ·mol^{-1}. The same authors estimated a value of 50.4 kJ·mol^{-1} for the enthalpy of vaporization, and derived for the standard molar enthalpy of formation for gaseous 1,4-benzodioxan the value −204 kJ·mol^{-1}. In this work the standard molar enthalpy of vaporization, 67.4 ± 1.7 kJ·mol^{-1}, was obtained by Calvet microcalorimetry and the derived value for the standard molar enthalpy of formation of gaseous 1,4-benzodioxan is −178.3 ± 2.5 kJ·mol^{-1}. As explained later, this value is in a much better agreement with the DFT and more accurate calculations derived values.

Let us for now consider the energetic effect of the entrance of a $-CH_2$ group in the five-membered ring of 1,3-benzodioxole to originate 1,4-benzodioxan: we obtain an energetic change of −61.4 ± 4.0 kJ·mol^{-1} or of −35.6 ± 3.8 kJ·mol^{-1}, respectively, when we use the 1958 enthalpy of formation of 1,4-benzodioxan or our own value obtained now. Disregarding the large difference of about 26 kJ·mol^{-1} between the two values, we recognize that the $-CH_2$ group entrance affords a negative energetic increment which can be compared to the homologous effect within the pair of molecules 1,3-dioxole/1,4-dioxan (−17.3 ± 1.6 kJ·mol^{-1}) which, independently of the choice of tabulated data for 1,4-dioxan, evidence a clear loss of relative stabilization. This loss of stabilization can, at least partly, be attributed to the fact already observed that the anomeric effect which occurs within the dioxole ring becomes severely suppressed when this ring experiments benzoannelation. We can now proceed with the analysis of the energetic effect of the entrance of a -CH_2 group in the following pairs of molecules (using tabulated data[35]): Indan/tetralin (−34.3 ± 2.5 kJ·mol^{-1}), tetrahydrofuran/tetrahydropyran (−39.3 ± 1.2 kJ·mol^{-1}), 2,3-dihydrobenzofuran/3,4-dihydrobenzopyran (−35.9 ± 1.4 kJ·mol^{-1}), cyclopentanone/cyclohexanone (−34.0 ± 2.8 kJ·mol^{-1}). Even if we consider other odd pairs: cyclopentanol/cyclohexanol (−44.2 ± 1.7 kJ·mol^{-1}), tetrahydrothiophene/tetrahydrothiopyran (−30.0 ± 1.6 kJ·mol^{-1}), pyrrolidine/piperidine (−43.8 ± 1.0 kJ·mol^{-1}), cyclopentanamine/cyclohexanamine (−50.04 ± 1.6 kJ·mol^{-1}), the obtained data seem to support a fairly uniform energetic increment of about −30 to −45 kJ·mol^{-1} or, in the worst cases, of −30 to −50 kJ·mol^{-1}, which, in either case, agrees very well with the energetic increment derived from our experimental enthalpy of formation of 1,4-benzodioxan (−35.6 ± 3.8 kJ·mol^{-1}) and clearly disagrees with the one calculated (−61.4 ± 4.0 kJ·mol^{-1}) using the value of enthalpy of formation measured in 1958 for that compound. Thus we can be safely confident of our new experimental value of the enthalpy of formation of 1,4-benzodioxan and of its derivatives.

TABLE 8: Experimental Standard Molar Enthalpies of Formation in the Gas Phase, at T = 298.15 K Taken from the Literature

compound	$-\Delta_f H_m^0(g)$/kJ·mol^{-1}
1,3-benzodioxol	−142.7 ± 2.9[35]
1,3-benzodioxol-5-nitro	−176.0 ± 3.2[4]
1,3-benzodioxol-5-carboxaldehyde	267.2[a]
1,3-benzodioxol-5-oxoethyl	−319.3 ± 2.8[4]
1,3-benzodioxol-5-carboxylic acid	−528.9 ± 2.6[3]
1,3-benzodioxol-5-ethanoic acid	−544.5 ± 2.9[3]
1,3-benzodioxol-5-hidroxyde	−325.7 ± 1.9[3]
1,3-benzodioxol-5-hidroxymethyl	−329.0 ± 2.0[3]
1,3-benzodioxol-5-cyano	−23.2 ± 2.2[4]
1,3-benzodioxol-5-methyl	−184.7 ± 3.5[4]
indane	60.3 ± 1.7[35]
tetralin	26.0 ± 1.9[35]
benzene	82.6 ± 0.7[35]
nitrobenzene	67.5 ± 0.5[35]
benzyl alcohol	−100.4 ± 1.3[35]
benzaldehyde	−36.7 ± 2.8[35]
phenylacetic acid	−302.3 ± 2.0[42]
benzoic acid	−294.0 ± 2.2[35]
acetophenone	−86.7 ± 1.5[35]
phenol	−96.4 ± 0.9[35]
toluene	50.0 ± 0.5[35]
cyanobenzene	215.7 ± 2.1[35]

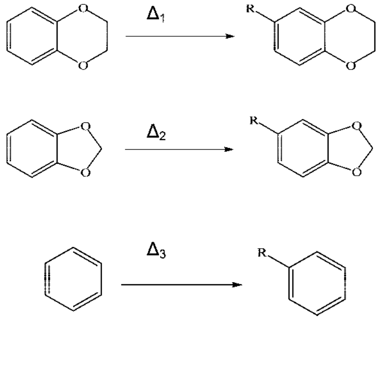
[a] This value was estimated from atomization energies calculated at the MC-UT/3 level.

TABLE 9: Enthalpic Increments

R	Δ_1/kJ·mol^{-1}	Δ_2/kJ·mol^{-1}	Δ_3/kJ·mol^{-1}
$-COCH_3$	−176.2 ± 3.8	−176.6 ± 4.0	−169.3 ± 1.7
$-NO_2$	−34.9 ± 3.4	−33.3 ± 4.3	−15.1 ± 0.9
$-CHO$	−130.9 ± 3.4	−125.7	−119.8 ± 3.0
$-COOH$	−380.9	−386.2 ± 3.9	−376.6 ± 2.3
$-CH_2OH$	−181.4	−186.3 ± 3.5	−183.0 ± 1.5
$-OH$	−172.7	−183.0 ± 3.5	−179.0 ± 1.1
$-CH_2COOH$	−397.4	−401.8 ± 4.1	−384.9 ± 2.1
$-CH_3$	−30.2	−42	−32.2 ± 0.9
$-CN$	129.3	119.5	133.1 ± 2.2

[a] $\Delta_{1,2,3}$ = energetic effect of the different substitutions (−R) in 1,4-benzodioxan, 1,3-benzodioxol and in benzene, respectively.

We can also try an analysis of the energetic effect of the different substituents R in position 6 of 1,4-benzodioxan, comparatively with the corresponding substitutions either in 1,3-benzodioxole or in benzene. For that we consider the hypothetical gaseous processes we present below and calculate the respective enthalpic increments $\Delta_{1,2,3}$. The standard molar enthalpies of formation in the gaseous phase for the different compounds not studied in this work were taken from the literature[3,4,35] and are listed in Table 8. From the values of $\Delta_{1,2,3}$ collected in Table 9, it seems that the energetic effect of the different substitutions (−R) either in 1,4-benzodioxan or 1,3-benzodioxol are similar in magnitude to the corresponding substitutions in benzene, with the exception of $-NO_2$ (π-electron acceptor) for which the stabilization afforded to either of the bicyclical compounds is some 2-fold that afforded to benzene.



Considering the following hypothetical gaseous reaction the fact that it is practically thermoneutral seems to be indicative

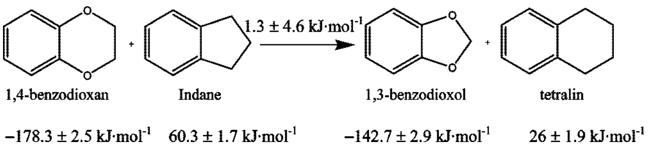
TABLE 10: Nucleus Independent Chemical Shifts (ppm)[a]

	benzene ring		dioxan ring	
	NICS(0)	NICS(1.0)	NICS(0)	NICS(1.0)
benzene	−9.7	−11.5		
1,4-benzodioxan	−10.9	−10.7	−0.7 (−5.6)	−1.2 (−3.5)
1,4-benzodioxan-6-nitro	−11.2	−10.5	−0.7 (−5.8)	−1.2 (−3.6)
1,4-benzodioxan-6-carboxaldehyde	−10.2	−10.4	−0.6 (−6.9)	−1.1 (−3.9)
1,4-benzodioxan-6-yl methyl ketone	−10.3	−10.4	−0.6 (−7.1)	−1.1 (−4.4)
1,4-benzodioxan-6-carboxylic acid	−10.5	−10.4	−0.7 (−6.0)	−1.1 (−3.9)
1,4-benzodioxan-6-ethanoic acid	−10.7	−10.5	−0.8 (−6.1)	−1.2 (−4.0)
1,4-benzodioxan-6-hydroxyde	−11.6	−10.3	−1.0 (−5.7)	−1.3 (−3.6)
1,4-benzodioxan-6-hydroxymethyl	−10.7	−10.6	−0.7 (−5.8)	−1.2 (−3.7)
1,4-benzodioxan-6-cyano	−11.0	−10.5	−0.8 (−6.0)	−1.4 (−3.8)
1,4-benzodioxan-6-methane	−10.8	−10.5	−0.8 (−5.7)	−1.2 (−3.8)

	benzene ring		dioxole ring	
	NICS(0)	NICS(1.0)	NICS(0)	NICS(1.0)
1,3-benzodioxol	−10.4	−10.3	−4.8 (−10.6)	−1.2 (−5.1)
1,3-benzodioxol-5-nitro	−10.6	−10.0	−4.6 (−8.5)	−1.4 (−4.0)
1,3-benzodioxol-5-carboxaldehyde	−9.6	−10.0	−4.6 (−8.8)	−1.5 (−4.3)
1,3-benzodioxol-5-oxoethyl	−9.8	−10.2	−4.6 (−10.6)	−1.5 (−6.0)
1,3-benzodioxol-5-carboxylic acid	−10.0	−10.0	−4.6 (−10.5)	−1.3 (−5.4)
1,3-benzodioxol-5-ethanoic acid	−10.1	−10.0	−4.8 (−11.2)	−1.3 (−5.8)
1,3-benzodioxol-5-hidroxyde	−11.0	−9.9	−5.2 (−10.3)	−1.9 (−5.8)
1,3-benzodioxol-5-hidroxymethyl	−10.1	−10.2	−4.9 (−10.7)	−1.7 (−6.3)
1,3-benzodioxol-5-cyano	−10.4	−10.2	−4.7 (−10.2)	−1.6 (−5.6)
1,3-benzodioxol-5-methyl	−10.2	−10.1	−4.9 (−10.6)	−1.3 (−5.1)

[a] In parenthesis we show the total contribution from donor−acceptor interactions to the NICS values.

of analogous aromatic character of both 1,4-benzodioxan and 1,3 benzodioxole.



This energetic assessment of aromaticity, a quantity that is not directly measurable, can fortunately be complemented by other types of approaches. In this respect, approaches based on magnetic criteria are generally considered particularly reliable because the magnetic properties of aromatic molecules depend directly on the induced ring currents associated with cyclic electron delocalization. In this work we choose to quantify aromaticity through the computation and analysis of the nuclear magnetic resonance chemical shifts (magnetic shielding) felt by a probe nucleus at the center of the ring, the so-called NICS (nucleus independent chemical shift) values, as suggested initially by Schleyer et al.[30] Within this approach sign reversed NICS values are used to quantify aromaticity effects: significantly negative (magnetically shielded) NICS values inside the rings result from induced diatropic ring currents which are associated with aromaticity whereas positive values, resulting from induced paratropic ring currents, indicate antiaromatic behavior, or deshielding of the nucleus. We have used the optimized B3LYP/6-311G** geometries and B3LYP/6-311G** wavefunctions to obtain NICS values at the center of each ring, denoted NICS(0), and 1.0 Å above that point, NICS (1.0), both for the substituted 1,4-benzodioxans and, for comparison purposes, for the substituted 1,3-benzodioxoles studied earlier.[3,4] The obtained NICS values are collected in Table 10. Observing the NICS values we can easily conclude that the benzenic ring of both benzodioxoles and benzodioxans evidence very similar aromatic features and they do not differ appreciably, in that respect, from the isolated benzene ring. In addition, we can also observe that the NICS values at the benzenic ring are not very sensitive to the nature of the substituents attached to that ring. On the other hand, the heterocyclic ring of both families of compounds does not display any appreciable aromatic character. However, we can observe that the NICS(0) values inside the heterocyclic ring of benzodioxoles are moderately negative (ca. −5 ppm), and this feature becomes clearly attenuated when we consider the NICS(1.0) values. This attenuation is not observed for the benzodioxan family of compounds, and, instead the reverse behavior is observed in this case. Even though we are aware of the difficulties inherent to the generalization of the NICS concept to nonplanar rings, we believe, however, that the small deviations from planarity encountered by us for these systems still allow using the NICS concept with presumed usefulness. As so, we believe that the difference in behavior observed for both families of compounds can be attributed to the delocalization of the π-lone electronic pairs of the two oxygen atoms into the antibonding orbitals of the C−O bonds, as implied by the occurrence of the hyperconjugative anomeric interaction in the five-membered heterocyclic ring. The electron transfers from the π-symmetry orbitals to σ antibonding orbitals can then be invoked to explain the enhancement of the screening of the probe nucleus observed when it is shifted to the geometrical center of the heterocyclic ring in the benzodioxole family of compounds. Fortunately, the contribution from such electron interactions can be analyzed in the framework of Natural Bonding Orbital (NBO) Theory. To do that, the NICS values are analyzed as resulting from two contributions: the contributions resulting from localized (i.e., Lewis type) natural bonding orbitals and the contribution arising from the donor−acceptor type interactions associated with delocalization effects. The last mechanism only contributes to the shielding of a nucleus when conjugative or hyperconjugative delocalization effects are present. The results of such analysis are also resumed in Table 10 by the numbers in parentheses. We present only the analysis of the NICS for the dioxole and dioxan rings because delocalization effects at the benzenic rings of both families of compounds must be similar. We can observe from the results of this analysis that the moderately negative NICS values inside the dioxole ring of benzodioxoles results from a large negative contribution arising from delocalization effects, on the order of −10 ppm; on the other hand, for the dioxan ring of benzodioxans the much less negative NICS values are always associated with contributions from delocalization effects, which are much less important than those observed for the dioxole rings: they have values on the order of −5 ppm and are seen to be almost completely balanced by the positive contributions arising from the localized NBOs. Thus the results of our analysis confirm our previous observation about the importance of anomeric interactions in the benzodioxole molecules and the absence of such interactions in the benzodioxan molecules. Finally, we believe that the NICS concept, when combined with the NBO analysis, can be generalized to give some insight into the nature and into the magnitude of the anomeric effect.

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Supporting Information Available: Table of electronic energies and thermal corrections. This material is available free of charge via the Internet at http://pubs.acs.org.

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