Substituent Effects on Enthalpies of Formation: Benzene Derivatives

Otilia Mó and Manuel Yáñez*

Departamento de Química, C-9, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

José Elguero

Instituto de Química Médica, C.S.I.C. Juan de la Cierva, 3, 28006-Madrid, Spain

María Victoria Roux, Pilar Jiménez, and Juan Z. Dávalos

Instituto de Química Física "Rocasolano", C.S.I.C. Serrano,119, 28006-Madrid, Spain

Manuel A. V. Ribeiro da Silva and Maria das Dores M. C. Ribeiro da Silva

Centro de Investigaçao em Química, Department of Chemistry, Faculty of Science, University of Porto,
Rua do Campo Alegre, 687, P-4169−007 Porto, Protugal

Pilar Cabildo and Rosa Claramunt

Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey 9,
28040-Madrid, Spain.

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High level density functional theory calculations have been carried out for a benchmark set of benzene derivatives, including methyl, ethyl, *n*-propyl, *i*-propyl, *tert*-butyl, phenyl, and benzyl groups as substituents. Geometries were obtained using the B3LYP method and three basis set expansions, namely 6-31G(d), 6-311G(d,p), and 6-311++G(d,p). Final energies were calculated in B3LYP/6-311+G(3df,2p) single-point calculations. Based on these calculations the performance of different theoretical schemes aiming at reproducing substituent effects on enthalpies of formation has been assessed. The poorest performance is obtained when atomization energies or isodesmic reactions are used. No significant improvement is found when using homodesmotic processes. A significant improvement is achieved when the isodesmic processes used involve the unsubstituted parent compound. That means that this procedure can be a good alternative to explore substituent effects on the enthalpies of formation, although the absolute values of this thermodynamical magnitude have still a significant error. The best performance is obtained when different atom equivalent schemes are used, the correlation coefficient of the linear relationship between calculated and experimental values being greater than 0.999.

Introduction

Enthalpies of formation are crucial thermodynamic magnitudes. They are needed to estimate the amount of energy released or absorbed in a chemical reaction, to calculate other thermodynamic functions and, what is more important, to asses the stability of a molecule. Unfortunately, not always is this magnitude experimentally available because of the difficulties inherent to the usual experimental procedures, and sometimes because of the difficulty in having a pure sample of the compound whose enthalpy of formation is going to be measured. In other cases, the systems of interest are of low stability or even elusive to experimental observation. This situation can be partially alleviated by means of computational chemistry techniques. Quantitative determination of thermodynamic properties of a molecule by using standard quantum chemical procedures is a long-sought goal of computational chemistry. Nowadays, different theoretical schemes, such as the G2,[1] CBS,[2] or the G3[3] theory, are able to provide enthalpies of formation for small systems within ±2 kcal mol^{-1}. However, its extension to large systems is still prohibitively costly. Different DFT approaches are possible alternatives and they have been frequently used,[4−9] but in general the overall accuracy is lower than that achieved with high-level ab initio schemes. In fact, a calibration of G2, CBS, and DFT methods[10] for the G2, G2(MP2), CBS-Q, G2(MP2,SVP), CBS-q, CBS-4, and B3LYP/6-311+G(3df,2p) methods yielded the following mean absolute deviations from experiment: 5.98, 7.4, 4.98, 6.86, 9.79, 11.13, and 14.35 kJ mol^{-1}. A more recent review on the use of different theoretical methods for computing enthalpies of formation was published by Curtiss et al.[11]

Most of the calculations are based on the use of isodesmic reactions,[12] in which calculated values are combined with experimental enthalpies of formation of suitable reference systems. The problem is that the experimental enthalpies of formation of the species involved in the isodesmic process are not always known or some of them are affected by a large error. Alternatively, other schemes, usually based in atom equivalent or group equivalent components, have been proposed[4,7,9,13−16]

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TABLE 1: Enthalpies of Formation[a] of Benzene Derivatives

derivative	atomization energies	isodesmic reactions		homodesmotic reactions	atom equivalent schemes		exp.
		A[b]	B[c]		scheme 1	scheme 2	
H	102	70		71	65	64	82.9
Me	88	49	62	51	37	36	50.0
Et	89	43	45	45	18	19	29.8
Pr	77	27	28	29	−2.0	−0.6	7.8
i-Pr	79	30	30	31	0.5	2.0	3.9
t-Bu	81	23	22	24	−10	−7	−22.7
Ph	263	190	203	192	156	154	181.1
CH_2−Ph	264	181	193	184	146	145	164.8

[a] All values in kJ mol^{-1}. [b] Isodesmic reactions 3−6. [c] Isodesmic reactions 11−13 in which the unsubstituted parent compound is one of the references.

with relatively good success. The advantage of the atom equivalent schemes is that the empirical correction depends only on the atoms present, not on the bonds they form. Recently, a modification of this general procedure has been proposed by Cioslowski et al.,[9] in which, in addition to the atom equivalent terms, is included a further correction based on the topological characteristics of the bonds each atom forms. The disadvantage of this procedure is that one needs a very large number of parameters to be obtained through the use of the atoms in molecules theory.[17]

One interesting question associated with enthalpies of formation that has not been much investigated is that of substituent effects, and in this respect some calibration of the available methods is still needed. We have recently shown,[8] in a combined experimental and theoretical study of substituent effects on the enthalpy of formation of pyrazoles and imidazoles, that certain unexpected anomalies appear. Indeed, when the substituent effects on the enthalpies of formation of pyrazoles and imidazoles were correlated with those of the corresponding benzene derivatives, the following equations were obtained:

$$R_1 - \mathrm{PYR} = (1.13 \pm 0.12)\, R_1 - \mathrm{BEN} + (98 \pm 14) \qquad r = 0.982 \quad (1)$$

$$R_1 - \mathrm{IMI} = (1.09 \pm 0.18)\, R_1 - \mathrm{BEN} + (73 \pm 20) \qquad r = 0.963 \quad (2)$$

However, according to the Hess law the slope should be strictly 1, and we could not find a plausible explanation for the large fluctuations found. This moved us to pursue a systematic investigation on substituent effects on enthalpies of formation. In this paper we will consider some benzene derivatives as a good benchmark set to calibrate the performance of different theoretical models. Then, using the most accurate ones, we will analyze similar substituent effects for the series of imidazole and pyrazole N-substituted derivatives in order to gain some insight on the influence of the substrate. The final goal of this kind of analysis is to assess whether it is possible to generate an enormous collection of estimated data for different substituted heterocycles (pyrazole-derivatives, imidazole-derivatives, pyridine-derivatives, etc.) from the great amount of $\Delta_f H^\circ_m(g)$ values available for substituted benzenes.

Computational Details

The geometries of the compounds under scrutiny as well as those of the reference systems used in the different isodesmic or homodesmotic reactions considered were optimized at the B3LYP/6-31G* level. Harmonic vibrational frequencies were calculated also at this level, to assess that the stationary points found corresponded to local minima of the potential energy surface and to estimate the corresponding zero point energies (ZPE). Final energies were obtained in single-point calculations at the B3LYP/6-311+G(3df,2p) level. This theoretical scheme has been found to be fairly well suited to estimate enthalpies of formation and other thermodynamic magnitudes such as proton affinities or gas-phase basicities. The B3LYP functional, as implemented in the Gaussian 98 suite of programs,[18] combines the Becke three parameter nonlocal hybrid exchange potential[19] and the nonlocal correlation functional of Lee, Yang, and Parr.[20]

To apply the atom equivalent scheme of Mole et al.,[4] hereafter called scheme 1, the aforementioned B3LYP/6-31G* geometries were refined at the B3LYP/6-311G(d,p) level. Similarly, to use the atom equivalent scheme of Cioslowski et al.,[7] hereafter called scheme 2, B3LYP/6-311++G(d,p) geometries and energies were also evaluated.

Results and Discussion

The enthalpies of formation of benzene, toluene, ethyl-, *n*-propyl-, *i*-propyl-, *tert*-butyl-benzene, biphenyl, and benzylbenzene at the different levels of theory considered in this work are summarized in Table 1. The corresponding optimized geometries and total energies are provided as Supporting Information. Although a discussion of the structures of these compounds is not the aim of this work, it is worth mentioning that the optimized structure for *tert*-butyl-benzene is in agreement with that obtained by gas-phase electron diffraction methods and ab initio methods,[21] which indicate that the system presents a coplanar conformation of the molecule, with a C−Me bond in the ring plane. This is important because, as we shall show later, *tert*-butyl-benzene is the only derivative that deviates from the correlations between experimental and calculated enthalpies of formation.

Let us now discuss the different theoretical models used to estimate the enthalpies of formation of this set of compounds.

Atomization Energies. Enthalpies of formation can be estimated from the corresponding atomization reactions, following the procedure outline in ref 6. In this procedure, the enthalpy of formation of an $A_xB_yH_z$ molecule at 0 K in the gas phase is given by

$$\Delta_f H_m^\circ\,(A_xB_yH_z, 0\ \mathrm{K}) = x\Delta_f H_m^\circ\,(A, 0\ \mathrm{K}) + y\Delta_f H_m^\circ\,(B, 0\ \mathrm{K}) + z\Delta_f H_m^\circ\,(H, 0\ \mathrm{K}) - \Sigma D_0 \quad (3)$$

where ΣD_0 is the calculated atomization enthalpy, and $\Delta_f H_m^\circ$ (A, 0 K), $\Delta_f H_m^\circ$ (B, 0 K), $\Delta_f H_m^\circ$ (H, 0 K) the experimental enthalpies of formation of the isolated atoms at 0 K.

The corresponding enthalpies of formation at 298.15 K in the gas phase are estimated $\Delta_f H_m^\circ$ (H, 0 K) $b\Delta_f H_m^\circ$ (H, 0 K) by including the following corrections into the $\Delta_f H_m^\circ$ (0 K) value:

$$\begin{aligned}\Delta_f H_m^\circ (A_xB_yH_z, 298.15\ \text{K}) = {}& \Delta_f H_m^\circ (A_xB_yH_z, 0\ \text{K}) + \\ & [H_m^\circ (A_xB_yH_z, 298.15\ \text{K}) - H_m^\circ (A_xB_yH_z, 0\ \text{K})] - \\ & x[H_m^\circ (\text{A}, 298.15\ \text{K}) - H_m^\circ (\text{A}, 0\ \text{K})]_{st} - \\ & y[H_m^\circ (\text{B}, 298.15\ \text{K}) - H_m^\circ (\text{B}, 0\ \text{K})]_{st} - \\ & z[H_m^\circ (\text{H}, 298.15\ \text{K}) - H_m^\circ (\text{H}, 0\ \text{K})]_{st} \quad (4)\end{aligned}$$

where the vibrational contribution to the heat capacity correction for the $A_xB_yH_z$ molecule is estimated by employing the calculated harmonic frequencies. The translational, rotational and PV contributions are calculated as (3/2)RT, (3/2)RT (or RT for linear molecules), and RT, respectively. For the elements, in our case only carbon and hydrogen, the heat capacity corrections for the standard states are those reported in ref 6.

The corresponding calculated values are given in Table 1. There is a linear correlation between these values and the experimental ones[22] which obeys the equation:

$$\Delta_f H^\circ\ (\text{calc.}) = 1.038\ \Delta_f H^0(\text{exp.}) + 64.6\ \text{kJ mol}^{-1} \qquad r = 0.933 \quad (5)$$

The correlation coefficient clearly shows that there is a significant scatter. It is also worth noting that the quality of this correlation is poorer than the one reported previously in the literature for imidazole and pyrazole substituted derivatives, indicating that the composition of the systems may have a nonnegligible influence in the reliability of the method. It can be also observed that, although the method reproduces the general trends and indicates, for example, that toluene has an enthalpy of formation lower than benzene, or that biphenyl has a much higher enthalphy of formation than benzene, it fails to differentiate between *i*-propyl- and *tert*-butyl-benzene, for which practically identical values of $\Delta_f H^\circ$ are obtained. Something similar can be said when the substituents are Ph and $-CH_2-$Ph.

Isodesmic Reactions. As mentioned in the Introduction, a useful alternative to estimate enthalpies of formation is the use of appropriate isodesmic reactions, which imply that the number of bonds of each formal type are conserved.

In our case the reactions of this type that can be envisaged are as follows. For benzene:

$$C_6H_6 + 6\ CH_4 \rightarrow 3\ CH_3CH_3 + 3\ CH_2{=}CH_2 \quad (6)$$

for the corresponding alkyl derivatives:

$$C_nH_{2n-6} + nCH_4 \rightarrow (n-3)\ CH_3CH_3 + 3\ CH_2{=}CH_2 \quad (7)$$

and for biphenyl and diphenylmethane:

$$C_{12}H_{10} + 14\ CH_4 \rightarrow 7\ CH_3CH_3 + 6\ CH_2{=}CH_2 \quad (8)$$

$$C_{13}H_{12} + 14\ CH_4 \rightarrow 6\ CH_3CH_3 + 6\ CH_2{=}CH_2 + CH_3CH_2CH_3 \quad (9)$$

respectively.

The correlation between the estimated values, obtained at the B3LYP/6-311+G(3df,2p) level, and the experimental values has been plotted in Figure 1. It can be observed that the quality of the correlation improves significantly with respect to that based on atomization energies, as reflected in a correlation coefficient ($r = 0.974$) closer to unity. This correlation shows, however, a clear deviation of the *tert*-butyl derivative. Actually, when this derivative is eliminated from the correlation the correlation coefficient becomes much closer to unity ($r = 0.994$). Also the enthalpy of formation of the unsubstituted parent compound seems slightly underestimated.

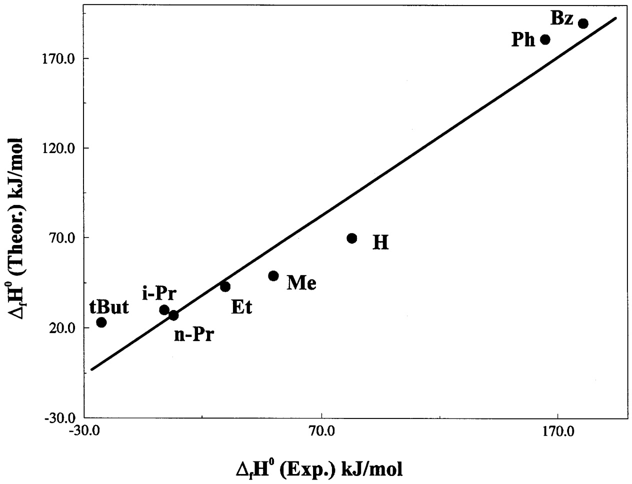

Figure 1. Linear correlation between calculated enthalpies of formation and experimental values for substituted benzenes. Calculated values were obtained using the isodesmic reactions 6−9. This linear correlation obeys the equation $\Delta_f H^\circ$ (theor.) = 0.889 $\Delta_f H^\circ$ (exp.) + 21.3k J mol^{-1} ($r = 0.974$).

An improvement of the model should be achieved by using homodesmotic reactions, i.e., reactions in which not only are the types of bonds the same in both sites of the reaction, but also the number of atoms in a given hybridization state.

For benzene an appropriate homodesmotic reaction would be[23]

$$C_6H_6 + 3CH_2{=}CH_2 \rightarrow 3CH_2{=}CH{-}CH{=}CH_2 \quad (10)$$

and for the corresponding alkyl derivatives

$$C_nH_{2n-6} + 3CH_2{=}CH_2 + (n-6)CH_4 \rightarrow 3CH_2{=}CH{-}CH{=}CH_2 + (n-6)CH_3CH_3 \quad (11)$$

and for biphenyl and diphenylmethane

$$C_{12}H_{10} + 6CH_2{=}CH_2 + 2CH_4 \rightarrow 6CH_2{=}CH{-}CH{=}CH_2 + CH_3CH_3 \quad (12)$$

$$C_{13}H_{12} + 6CH_2{=}CH_2 + 2CH_4 \rightarrow 6CH_2{=}CH{-}CH{=}CH_2 + CH_3CH_2CH_3 \quad (13)$$

As illustrated in Figure 2 and by the values in Table 1, the improvement is really negligible and the correlation coefficient is identical to that obtained when isodesmic reactions were employed. Importantly, however, the *tert*-butyl-derivative deviates again and the enthalpy of formation of benzene appears also underestimated.

Since we are interested in substituent effects, the most reasonable model would be the use of isodesmic reactions, in which one of the reference systems is the unsubstituted parent compound. For the alkyl-benzene derivatives these reactions are

$$C_nH_{2n-6} + (n-6)CH_4 \rightarrow C_6H_6 + (n-6)CH_3CH_3 \quad (14)$$

and for biphenyl and diphenylmethane

$$C_{12}H_{10} + 2CH_4 \rightarrow 2C_6H_6 + CH_3CH_3 \quad (15)$$

$$C_{13}H_{12} + 14CH_4 \rightarrow 2C_6H_6 + CH_3CH_2CH_3 \quad (16)$$

respectively.

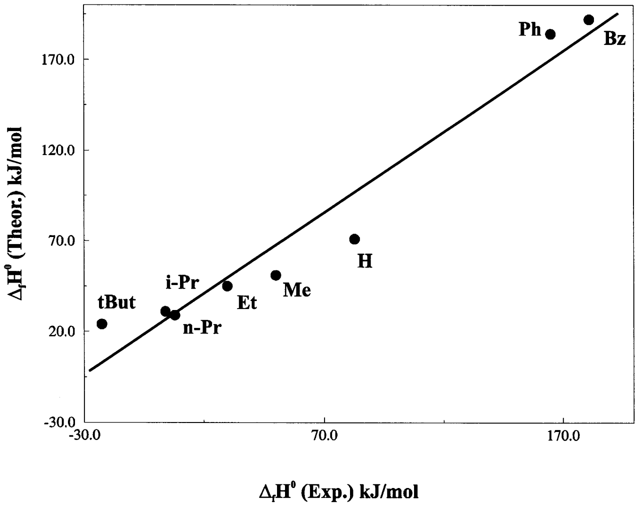

Figure 2. Linear correlation between calculated enthalpies of formation and experimental values for substituted benzenes. Calculated values were obtained using the homodesmotic reactions 10−13. This linear correlation obeys the equation $\Delta_{f}H^{\circ}$ (theor.) = 0.895 $\Delta_{f}H^{\circ}$ (exp.) + 22.74 kJ mol^{-1} (r = 0.974).

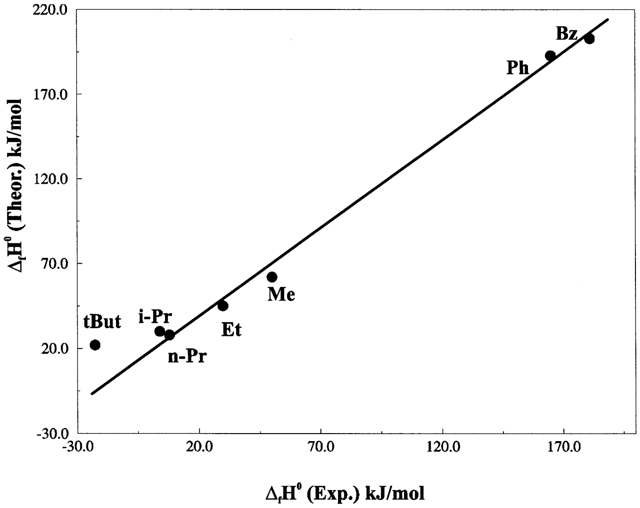

Figure 3. Linear correlation between calculated enthalpies of formation and experimental values for substituted benzenes. Calculated values were obtained using the isodesmic reactions 14−16, taking as a reference compound the unsubstituted benzene. This linear correlation obeys the equation $\Delta_{f}H^{\circ}$ (theor.) = 1.029 $\Delta_{f}H^{\circ}$ (exp.) + 18.47 kJ mol^{-1}) (r = 0.997).

As shown in Figure 3, the correlation between calculated and experimental values significantly improves, yet calculated values slightly overestimate experimental ones. Two important points should be singled out for comment. Again the *t*-butyl derivative deviates from the correlation, and the relative stability predicted from the theoretical calculations for the *n*-propyl and the *i*-propyl derivative appears reversed with respect to experimental data. Both results seem to indicate that the stability of the derivatives with congested substituents, such as *tert*-butyl and *i*-propyl, is underestimated by the theoretical calculations. Indeed, our results predict *i*-propylbenzene to be slightly less stable than the *n*-propyl isomer, whereas the enthalpy of formation of the former is more positive than that of the latter. Similarly, from the correlation in Figure 3 one should expect *tert*-butylbenzene to have a more negative enthalpy of formation than that predicted by the theoretical estimates.

Atom Equivalent Schemes. In this section we shall present the results obtained by using the atom equivalent schemes 1 and 2, which differ only in the flexibility of the basis set used. The estimated enthalpies of formation are given in Table 1, and they have been plotted vs the experimental ones in Figures 4 and 5, respectively. The first important finding is that both methods yield estimates for the enthalpies of formation closer to the experimental ones, as reflected in values of the slopes very close to unity, although in both cases the calculated values are systematically smaller than the experimental ones. The second important finding is that both correlations are very good as mirrored in the values of the correlation coefficients. Once more, however, *tert*-butylbenzene deviates from the correlations. Also, as expected, the relative stability of *n*-propyl and *i*-propyl derivatives appears reversed with respect to the experimental enthalpies of formation, although the gap is small. This seems to indicate that either the theoretical methods underestimate the intrinsic stability of compounds with bulky substituents, or the experimental values are slightly too low, or both things are happening simultaneously. To solve this dichotomy it would be necessary to investigate the enthalpies of formation of different families of compounds presenting also the same or

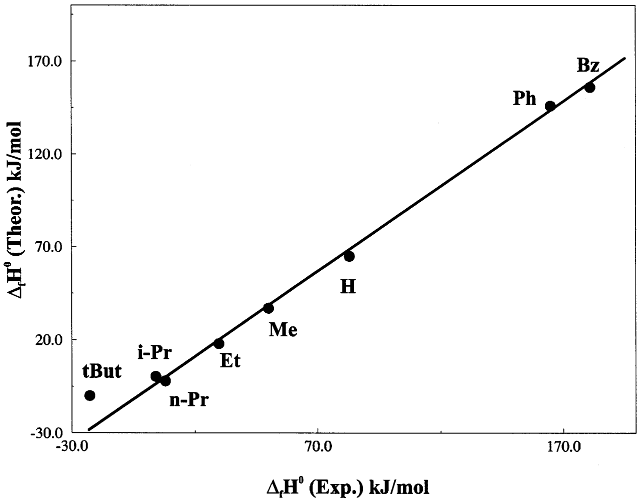

Figure 4. Linear correlation between calculated enthalpies of formation and experimental values for substituted benzenes. Calculated values were obtained using the atom equivalent scheme of ref 4. This linear correlation obeys the equation $\Delta_{f}H^{\circ}$ (theor.) = 0.911 $\Delta_{f}H^{\circ}$ (exp.) −7.67 kJ mol^{-1}) (r = 0.999).

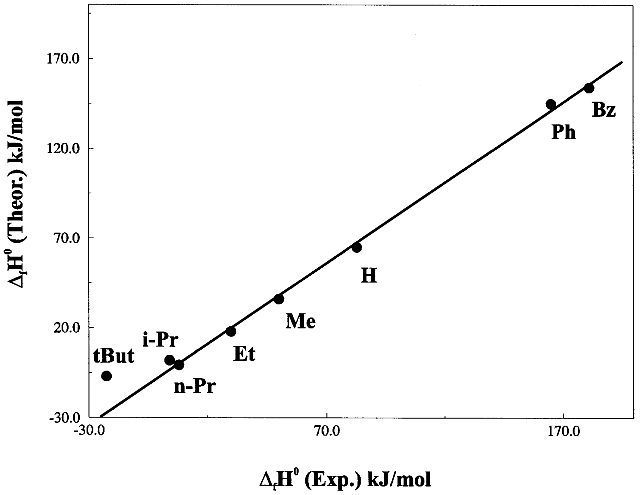

Figure 5. Linear correlation between calculated enthalpies of formation and experimental values for substituted benzenes. Calculated values were obtained using the atom equivalent scheme of ref 7. This linear correlation obeys the equation $\Delta_{f}H^{\circ}$ (theor.) = 0.896 $\Delta_{f}H^{\circ}$ (exp.) −6.71 kJ mol^{-1}) (r = 0.999).

TABLE 2: Enthalpies of Formation[a] for N-Substituted Imidazoles and Pyrazoles

imidazoles	$\Delta_f H°$ (calc.) scheme 2[b]	$\Delta_f H°$ (exp.)[c]	pyrazoles	$\Delta_f H°$ (calc.) scheme 2[b]	$\Delta_f H°$ (exp.)[c]
H	145	132.9 ± 0.6	H	190	179.4 ± 0.8
Me	140	137.8 ± 4.0	Me	179	156.5 ± 2.1
Et	115	110.8 ± 4.3	Et	151	132.6 ± 3.3
Pr	98		Pr	121	
i−Pr	94		*i*−Pr	127	
t−Bu	79		*t*−Bu	115	
Ph	257	264.7 ± 4.3	Ph	295	291.4 ± 4.5
−CH$_2$−Ph	243	244.1 ± 3.4	−CH$_2$−Ph	280	276.6 ± 2.9

[a] All values in kJ mol^{-1}. [b] Calculated values were obtained using the atom equivalent scheme described in ref 7. [c] Experimental values taken from ref 8.

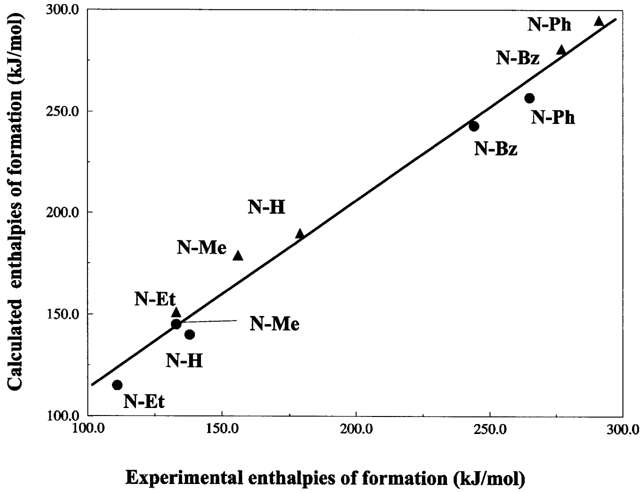

Figure 6. Linear correlation between calculated enthalpies of formation and experimental values for N-substituted imidazoles (●) and N-substituted pyrazoles (●). Calculated values were obtained using the atom equivalent scheme of ref 7. This linear correlation obeys the equation $\Delta_f H°$ (theor.) = 0.927 $\Delta_f H°$ (exp.) +20.9 kJ mol^{-1}) (r = 0.993).

similar bulky substituents. It is also interesting to note that there is no significant improvement on going from the 6-311G(d,p), which is the basis set expansion used in scheme 1, to the 6-311++G(d,p) basis set, which is the basis set used in scheme 2. This seems to indicate that diffuse components are not significantly important in describing the stability of this kind of compounds.

Comparison Between Benzene and Azole Derivatives. As we have mentioned in the Introduction, according to the Hess law the correlation between substituent effects on the enthalpies of formation of pyrazoles and imidazoles with respect to benzene derivatives should be linear with slope unity, although this is not exactly fulfilled when experimental values are used. The question we are addressing here is whether a similar behavior is observed when using calculated values obtained through the same theoretical scheme. For this purpose we have chosen the atom equivalent scheme of Cioslowski et al.[7] because it provides the necessary parameters not only for C and H but also for N. The optimized geometries and the total energies of the N-substituted imidazoles and pyrazoles included in this survey are given as Supporting Information. The estimated enthalpies of formation are summarized in Table 2. The first important finding is that there is a very good linear correlation between calculated and experimental values for both series of compounds (See Figure 6). It should be also emphasized that the quality of the correlation is higher than that obtained when the theoretical estimates are based on the used of quasiisodesmic reactions.[8] More importantly, the correlations with the calculated enthalpies of formation of the benzene derivatives analogues are also very good:

$$R_1 - \mathrm{PYR} = 1.075\, R_1 - \mathrm{BEN} + 127 \quad r = 0.996 \quad (17)$$

$$R_1 - \mathrm{IMI} = 1.09\, R_1 - \mathrm{BEN} + 91 \quad r = 0.994 \quad (18)$$

Two points should be singled out for discussion. First, that similarly to what was found when experimental values are employed (eqs 1 and 2), the slopes of both correlations are greater than unity, indicating that substituent effects for imidazoles (or pyrazoles) and for benzene derivatives are not strictly equivalent. Second, correlations (eqs 17 and 18) include also the propyl-, *i*-propyl, and the *tert*-butyl derivatives, which were not included in obtaining eqs 1 and 2. The goodness of correlations (eqs 17 and 18) clearly seems to indicate that the estimated enthalpies of formation for propyl-, *i*-propyl, and the *tert*-butyl-benzene are correct. This suggests that the experimental value, mainly for *tert*-butyl-benzene, should be revised.

Conclusions

From our survey of different theoretical schemes aiming at reproducing substituent effects on enthalpies of formation, we may conclude that all of them are able to correctly reproduce the experimental trends. In no case, however, the correlation between calculated and experimental values has slope 1. Some of the models tend to systematically overestimate the experimental data, while others systematically underestimate them. The poorest performance is obtained when atomization energies are used. A clear improvement is found when isodesmic reactions are employed. No significant improvement is obtained, however, when using homodesmotic processes instead. One of the drawbacks of these methods is the large number of reference compounds that intervene in the reaction, which increases the error inherent to these theoretical models. A further improvement, if we are just interested in estimating substituent effects, is achieved when the isodesmic processes used involve the unsubstituted parent compound as a reference in the reaction. That means that this procedure can be a good alternative to explore substituent effects on the enthalpies of formation, although the absolute values of this thermodynamical magnitude are still affected by a significant error. The best performance is obtained when different atom equivalent schemes are used, based on B3LYP calculations. The correlation with the experimental values is extremely good, with correlation coefficients greater than 0.999, although the absolute enthalpies of formation slightly underestimate the experimental values.

Similar correlations to those found between the experimental enthalpies of formation of N-substituted imidazoles or pyrazoles and benzene derivatives are obtained when atom equivalent schemes are used to estimate their enthalpies of formation. This seems to confirm that substituent effects are not strictly transferable from one family of compounds to another, in contrast with what should be expected from the strict application of the Hess law.

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Supporting Information Available: Optimized geometries and total energies of benzene, toluene, ethyl-, *n*-propyl-, *i*-propyl-, *tert*-butyl-benzene, biphenyl, and benzyl-benzene at the different levels of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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