Inductive and Mesomeric Effects of the [60]Fulleropyrrolidine Fragment and [60]Fullerene Sphere: A Quantitative Evaluation Based on Theory and Experiments

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Inductive and mesomeric effects of the [60]fulleropyrrolidine (Pyr=C₆₀) and the [60]fullerene (C₆₀) molecular frameworks have been investigated by linear free energy relationship analyses. The electronic effects of these moieties have been studied by expressly designing [60]fulleropyrrolidine derivative **1**, which has a C–H bond α to both a carbonyl group (C– H_{α}) and a C₆₀ cage. The extent of polarization of such a bond was then used to probe electron-withdrawing perturbation induced by the fullerene sphere. Thermodynamic measurements based on both theoretical and experimental approaches allowed the acidity of ketone **1** to be measured; this resulted in about a 1×10^6 -fold increase in acidity with respect to that of the structurally correlated acetophenone. Experimental and theoretical kinetic determinations were used

Introduction

Fullerene derivatives have a number of attractive features that make them well suited for a variety of applications, ranging from new materials^[1] to nanomedicine.^[2] Monofunctionalized [60]fullerenes are easily obtained by reproducible synthetic procedures and are amenable to thorough physico-chemical characterization, particularly in view of their higher solubility in common solvents than that of pristine [60]fullerene (C₆₀). Functional fragments introduced onto the C₆₀ spheroid alter its properties and the induced perturbations have been studied and understood for a large number of substituents. However, the effects of the C₆₀ fragment on the physico-chemical properties of a molecular framework are less well known and no systematic study has

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to determine the stereolability of ketone **1**, which was, in fact, chiral due to the stereogenic carbon *a* to the carbonyl group. Also, these results confirmed the very strong tendency for the C₆₀ sphere to promote breaking of the C–H_{*a*} bond. This means that the Pyr=C₆₀ and C₆₀ fragments are able to express electron-withdrawing effects stronger than those of halogen atoms, but less effective than those of carbonyl derivatives (e.g., ketones, carboxylic acids or acyl derivatives). Finally, the $\sigma_{\rm pr}$, $\sigma_{\rm I}$ and $\sigma_{\rm R}^-$ descriptors of inductive and/or mesomeric effects were successfully estimated for both Pyr=C₆₀ and C₆₀ fragments thanks to the integrated use of an original procedure based on semi-empirical calculations and Hammett/Taft correlations involving mono- or dual-parameter equations.

been undertaken to characterize C₆₀ as a substituent. Generally, it is well known that the C_{60} sphere is able to express electron-withdrawing properties as both a fragment covalently linked to a suitable molecular derivative^[3] and as a guest involved in supramolecular systems.^[4] In particular, these effects were studied for the basic properties and nucleophilicity of a fulleropyrrolidine derivative,^[3] as well as for the acidity of a benzoic acid para-substituted with a cyclopropylfullerene, which allowed a σ_p value for the C₆₀ sphere to be assessed.^[3] However, although of significant importance, the quantitative evaluations reported were based on a C_{60} cage separated from the reaction site by more than a single σ bond; therefore, affording information that was probably not solely as a result of the pure C_{60} fragment. Herein, we focused our attention on the possibility of overcoming this limitation by resorting to a carefully designed model molecule that incorporated a C₆₀ sphere. We obtained the required information through an integrated experimental and theoretical approach.

Results and Discussion

In the first step of our study, we focused on the design of a [60]fullerene derivative endowed with structural properties

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suitable to allow effective and quantitative analyses of the electron-withdrawing ability of the C₆₀ sphere. As a fundamental requirement, it was ensured that a structure was present in the molecular framework able to act as a sensible probe of the fullerene effect. Electron-donating or -withdrawing effects of molecular moieties substituted for suitable species can be properly monitored through either kinetic or thermodynamic measurements (e.g., values of either rate constants of substitution/isomerization reactions or equilibrium constants of isomerization/acid-base reactions, respectively), providing that their relative position within the structure may directly affect the sensitivity of the reaction site by inductive and/or mesomeric perturbation. For this purpose, we considered it particularly attractive to correlate the electron-withdrawing properties of a fullerene sphere with the acid strength of a C–H bond α to a keto group and also in close proximity to the C₆₀ fragment. Taking into account the well-established, effective procedure available for the synthesis of fulleropyrrolidines through 1,3-dipolar cycloaddition,^[3,4] this molecular framework was the structural unit conceived to host the required keto group. Accordingly, compound 1 was the fullerene derivative designed for our purposes (Scheme 1).



Scheme 1. Compounds involved in the present study. TEG: triethylene glycol.

In this species the hydrogen α to the C=O group (H_a) is also α to the fullerene sphere. It is therefore intended that the extent of polarization of the C-H_a bond may act as a probe of the electron-withdrawing properties of C₆₀, which, in turn, should be reflected in the acidity of H_a. Thus, measurement of the acidity of compound **1** (i.e., the pK_a values in water or other solvents) compared with that of other suitably substituted ketones should afford the required information. In addition, an independent approach, capable of the stereogenic feature of the carbon atom α to the C=O group (C_{α}) , which renders 1 a chiral species, the stereochemical stability of which is directly linked to $C-H_{\alpha}$ acidity. In fact, proton abstraction from C_a would necessarily lead to a loss of the configuration of this centre, which could be inverted or restored by subsequent reprotonation. Within an established solvent and base catalyst, the rate constant governing this process (i.e., the enantiomerization rate constant of 1, k^{e}) will be strictly related to the acidity of H_{α} ^[5] and therefore, also to the electron-withdrawing properties of C_{60} . Thus, measuring k^e might also provide a decisive contribution toward achieving our goal. However, before starting the non-trivial synthesis of compound 1, we searched, by assessing acidity, for prior theoretical confirmation of the suitability of such a ketone to be an effective model in this study. Initially, we faced the problem of the unsuitability of common commercial or free computer software, such as the well-known packages ACD/pK_a ,^[6a] Marvin,^[6b] Mo- K_a ,^[6c] or the online computer program SPARC.^[6d] Indeed, these software estimate pK_a values on the basis of extensive experimental parameterization of the chemical/physical effects related to a large number of molecular moieties typically encountered within chemical organic species^[6e] (in ACD/p K_a , however, the p K_a estimation of carboxylic acids is not available). Unfortunately, the C_{60} sphere was not among the parameterized groups. For this reason, we were forced to perform the pK_a estimation by elaborating an empirical approach specifically for monoketones and based on multi-parameter Equation (1) containing density charge values (δ_i) as molecular descriptors of acidity, which are very effective for this purpose.^[5a,5b,7]

yielding the same kind of information, might be based on

$$pK_a = \Sigma C_i \delta_i + C_0 \tag{1}$$

The δ_i values were calculated by a semi-empirical procedure (Hamiltonian AM1) on both the H_a and oxygen atoms of the neutral ketone form and the oxygen atom of the enolate ion of the monoketones used as empirical references (see Scheme 2), the acidity values of which in water (p K_a) were available from the literature (see Table S1 in the Supporting Information).



Scheme 2. Multi-parameter equation and molecular descriptors used within the theoretical estimation of pK_a values of monocarbonyl ketones.

On the basis of statistical analysis, the 3 descriptors in Equation (1) were selected from a set of 14 candidates (see the Supporting Information), whereas parameters C_0 and C_i were optimized by linear regression analysis of a set of equations related to 42 (n = 42) p K_a data points (Table S1

and Scheme S1 in the Supporting Information). The final statistical significance of each δ_i descriptor was checked by a T test. The exclusion of randomness of the obtained results was checked by an F test. After such an analysis (for more details, see the Exp. Section), we obtained Equation (2).

$$pK_{a} = -148.133\delta_{H\alpha} - 28.7157\delta_{O1} - 21.8184\delta_{O2} + 13.3510$$
(2)

with n = 42, $R^2 = 0.950$, and standard deviation (SD) = 0.9. All three employed descriptors were highly significant and any reasonable possibility of casualness was excluded $(F = 7 \times 10^{-26})$. By inserting the density charge values δ_{Hg} , δ_{O1} and δ_{O2} calculated on the sensitive H_a, O₁, and O₂ atoms within the optimized structure of 1 (see Scheme 2) into Equation (2), we obtained a p K_a value of 11.9 ± 0.9 for this fullero ketone. A first rough comparison between this result and the typical acidity expressed by simple alkyl ketones, in particular, by the more strictly correlated acetophenone (Scheme 1 and Table 1), suggests an impressive ability of the fulleropyrrolidine molecular framework to promote $C-H_{\alpha}$ bond polarization, which, for example, would lead to an ionization equilibrium constant about 1×10^{6} -fold higher than that of acetophenone.

Table 1. Co-logarithms/logarithms of the ionization constants (K_a) and second-order enolization rate constants promoted by $OH^{-}(k^{t})$ of the carbonyl derivatives in water analyzed in this study.

	pKa	$logk^{[e]}$		pK _a	$logk^{[e]}$		pK _a	logk
	10.1 ^[a]	3.07 ^[i]	8	13.3 ^[f]	1.91 ^[f]	15	_	2.11 ^[g]
1	10.1 ^[b]	4.36 ^[j]						
	11.9 ^[c]							
2	17.1 ^[c]	$-0.41^{[k]}$	9	14.8 ^[g]	0.55 ^[g]	16	21.0 ^[g]	-2.65 ^[g]
	17.7 ^[d]							
3	11.3 ^[e]	3.20 ^[e]	10	8.9 ^[g]	4.30 ^[g]	17	8.9 ^[g]	3.24 ^[f]
4	18.3 ^[f]	$-1.08^{[f]}$	11	5.1 ^[h]	8.09 ^[1]	18	5.2 ^[h]	7.51 ^[h]
5	19.3 ^[f]	$-1.14^{[f]}$	12	19.0 ^[g]	$-1.72^{[g]}$	19	12.7 ^[g]	2.03 ^[g]
6	20.5 ^[g]	-1.72 ^[g]	13	10.7 ^[g]	3.53 ^[g]	20	7.0 ^[g]	-
7	15.9 ^[f]	0.20 ^[f]	14	25.0	_	21	11.0 ^[g]	_

[a] Obtained by titration in the presence of cetyltrimethylammonium bromide (CTAB). [b] Obtained by titration in the presence of Triton X-100 (TX-100). [c] Assessed by Equation (3). [d] Assessed by Marvin software.^[5b] [e] From ref.^[5a] [f] From ref.^[5b] [g] From ref.^[8] [h] From ref.^[7a] [i] Assessed by Equation (3) with $pK_a = 10$. [j] Assessed by Equation (3) with $pK_a = 12$. [k] Assessed by Equation (3) with $pK_a = 17.4$. [1] Assessed by the difference between the $\log k^t$ values from compounds 6 and 18 and the sum with $\log k^t$ of 5.

To gain a more direct indication of the effect of only the C_{60} sphere, we estimated the pK_a value of ketone 2 [Scheme 1, $pK_a = 17.1$ and 17.7 from Equation (2) and Marvin software, respectively; average $pK_a = 17.4$], the structure of which corresponds to that of 1 without the C_{60} moiety. Inspection of Table 1, shows that $\Delta p K_a$ between ketones 1 and 2 amounts to about 6 units, that is, an acidity gap larger than that produced by monochlorine or phenyl substitution on acetone, but also very similar to that of monobromination of the same reference ketone. Therefore, these theoretical findings confirmed the suitability of compound 1 to act as an effective model for our purposes and induced us to carry out its synthesis. Fulleropyrrolidine 1



was isolated in 38% yield through the cycloaddition of [60] fullerene with the azomethine ylide formed when Nmethylglycine and phenylglyoxal were heated to reflux in chlorobenzene for 2 h. HPLC analysis was employed to assess the purity of 1 (Figure S1 in the Supporting Information), whereas NMR spectroscopy (Figures S2 and S3 in the Supporting Information) and mass spectrometry (Figure S4 in the Supporting Information) were used to validate the proposed molecular structure. Further details are reported in the Exp. Section.

To achieve preliminary experimental evidence of the ability of C_{60} to promote polarization of the C-H_a bond in 1, we studied the tendency of this ketone to enantiomerize. In fact, for the monoketones, there was a clear linear relationship between enolization rate constant (k^{t}) and the acidity of the C–H_{α} moiety.^[5a] Thus, due to the stereogenic nature of the C_{α} atom in 1, the propensity of this ketone to enolize will also give a direct measure of its stereolability, according to the relationship that exists between enantiomerization and enolization rate constants: $k^{t} = 2k^{e}$.^[5a,9,10] For this purpose, the kinetic determination of the enantiomerization rate constant of 1 was performed by monitoring the racemization process of the pure enantiomers [enantiomeric excess (ee) values greater than 99.8%], previously separated by enantioselective HPLC at the semi-preparative level using a bonded polysaccharide-based stationary phase in a thermostatted reactor (Figure 1). Stereoisomerization was performed at 50 °C with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the basic catalyst employed at different concentrations in three different media: pure chloroform, mix1 = hexane/2-propanol 90:10 (v/v) and mix2 = hexane/2-propanol/chloroform 85:10:5 (v/v/v).

The progress of the racemization process was monitored by resolving the enantiomers of 1 through enantioselective HPLC and then integrating the areas of the relevant peaks. Measurements of pseudo-first-order enantiomerization rate constants ${}^{1}k^{e}$ were then carried out by fitting a plot of *ee* values as a function of time through the equation $\ln(ee)$ $= (-2^{1}k^{e})t$. Eventually, second-order enantiomerization rate constants, k^{e} , were obtained from the slope of linear plots of ${}^{1}k^{e}$ versus [DBU]. The obtained results, given in Table 2, clearly indicated the sensitivity of 1 to changes in configuration under quite mild conditions; this would be expected for strongly activated polarization of the $C-H_{\alpha}$ bond.

For comparison, the enolization rate constant of 1 in mix1 was only twofold smaller than that calculated under the same solvent and temperature conditions for ketone 3, shown in Scheme 1, the acidity of which in water was reported to be 11.3 p K_a units.^[5a] Therefore, this finding shows the reliability, within an estimated error of 1 pK_a unit, of the obtained pK_a value of 11.9. Nevertheless, we considered it essential to confirm further this value through experimental pK_a determination. To perform this measurement, we faced the non-trivial problem of the scant solubility of pristine and mono-substituted fullerenes in water. It is well known that strong hydrophobic interactions drive the fullerene cages to form colloidal clusters in different hydrophilic media.^[12] However, the water solubility of pristine



Figure 1. (a) Enantioselective HPLC traces of enantiomers a and b of compound 1 detected by UV (top left) and circular dichroism (CD; top right); analytical control of the purified enantiomers (traces revealed by UV detector on middle and bottom left; online CD spectra of the first and second eluted enantiomers on middle right). (b) Racemization trend in solvent mix1. (c) Racemization trend in solvent mix2. For the analytical conditions used, see the Exp. Sect.

Table 2. Second-order enantiomerization rate constants of ketones 1 and 3 in organic media at 50 °C.

	Solvent	Basic catalyst	$\log k^{\rm e}$
1	mix1	DBU	-2.83
1	mix2	DBU	-2.98
1	CHCl ₃	DBU	-3.34
3	mix1	DMA	$-2.49^{[a]}$

[a] Extrapolated to 50 °C by a straight line regression ($R^2 = 0.983$) from four relevant kinetic data at temperatures of 30, 35, 40, 45 °C (ref.^[11]).

[60]fullerene,^[13] higher fullerenes^[14] and some fullerene derivatives^[15] has been successfully promoted by the addition of surfactants, such as TX-100, BrIJ 35, sodium dodecyl sulfate (SDS) and cetyltrimethylammonium chloride. In the micellar system, the hydrophobic fullerene cage is expected to be incorporated in the micellar core, while the polar groups are located close to the aqueous phase. In this system, the formation of clusters is prevented and ensures the dissolution of fullerene monomers.^[15]

It has recently been demonstrated that the proton transfer reaction takes place within an enolate-water cluster in the head polar region of the micelle, where the reacting partners actually experience environmental conditions, for example, micropolarity effects, very similar to those of bulk water.^[16,17] These characteristics enable us to consider the micellar environments described as suitable for our intents. In fact, the solubility of 1 in an aqueous micellar solution of CTAB or TX-100 allowed us to study its acid properties in water. Consequently, the acid dissociation constant, $K_{\rm a}$, was measured potentiometrically by titrating 1 with standardized NaOH. The obtained pK_a values were 10.06 ± 0.03 and 10.1 ± 0.5 in the presence of CTAB and TX-100, respectively (both values are averages of two determinations). These figures are impressive because they suggest an acidity for 1 even stronger than that assessed by calculation. However, the effect produced by the micelles on the ionization reaction has to be taken into account and some considerations deserve to be highlighted.

Previous studies on the keto-enol interconversion of some heterocyclic ketones have demonstrated that the apparent acidities of enols and ketones increase on passing from water to surfactant solutions.[18-20] As a relevant example, the $\Delta p K_a$ ($p K_a^{water} - p K_a^{micellar solution}$) of 2-phenylacetylfuran is 2.3 in the presence of the cationic CTAB.^[19] The increase of acidity upon micellization has been explained in terms of electrostatic interaction between the enolate and the CTAB micelle in which the enolate is stabilized. However, an acidity increase has also been observed in the presence of a neutral zwitterionic surfactant ($\Delta p K_a =$ 1.1).^[19] These results suggest that other effects must also play a role in the observed increase of acidity upon micellization and that thermodynamic data of ionization achieved through such an approach should be considered as the lower limit of a pK_a range that might extend its extremes up to about 1 or 2.3 p K_a units, depending on the nature of the surfactant and the structure of the analyzed substrate. Then, it seemed reasonable to assume that the experimental acidity of ketone 1 lay between the pK_a values 10.1 and 12.4 from the determination with CTAB and between 10.1 and 11.2 from the determination with Triton; these values were in good agreement, by associated determination errors, with experimental results and theoretical estimations. From the largest and smallest possible values of acidity of 1 (i.e., the extreme pK_a values of 10 and 12), the relevant enolization rate constants, k^{t} , in water for the process catalyzed by the OH⁻ ions at 25 °C may be estimated through Equation (3), which was reported within ref.^[5a] in which p is the number of acidic hydrogen atoms considered for statistical correction.

$$\log(k^{\rm e}/p) = 0.6434 \log(K_{\rm a}/p) + 10.79$$
(3)

The data obtained, reported in Table 3, can then be compared with the enolization kinetic data related to several other ketones mono- or disubstituted at the C_{α} atom with different functional groups. To dissect the contribution of the elected substituents from all of the possible contributions affecting k', we considered the differences given by Equation (4) in which *i* refers to the generic i^{th} group ranked in Table 3, whereas ref. refers to the relevant ketone with hydrogen instead of the *i* group.

$$\Delta \log(k^{t}) = \log(k^{t})_{i} - \log(k^{t})_{\text{ref.}}$$
(4)

Table 3. Kinetic data used in the Hammett and Taft correlations [Equations (5) and (7)] of linear free energy relationship (LFER) values and an estimation of σ_p values.

Group	C ^[a] (ref.)	<i>P</i> _e ^[b]	σ_{I}	$\sigma_{ m R}^{-}$	$\sigma_{\rm p}$	$\sigma_{\rm m}$	$\sigma_{\rm p}$ ^[c]	$P_{\rm c}$ ^[d]
Н	5 (5)	0.00	0	0	0	0	-0.09	0.21
CH ₃	6 (5)	-0.58	-0.04	-0.11	-0.17	-0.07	-0.15	-0.82
Ph	(5) 7 (5)	1.34	0.1	0.04	-0.01	0.06	0.04	1.25
Br	(5) 8 (5)	3.05	0.5	-0.19	0.23	0.39	0.21	2.81
Cl	(5) 9 (5)	1.69	0.47	-0.23	0.23	0.37	0.07	2.32
COCH ₃	(5) 10 (5)	5.44	0.28	0.47	0.5	0.38	0.44	5.48
NO ₂	(5) 11 (6)	9.23	0.76	0.47	0.78	0.71	0.81	9.18
OCH ₃	(0) 12 (5)	-0.58	0.27	-0.45	-0.27	0.12	-0.15	-0.68
COOEt	(3) 13 (5)	4.67	0.3	0.34	0.45	0.37	0.36	4.77
SO_3^-	(5) 15 (5)	3.25			0.09	0.05	0.23	
CH_3	(5) 16 (5)	-1.51	-0.08	-0.22	-0.34	-0.14	-0.24	-1.86
Cl	(5) 17 (5)	4.38	0.94	-0.46	0.46	0.74	0.34	4.42
CH ₃	(5) 18 (5)	8.65	0.72	0.36	0.61	0.64	0.75	8.14
CH ₃	(5) 19 (5)	3.17	0.26	0.23	0.28	0.02	0.22	3.74
C ₆₀	(3) 1 (2)	3.48 4.77	0.40	0.03 ^[e] 0.22 ^[e]			0.25 0.37	3.16 ^[f] 4.46 ^[f]
Pyr=C ₆₀	1 (4)	4.15 5.44	0.47	0.05 ^[e] 0.24 ^[e]			0.31 0.44	3.74 ^[f] 5.04 ^[f]
Pyr	2 (4)	0.67	0.03	0.04 ^[e]			-0.03	0.53 ^[f]

[a] C: carbonyl derivative; ref.: carbonyl derivative used as the reference. [b] $P_{\rm e}$: experimental $\log(k^{\rm e}_{\rm C}/k^{\rm e}_{\rm ref})$. [c] $\sigma_{\rm p}$ parameter calculated from Equation (5). [d] $P_{\rm c}$: $\log(k^{\rm e}_{\rm C}/k^{\rm e}_{\rm ref})$ calculated from Equation (7). [e] Values that minimize the difference between experimental and calculated $\Delta \log(k^{\rm t})$. [f] Values calculated by inserting the $\sigma_{\rm R}^{-}$ data averaged from those obtained by kinetic (Table 3) and thermodynamic Taft correlations into Equation (7) (see below in Table 5).

In order to remove the contribution of the C₆₀ sphere from that expressed by the whole fullero-pyrrolidine framework, the enolization rate constant of ketone **2** was assessed by Equation (3), using average $pK_a = 17.4$ estimated by both Equation (1) and Marvin software (see above) for this purpose.

Inspection of Table 3 shows that the C_{60} cage demonstrates an electron-withdrawing effect stronger than that related to halogen atoms (chlorine and bromine) and groups such as phenyl or $-SO_3^-$. Additionally, the C_{60} cage has a



weaker electron-withdrawing effect than moieties involving carbonyl as the framework directly linked to the C_{α} atom (i.e., -COCH₃ or -COOEt). The same conclusions may also be stated when considering the fulleropyrrolidine framework as a whole substituting group, with the only difference being a more marked effect. This evidence leads to possible reconsideration of the small electron-withdrawing ability attributed to the C₆₀ sphere in the research work reported in ref.^[3a] and quantified as the σ_p Hammett parameter (σ_p = 0.06). In such a study, in fact, the fullerene cage incorporated into the chemical species used for the evaluation (i.e., compound 22 of Scheme 1) is linked to the *para* position of a benzoic acid through a carbon bridge, so that its effect in the ionization process of the benzoic acid should be more properly referred to as the cyclopropylfullerene molecular framework (hereafter symbolized as C<C₆₀). Thus, the small $\sigma_{\rm p}$ value measured for this composite moiety might be explained by the well-known strong dependence that relates inductive effects to the number of sigma bonds separating the group from the reaction site or from a site directly conjugated to the centre of reaction (in this case, two σ bonds between the *para* position of the benzoic acid and the C_{60} sphere). In addition, it has also to be stressed that the electron-withdrawing effect expressed by $\sigma_{\rm p}$ is inclusive of both inductive and resonance factors and that the latter could play a non-negligible part in the process, even in opposition to inductive perturbation. Therefore, we determined if it would be possible to assess a σ_p value at the C₆₀ cage starting from the kinetic datum of stereolability achieved for the fulleroketone 1, which features a direct link from the C_{60} group to the reaction site (only a σ bond between C_a and C_{60}). For this purpose, we plotted $\Delta \log(k^t)$ values related to 10 mono- and 4 disubstituted ketones against the relevant $\sigma_{\rm p}$ values available in the literature (see Table 3).^[21] Linear correlation analysis afforded quite good agreement among the data, with an R^2 coefficient of 0.911, see Equation (5).

$$\sigma_{\rm p} = 0.0978 \Delta \log(k^{\rm t}) - 0.0918 \tag{5}$$

When analysis was attempted with $\sigma_{\rm m}$ instead of the $\sigma_{\rm p}$ parameters, the regression afforded a correlation of unacceptable quality ($R^2 = 0.689$), indicating that resonance contributions were involved in the enolization process of the ketones analyzed during enolate formation. Equation (5) was then used to estimate the σ_p values of all functional groups employed within the relevant correlation, as well as those of [60]fulleropyrrolidine (Pyr=C₆₀, $\sigma_p = 0.31-0.44$), pyrrolidine (Pyr, $\sigma_p = -0.03$) and [60]fullerene (C₆₀, $\sigma_p =$ 0.25-0.37) molecular frameworks (Table 3). The standard error was 0.1 σ_p units. Thus, by comparison of the [60]fullerene effect with that reported for the framework $C < C_{60}^{[3]}$ it was possible to evaluate the reduction of electron-withdrawing ability triggered by insertion of a sigma bond between C₆₀ and the reaction site (about 0.2–0.3 σ_p units). Intrigued by the good findings achieved through the use of the descriptor $\sigma_{\rm p}$, but not $\sigma_{\rm m}$, we were encouraged to verify if it was possible to separate pure inductive effects from those of resonance. Therefore, we repeated the correlation

analysis that led to straight line 5 by resorting to following dual-parameter Equation (6) of the type proposed by Taft.^[22]

$$\Delta \log(k^{t}) = p_1 \sigma_{\rm I} + p_2 \sigma_{\rm R}^{-} + p_3 \tag{6}$$

This equation can take into account both inductive and mesomeric effects through the use of the two distinct descriptors $\sigma_{\rm I}$ and $\sigma_{\rm R}^-$, respectively, and modulate their effect by means of the calculable regression coefficients p_1 and p_2 , respectively; p_3 is a constant term also determined by the regression. By excluding the SO₃⁻ group from the analysis (due to the unavailability of the relevant $\sigma_{\rm R}^-$ value), the regression afforded a very good correlation [Equation (7)] with $R^2 = 0.991$ and a standard error of 0.34 $\Delta \log(k^t)$ units (Figure 2). Thus, Equation (7) might be a useful tool for testing inductive and resonance effects of C₆₀ or other groups, providing at least one σ value (either $\sigma_{\rm I}$ or $\sigma_{\rm R}^-$) is available independently.

$$\Delta \log(k^{\rm t}) = 7.713\sigma_{\rm I} + 6.606\sigma_{\rm R}^{-} + 0.2111 \tag{7}$$



Figure 2. Taft correlations (diamond data points) performed by using kinetic (a) and thermodynamic data (b) on the carbonyl compounds reported in Tables 3 and 5, respectively. Square and triangle points: estimation of $\Delta \log(k^t)$ and $\Delta p K_a$ values for the C_{60} and $Pyr=C_{60}$ fragments, respectively, starting from the average σ_R^- (these data refer to the findings obtained by considering the acidity of 1 as an average of the extremes of the range 10–12 considered in the text, i.e., $pK_a = 11$).

Recently some of us reported a very simple theoretical procedure, based on semi-empirical calculations, suitable for characterizing the ability of a molecular framework to exercise electron-withdrawing or -donating effects through the quantity EE_X (EE_X = electron-withdrawing effect; X distinguishes the functional group).^[5a] In such an approach, the charge density on a hydrogen atom of a methane molecule $(\delta_{\rm H}^{\rm CH_4})$ is used as the reference to perform a comparison with the equivalent quantity calculated when a gemhydrogen is substituted with a selected X functional group $(\delta_{\rm H}{}^{\rm X})$. In the absence of direct conjugation between the X group and the reaction site, EE_X should essentially monitor purely inductive effects. We evaluated the $EE_{ref,X}$ quantities for nine functional groups, the σ_{I} values of which were homogeneously distributed over a rather wide range from the weakly electron-donating methyl moiety to the strongly electron-withdrawing nitro group. The substitution was related to the structure of three reference molecules: (i) methane (R_{1H}) ; (ii) N-methylpyrrolidine (R_{2H}) and (iii) Nmethyl-[60]fullero-pyrrolidine (R_{3H} ; see Scheme 3).

rotation around C–X bond: 0–360°	$\stackrel{\text{the}}{\stackrel{\text{H}}{\longrightarrow}} \stackrel{\text{X}}{\stackrel{\text{H}}{\longrightarrow}} \stackrel{\text{H}}{\stackrel{\text{R}}{\longrightarrow}} \stackrel{\text{R}}{\stackrel{\text{R}}{\longrightarrow}} \stackrel{\text{R}}{\rightarrow} \stackrel{\text{R}}\rightarrow} \stackrel{\text{R}}{\rightarrow} \stackrel{\text{R}}{\rightarrow} \stackrel{\text{R}}\rightarrow} \stackrel{\text{R}}{\rightarrow} \stackrel{\text{R}}\rightarrow} R$	 ^N [×] δH ^{P2}	x C ₆₀ δH ^{R_{3x}}
X	compound	compound	compound
н	R _{1H}	R _{2H}	R _{3H}
CH3	R _{1X1}	R _{2X1}	R _{3X1}
$-N^{CH_3}_{CH_3}$	R _{1X2}	R _{2X2}	R _{3X2}
Ph	R _{1X3}	R _{2X3}	R _{3X3}
−c´́O	R _{1X4}	R _{2X4}	R _{3X4}
	R _{1X5}	R _{2X5}	R _{3X5}
CI	R _{1X6}	R _{2X6}	R _{3X6}
Br	R _{1X7}	R _{2X7}	R _{3X7}
CN	R _{1X8}	R _{2X8}	R _{3X8}
NO ₂	R _{1X9}	R _{2X9}	R _{3X9}

Scheme 3. Structures used to assess σ_1 values through EE_X versus σ_1 correlations.

Therefore, according to the procedure described in detail in the Exp. Section, 27 estimations of EE_X were performed for 3 classes of compounds, each of which derived from the basic structures of R_{1H} (ensemble R_{1X}), R_{2H} (ensemble R_{2X}) and R_{3H} (ensemble R_{3X}), respectively. It was found that σ_I and EE_X values from the ensembles of compounds R_{1X} (i.e., EE_{1X}), R_{2X} (i.e., EE_{2X}) and R_{3X} (i.e., EE_{3X}) correlated in a satisfactory way, according to Equations (8), (9) and (10).

$$\sigma_{\rm I} = 11.632 \,{\rm EE}_{1\rm X} - 0.0328 \,(R^2 = 0.926; \,{\rm SD} = 0.08, \, n = 9) \tag{8}$$

$$\sigma_{\rm I} = 11.872 \,{\rm EE}_{2\rm X} - 0.0625 \,(R^2 = 0.943; \,{\rm SD} = 0.07, \, n = 9) \tag{9}$$

$$\sigma_{\rm I} = 14.506 \,{\rm EE}_{3\rm X} - 0.0658 \,(R^2 = 0.946; \,{\rm SD} = 0.07, \, n = 9) \tag{10}$$

Consequently, the σ_{I} values associated with the pyrrolidine, fulleropyrrolidine and C₆₀ molecular frameworks have been assessed and are collected in Table 4 by inserting the following EE_x charge differences into Equation (8): EE_{Pyr=C60} = $\delta_{H}^{R_{3H}} - \delta_{H}^{R_{1H}}$; EE_{Pyr} = $\delta_{H}^{R_{2H}} - \delta_{H}^{R_{1H}}$; EE_{C60} = $\delta_{H}^{R_{3H}} - \delta_{H}^{R_{2H}}$.

Table 4. EE_x data employed within the correlations expressed by Equations (8), (9) and (10) and estimation of σ_{I} parameters by Equation (8).

X	EE _{R1X}	EE _{R21X}	EE _{R3X}	$\sigma_{\mathrm{I}}^{\mathrm{[a]}}$	$\sigma_{\rm I}^{\rm [b]}$
CH ₃	0.005	-0.006	-0.002	-0.04	-0.02
Н	0.000	0.000	0.000	0.00	0.00
$N(CH_3)_2$	0.004	-0.010	-0.010	0.06	-0.08
Ph	0.017	0.006	0.004	0.10	0.11
COCH ₃	0.036	0.023	0.018	0.29	0.34
Ι	0.042	0.034	0.025	0.39	0.45
Cl	0.032	0.033	0.026	0.47	0.41
Br	0.042	0.036	0.029	0.50	0.48
CN	0.044	0.032	0.029	0.53	0.47
NO_2	0.069	0.057	0.047	0.76	0.77
Pyr	0.006				0.04
$Pyr=C_{60}$	0.043				0.47
C ₆₀	0.037				0.40

[a] $\sigma_{\rm I}$ values given in ref.^[23]. [b] $\sigma_{\rm I}$ values calculated with Equation (8).

By inspecting the values given in Table 4, some important conclusions may be derived. As far as the inductive effect is concerned, the calculated σ_{I} values qualify both C₆₀ and $Pyr=C_{60}$ as among the strongest electron-withdrawing moieties considered in this study, with effects very close to those associated with halogen atoms and the cyano group and not too far from that of the alkylsulfonate group ($\sigma_{\rm I}$ = 0.59). As expected, the Pyr molecular framework is among the less active ones, very close to the properties of the structural analogue $-N(CH_3)_2$, with which it has a strong structural analogy. With the $\sigma_{\rm I}$ values in hand, we were now able to assess the $\sigma_{\rm R}^-$ parameters relevant to the Pyr=C₆₀, Pyr and C_{60} moieties by inserting their calculated σ_{I} values into Equation (7) and solving it with respect to the unknown term. The achieved values, reported in Table 3, indicated marginal resonance effects or C₆₀; therefore, it seems reasonable to infer that the estimated $\sigma_{\rm P}$ parameter should also include minimal resonance contributions. All of the obtained findings were confirmed by repeating the Taft analysis on K_a data, according to the Equations (11) and (12).

$$\Delta p K_a = (p K_a)_i - (p K_a)_{\text{ref.}}$$
⁽¹¹⁾

$$\Delta p K_a = v_1 \sigma_I + v_2 \sigma_R^- + v_3 \tag{12}$$

The substrates selected for analysis (see Table 5) were many of the mono- and disubstituted monocarbonyl compounds already considered within the kinetic study that led to Equation (7) and for which experimental data for acidity in water were available in the literature. Also, in this case, regression analysis afforded a good correlation coefficient $[R^2 = 0.960$, Figure 2 and Equation (13)], with the statistical



analysis indicating a great significance of the descriptors $\sigma_{\rm I}$ and $\sigma_{\rm R}^-$ and a reasonable absence of casualness in the obtained results.

$$\Delta p K_{\rm a} = 13.7925 \sigma_{\rm I} + 10.2149 \sigma_{\rm R}^{-} + 0.59009 \tag{13}$$

Table 5. Thermodynamic data used in the LFER-type Taft correlation [Equation (13)].

Group	D [a] (ref.)	<i>P</i> _e ^[b]	σ_{I}	$\sigma_{ m R}^-$	$P_{\rm c}$ ^[c]
Н	5	0.00	0	0	0.59
CH ₃	(5) 6	-1.3	-0.04	-0.11	-1.09
Ph	(5) 7	3.36	0.1	0.04	2.38
Br	(5) 8	6.00	0.5	-0.19	5.55
Cl	(5) 9	4.44	0.47	-0.23	4.72
COCH ₃	(5) 10	10.4	0.28	0.47	9.25
NO_2	(5) 11	14.17	0.76	0.47	15.87
OCH ₃	(6) 12	0.23	0.27	-0.45	-0.28
CO- OEt	(5) 13	8.6	0.3	0.34	8.20
NH ₂	(5) 14	-5.8	0.12	-0.48	-2.66
CH_3	(5) 16 (5)	-1.7	-0.08	-0.22	-2.76
CH ₃ Cl	(5) 17 (5)	10.4	0.92	-0.46	8.58
CI CH ₃	(5) 18	14.1	0.72	0.36	14.20
CH ₃	(5) 19 (5)	6.6	0.26	0.23	6.53
OEt	(5)	12.2	0.72	0.28	12.29
Br	(5)	12.5	0.72	0.26	15.56
COCH ₃ CH ₃	21 (5)	8.27	0.24	0.36	/.58
C ₆₀	1 (2)	5.40 7.40	0.40	$-0.07^{[d]}$ $0.13^{[d]}$	5.89 ^[e] 7.91 ^[e]
Pyr=C ₆₀	1 (4)	6.30 8.30	0.47	$-0.08^{[d]}$ $0.12^{[d]}$	6.93 ^[e] 8.93 ^[e]
Pyr	2 (4)	0.90	0.03	$-0.01^{[d]}$	1.13 ^[e]

[a] D: carbonyl derivative; ref.: carbonyl derivative used as the reference. [b] P_c : experimental $-\log(K_a{}^{D}/K_a{}^{ref.})$. [c] P_c : $-\log(K_a{}^{D}/K_a{}^{ref.})$ calculated by using Equation (13). [d] Values that minimize the difference between experimental and calculated $\Delta p K_a$. [e] Values calculated by inserting σ_R^- data averaged from those obtained by kinetic (Table 3) and thermodynamic (Table 5) Taft correlations into Equation (13).

Note, the quality of the correlation increases to $R^2 = 0.977$ if the datum related to the $-NH_2$ group (which is characterized by a relatively high uncertainty) is excluded from the regression.

When the values of $\sigma_{\rm I}$ and $\sigma_{\rm R}^-$ assessed for Pyr=C₆₀ and C₆₀ by kinetic analysis were inserted into Equation (13), the relevant calculated values of $\Delta p K_{\rm a}$ resulted in good agreement with experimental values, within an error less, in the worst case, than 20% for Pyr=C₆₀ and 19% for C₆₀. This

clearly indicates good reliability of the assessed σ_{I} and σ_{R}^{-} parameters, especially those related to the purely inductive effects. As a refinement, by inserting only the σ_{I} data into Equation (13), for both Pyr=C₆₀ and C₆₀, we recalculated the relevant σ_{R}^{-} values as those that minimized ΔpK_{a} . Eventually, the averaged σ_{R}^{-} values from the kinetic and thermodynamic Taft analyses were also included in Equations (7) and (13) and the new estimations of $\Delta \log(k^{t})$ and ΔpK_{a} were compared with those of related experimental data. The final errors were equal to or less than 10% for Pyr=C₆₀ and 9% for C₆₀ from both the kinetic and thermodynamic data (Table 6).

Table 6. Estimation of $\sigma_{\rm R}^{-1}$	parameters from Equations	(7) and (13).
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	σ_{I}	$\sigma_{ m R}^{-[a]}$	$\% E^{[b]}$	$\sigma_{\rm R}^{-[c]}$	$\% E^{[d]}$	$\sigma_{\rm R}^{-[e]}$	$\% E^{[f]}$	%E ^[g]
C ₆₀	0.40	0.028	-18	-0.070	19	-0.021	9	_9
		0.223	-13	0.130	13	0.177	6	-7
Pyr=C ₆₀	0.47	0.047	-20	-0.075	19	-0.014	10	-10
		0.243	-15	0.120	15	0.182	7	8
Pyr	0.03	0.035	-51	-0.010	44	0.013	22	-26

[a] Assessed by re-solving Equation (7) with $\sigma_{\rm I}$ values reported in Table 4. [b] Errors associated with the $\log(k^{\rm e}_{\rm D}/k^{\rm e}_{\rm ref})$ quantities calculated by using the $\sigma_{\rm R}^{-}$ values in Equation (7). [c] Assessed by resolving Equation (13) with $\sigma_{\rm I}$ values reported in Table 4. [d] Errors associated with the $\log(K_{\rm a}^{\rm D}/K_{\rm a}^{\rm ref.})$ quantities calculated by using the $\sigma_{\rm R}^{-}$ values in Equation (13). [e] Average of the $\sigma_{\rm R}^{-[a]}$ and $\sigma_{\rm R}^{-[c]}$ values reported in Table 6. [f] Errors associated with the $\log(k^{\rm e}_{\rm D}/k^{\rm e}_{\rm ref.})$ quantities calculated by using the $\sigma_{\rm R}^{-}$ values in Equation (7). [g] Errors associated with the $\log(K_{\rm a}^{\rm D}/K_{\rm a}^{\rm ref.})$ quantities calculated by using the $\sigma_{\rm R}^{-}$ values in Equation (7).

Conclusions

Derivative 1 was employed as a suitable model to perform a quantitative estimation of the inductive and mesomeric effects of the C60 cage and the composite fulleropyrrolidine molecular framework Pyr=C₆₀. An original theoretical approach was specifically used to address the estimation of the pK_a value of 1 for which commercial software cannot be employed, due to the absence of a suitable parameter for the fullerene fragment. A significant increase of acidity, with respect to the unsubstituted analogue, was theoretically assessed and, next, confirmed by experimental determination of the aqueous pK_a value in the presence of suitable surfactants. The effective electron-withdrawing effects of the C₆₀ sphere were also evidenced by kinetic measurements of second-order enantiomerization rate constants of 1. Through LFER analyses and dedicated semi-empirical calculations such properties were successfully rationalized by a reliable assessment of Hammett (σ_p) and Taft (σ_I and $\sigma_{\rm R}$) parameters for the molecular frameworks Pyr=C₆₀ and C_{60} . We believe that the obtained results may actively contribute towards more in-depth knowledge of the properties of [60]fullerene derivatives, especially with respect to their perspective applications in the field of electronic devices.

Experimental Section

General: Phenylglyoxal, *N*-methylglycine and all solvents were purchased from Aldrich and used as received. [60]Fullerene was purchased from Bucky USA (99%). The reaction to prepare fulleropyrrolidine 1 was monitored by TLC using Merck pre-coated silica gel 60- F_{254} . NMR spectra were recorded in CDCl₃ on a Bruker AC 250 spectrometer at room temperature. Chemical shifts are given in parts per million (δ) relative to tetramethylsilane. UV/Vis spectra were recorded on a Perkin–Elmer Lambda 45 spectrophotometer. FTIR characterization was carried out on a Nicolet 5700 FTIR spectrophotometer. ESI-MS spectra were recorded with a MSD SL Trap mass spectrometer (Agilent Technologies): derivative 1 was dissolved in methanol in the presence of 0.1% (v/v) formic acid. HPLC analyses were performed on a Shimadzu LC10 ADVP binary pump system equipped with a Jasco 875 detector at 340 nm. Derivative 1 was eluted on a Nacalai Tesque Cosmosyl Buckyprep analytical column (250×4.6 mm, eluent: toluene, flow: 1 mLmin⁻¹, retention time for 1: 5.01 min).

Synthesis of Fulleropyrrolidine 1: [60]Fullerene (150 mg, 0.21 mmol), N-methylglycine (64 mg, 0.72 mmol) and phenylglyoxal (150 mg, 1.12 mmol) were dissolved in chlorobenzene (50 mL) and brought to reflux temperature. The reaction was monitored by TLC [SiO₂, toluene, $R_f(1) = 0.4$] and stopped just after the formation of traces of multiple adducts to [60]fullerene detectable by TLC with a lower retention factor than that of the pyrrolidine monoadduct. The crude mixture, loaded on top of a SiO₂ flash column chromatography, was eluted with toluene to remove unreacted [60] fullerene and then the product was isolated. The fractions containing fulleropyrrolidine 1 were concentrated at reduced pressure to a small volume and transferred to a centrifuge tube. The product was precipitated from acetonitrile, washed twice with the same solvent and dried under reduced pressure to give 1 as a brownish powder (71 mg, 38%). ¹H NMR (250 MHz, CDCl₃, 25 °C): δ = 2.9 (s, 3 H), 4.3 (d, 1 H), 5.0 (d, 1 H), 5.6 (s, 1 H), 7.4–7.6 (m, 5 H) ppm. ¹³C NMR (62.9 MHz, CDCl₃/CS₂, 25 °C): δ = 40.0, 69.2, 70.1, 73.8, 81.6, 128.3, 128.8, 129.0, 129.7, 133.9, 135.5 136.0, 136.7, 137.1, 139.4, 139.5, 140.3, 140.4, 141.6, 141.7, 141.8, 142.0, 142.1, 142.2, 142.5, 142.6, 142.7, 143.1, 144.3, 144.5, 144.7, 145.2, 145.4, 145.5, 145.6, 145.7, 145.9, 146.0, 146.1, 146.2, 146.3, 147.3, 151.5, 152.8, 154.2, 154.6, 195.7 ppm. IR (KBr): $\tilde{v} = 2946$, 2848, 2780, 1687, 1594, 1446, 1228, 1215, 767, 688, 527 cm⁻¹. UV/Vis (CH₂Cl₂) $\lambda_{\rm max}$ (e) 255 (45237), 318 (14650), 430 (2080) nm. ESI-MS $(C_{70}H_{11}NO)$: m/z 882 [M + H]⁺. Figures of the relevant IR, NMR, ESI-MS and UV/Vis spectra are reported in the Supporting Information (Figures S1-S6).

Enantiomer Separation: Apparatus: Analytical liquid chromatography was performed on a JASCO chromatograph equipped with a Rheodyne model 7725i 20 μ L loop injector, a PU-980 HPLC pump, a Mod Jasco-975 single-wavelength absorbance detector and a Jasco Mod 995-CD circular dichroism detector. Chromatographic data were collected and processed by using Borwin software (Jasco Europe, Italy). Semi-preparative liquid chromatography was performed on a Waters chromatograph (Waters Associates) equipped with a Rheodyne model 7012 500 μ L loop injector, a UV Spectro-Monitor 4100 spectrophotometer and a refractive index (Waters R401 detectors).

Chromatographic Procedures: Enantiomers of **1** were collected by semi-preparative HPLC using Chiralpak-IA column ($250 \times 10 \text{ mm}$ I.D.), *n*-hexane/dichloromethane/2-propanol 60:10:30 as the eluent (flow rate 4.0 mLmin⁻¹ and T = 25 °C), UV ($\lambda = 300 \text{ nm}$) and IR detections. Sample **1** was dissolved in mobile phase ($c \approx 15 \text{ mgmL}^{-1}$) and each injection was loaded with 200 µL (process yield $\approx 90\%$). The enantiomeric excesses were determined by using the analytical Chiralpak-IA column ($250 \times 4.6 \text{ mm}$ I.D.), the same mobile phase employed for semi-preparative mode at flow rate

 1.00 mLmin^{-1} and the UV/CD detection at 300 nm. The chromatographic steps afforded 1-first eluted (25 mg, k = 1.67, *ee* 99.9%) and 1-second eluted (29 mg, k = 3.05, a = 1.80, *ee* 99.9%) isolated samples.

Enantiomerization of 1: Solutions of the individual enantiomers of **1** (concentration about 0.3 mgmL⁻¹) were held at constant temperature (50 °C) in mix1, mix2 or CHCl₃ and variable amounts of DBU (concentrations ranging from 1×10^{-2} to 4×10^{-2} M) were added. Samples were withdrawn at fixed time intervals and analyzed by HPLC on an analytical Chiralpak-IA column (250×4.6 mm I.D.) with *n*-hexane/dichloromethane/2-propanol 60:10:30 as the eluent at flow rate 1.00 mLmin⁻¹ and UV/CD detection at 300 nm. The *ee* values were estimated from the integrated areas in the chromatograms according to Equations (14) and (15).

$$ee (\%) \times (R^*) = (a - b^{\#})/(a + b^{\#}) \times 100$$
 (14)

$$ee \ (\%) \times (S^*) = (b - a^{\#})/(a + b^{\#}) \times 100$$
(15)

in which *a* and *b* are the peak areas of the (R^*) and (S^*) enantiomers remaining after enantiomerization, whereas $a^{\#}$ and $b^{\#}$ are the de novo enantiomeric peak areas. At 25 °C and in the absence of basic components in the eluent, the extent of enantiomerization during the chromatographic analysis was undetectable. According to the equation $\ln(ee) = (-2^{1}k^{e})t$, pseudo-first-order enantiomerization rate constants were calculated from plots of $\ln(ee)$ versus time. Eventually, second-order enantiomerization rate constants k^{e} were then obtained from the slope of linear plots of $^{1}k^{e}$ versus [DBU].

Experimental p K_a **Determination of Compound 1**: Potentiometric titrations were performed by using a standardized 2×10^{-2} mol dm⁻³ NaOH solution as the titrant. TX-100 was used without further purification. CTAB was purified by crystallization from acetone. The concentration of the surfactants were kept above the critical micellar concentration (CMC) values.^[24,25] The appropriate amount of 1 was dissolved in CS₂ to obtain a 2×10^{-3} mol dm⁻³ solution. A 20 mM aqueous surfactant solution was added whilst stirring and nitrogen gas was purged in the two-phase system until a limpid solution was obtained.

Computational Details: All molecular modelling calculations were performed with the computer program SPARTAN '04 (Wavefunction Inc., 18401 Von Karman Avenue, Suite 370 Irvine, CA 92612). Conformational searches, based on the molecular mechanics force field MMFF were performed on the ketones and their enolate forms used for the regression analysis, leading to Equation (2) (see the Supporting Information), as well as on the ketone and enolate forms of ketones 1 and 2. All of the structures inside an energy window of 3 kcalmol⁻¹ were further optimized by semiempirical calculations (Hamiltonian AM1). Coulson's charge densities on sensible atoms reported in Scheme 2 were averaged in terms of the relevant Boltzmann probability (at 25 °C) of each conformation. All structures belonging to the classes of compounds $R_{1\mathrm{X}},\,R_{2\mathrm{X}}$ and $R_{3\mathrm{X}}$ were optimized at the AM1 semi-empirical level and the atomic charges were calculated according to the Coulson definition. The quantity EE_X was expressed through $EE_X = \delta_{Hx}$ – $\delta_{\rm H}^{\rm CH_4}$, in which $\delta_{\rm Hx}$ refers to the charge of a hydrogen atom of a methane molecule substituted at the carbon by an X group (i.e., of a hydrogen gem to the X group), whereas $\delta_{\rm H}{}^{\rm CH_4}$ refers to the hydrogen charge in the pristine methane molecule. For X groups of nonspherical symmetry with respect to the C-X bond, the charge density on the hydrogen atom gem to the X group, δ_{Hx} , was obtained by averaging the charge values evaluated on the same atom inside

each conformer generated by rotating the X group around the C–X bond of an angle-step of 36°, from 0 to 360°, according to the dedicated procedure implemented in SPARTAN. Generalizing, for compounds belonging to the classes R_{1X} , R_{2X} and R_{3X} and ranked in Scheme 3, the hydrogen charge differences EE_X were calculated according to $EE_{ref.X} = \delta_H^{ref.X} - \delta_H^{ref.}$, in which the superscript ref. refers to one of the molecules R_{1H} , R_{2H} or R_{3X} employed as the reference instead of CH₄.

Regression Analyses: Linear regression procedures based on multiparameter equations were performed within the estimation of acidity of monocarbonyl ketones [Equation (2)] and Taft correlation analyses [Equations (7) and (13)]. The obtained results were analyzed according to *F* and *T* tests to exclude casualness (index *F*) and to quantify the statistical weight of each of the two descriptors (index *T* and factors t_i). Linear regression analyses and *F* and *T* tests were performed by the dedicated functions implemented in the Microsoft Office Excel[®] 2003 program. Probability related to the *t*-Student distribution in the *T* test was set to 0.05. In the three quoted cases, *T* values of 2.02, 2.22 and 2.16 were calculated. Regressions corresponding to Equations (2), (7) and (13) led to the following *F* indexes and t_i factors: (i) 1×10^{-24} , 9.49, 3.20, 5.36; (ii) 6×10^{-11} , 23.81, 20.94; and (iii) 8×10^{-10} , 12.41, 10.18.

Supporting Information (see footnote on the first page of this article): Evaluation of acidity of ketones by semi-empirical calculations (EASC method); HPLC analyses; NMR, ESI-MS, IR and UV/Vis spectroscopic data of **1**.

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