Quantitative Scale for the Extent of Conjugation of Carbonyl Groups: "Carbonylicity" Percentage as a Chemical Driving Force

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Despite the carbonyl group being one of the most pervasive chemical building blocks in natural, synthetic, and industrial processes, its exact description in terms of precise quantification of the degree of carbonyl conjugation has yet to be determined. The present work suggests a novel yet simple method for quantifying the conjugation in general carbonyl groups (such as ketones, aldehydes, carboxylic acids and their respective halogenides, amides, etc.) on a linear scale, defined as the "carbonylicity scale". This was achieved by use of the computed enthalpy of hydrogenation (ΔH_{H2}) of the >C═O group in the compounds examined. In the present conceptual work, the ΔH_{H2} value for formate ion is used to define complete conjugated character (carbonylicity = +100%), while formaldehyde represents complete absence of conjugation (carbonylicity = 0%). The component ΔH_{H2} values were computed at differing levels of theory, providing a nearly "method-independent" measure of carbonylicity computationally. A total of 49 common carbonyl compounds were used as accuracy scoring criteria of the methodology. For the compounds examined, correlations have been made between the computed carbonylicity percentage and the >C═O proton affinities, IR frequencies, and their reactivity values in a nucleophilic addition reaction. Selected chemical reactions were also studied to illustrate the utility of carbonylicity scale. Examples herein include demonstrating that change in the carbonylicity value represents a thermodynamic driving force in acylation reactions. The definition was extended to substituted thiocarbonyl and imino compounds.

1. Introduction

The carbonyl group is one of the most pervasive moieties in organic, bioorganic, and industrial chemistry. Ketones and aldehydes as well as carboxylic acids, their halogenides, amides, esters, acyl anhydrides, and other derivatives are also so-classified and are commonly found in peptides/proteins, lipids/membranes, and other biologically active compounds, such as penicillin, drugs, and toxins.[1] Moreover, these types of compounds and their reactions may be observed in interstellar medium (ISM) as well.[2−4] They may be characterized as very stable and resilient (amides,[5−7] esters, acids[8]) as well as very reactive systems (carboxyl acid halogenides and thiol derivatives).[8] There are numerous examples in the fields of organic chemistry and biochemistry where carbonyl derivatives undergo nucleophilic addition, such as esterification, transesterification, amidation, transamidation,[9] anhydride formation, and aldol addition, among others.[8] Examples also include the near-spontaneous or enzymatic hydrolysis of ester and amide bonds. Reduction of the carbonyl group by complex metal hydrides has significant synthetic importance in obtaining various alcohols[10] and amines and other compounds[10−13] (Scheme 1). The large variability in the chemical reactivity of the carbonyl group may be attributed to the potential for fine-tuning of the bond strength, facilitated by attached substituent groups. Stronger conjugation implies a larger contribution of resonance stabilization (lowering overall energy), with an associated increase in system stability. The extent of conjugation, measured in terms of resonance energy or resonance enthalpy (RE, ΔH_{RE}) of a general carbonyl compound, as illustrated by its associated resonance structures (**A-I** and **A-II** in Scheme 1), predetermines its specific chemical reactivity, analogous to the situation in amide systems.[14,15] The RE of a carbonyl system was studied first for the amide bond.[14−17] At the begining, the RE was estimated by amide bond rotation, introducing many uncertainties into the computations.[18] Three approaches were subsequently developed: methyl capping based on experimental data (MCE),[19] group increments (GI),[20] and carbonyl substitution nitrogen atom replacement (COSNAR),[16,17] each generating slightly different results. Recently, a new procedure was introduced to measure the RE, called amidicity (or earlier, amidity), based on a hydrogenation method,[9,21] where all the amides compared were considered in a common linear percentage scale.

For a stronger interaction, conjugation between the X group and the C atom of the carbonyl group is more extensive (larger resonance energy), implying that the contributions of the two most significant resonance structures (**A-I** and **A-II**) are more closely balanced than in systems with weaker interaction. Consequently, a more strongly conjugated carbonyl group (e.g.,

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SCHEME 1: Predominant Resonance Structures (A-I and A-II) of the Carbonyl Moiety, with Selected Common Reactions Involving the C=O Group

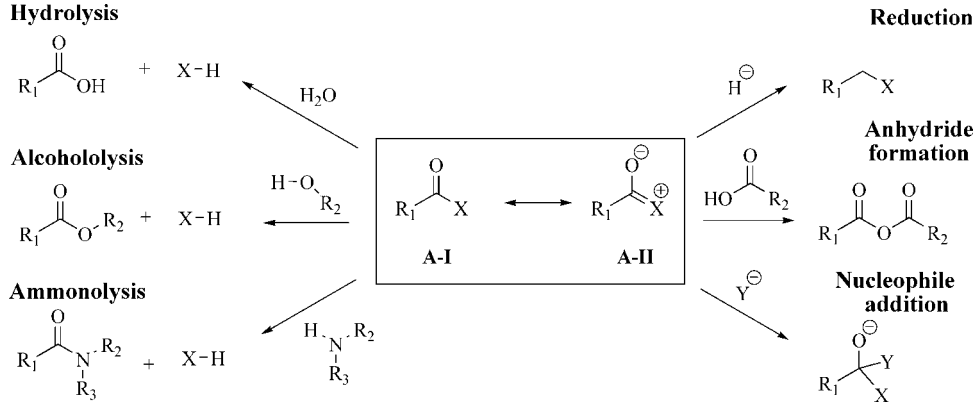


TABLE 1: Parameters for Linear Scale of Carbonylicity Percentage[a]

	method	ΔH_{H2}(**1**) 0%	ΔH_{H2}(**2**) 100%	*m*	(carbonylicity %)$_0$
A	HF/3-21G(d)	−108.16	127.35	0.4246	45.9273
B	HF/6-31G(d)	−77.67	151.25	0.4368	33.9284
C	B3LYP/6-31G(d)	−70.42	136.75	0.4827	33.9916
D	B3LYP/6-31G(d,p)	−80.21	126.81	0.4830	38.7459
E	B3LYP/6-311++G(2d,2p)	−86.78	110.13	0.5079	44.0705
F	MP2(fc)/6-31G(d)	−58.19	159.22	0.4600	26.7635
G	CCSD/6-31G(d)	−69.71	145.99	0.4636	32.3183
H	G3MP2B3	−83.11	113.25	0.5093	42.3255
	average	−79.28	133.84	0.4710	37.2600
	std deviation	14.75	17.65	0.0307	6.6107

[a] Calculated from theoretical ΔH_{H2} values (kilojoules per mole) obtained for reference compounds **1** and **2**, according to eq 2.

TABLE 2: Computed Parameters for Model Compounds 1−49[a]

	ΔH_{H2}[I]	carbonylicity (%)	ΔH_{RE}		ΔH_{H2}[I]	carbonylicity (%)	ΔH_{RE}
1	*−80.21*	*0.00*[b]	*0.00*	**2**	*126.81*	*100.00*[b]	*207.00*
3	−8.14	34.81	72.06	**4**	20.01	48.41	100.21
5	29.62	53.05	109.81	**6**	−53.71	12.80	26.50
7[c]	−28.08	25.18	52.12	**8**	−22.55	27.85	57.65
9	−52.12	13.57	28.09	**10**	−78.19	0.98	2.03
11	149.39	110.90	229.56	**12**	130.61	101.83	210.78
13	−116.40	−17.48	−36.18	**14**	61.81	68.60	142.00
15	63.46	69.40	143.66	**16**	9.96	43.56	90.17
17	−129.54	−23.83	−49.33	**18**	19.29	48.07	99.50
19	−14.09	31.94	66.11	**20**	−78.71	0.72	1.49
21	−74.66	2.68	5.55	**22**	−75.56	2.25	4.66
23	−15.44	31.29	64.77	**24**	−70.70	4.59	9.50
25	−31.82	23.37	48.38				
26[d]	35.63	46.25	95.74	**30**[d]	30.05	43.55	90.15
27[e]	41.27	61.36	127.01	**31**[e]	18.03	50.13	103.77
28[f]	27.66	51.61	106.83	**32**[f]	4.55	40.44	83.71
29[g]	21.62	47.16	97.62	**33**[g]	8.41	40.78	84.41
34[g]	54.05	64.35	133.20	**35**[g]	27.84	51.69	107.00
36[d]	−4.35	26.94	55.76	**37**[d]	−1.34	28.39	58.77
38	12.50	44.78	92.69	**39**	−5.51	36.08	74.68
40	15.11	46.05	95.32	**41**	11.03	44.07	91.22
42	−6.66	35.53	73.55	**43**	−9.83	34.00	70.38
44	−10.12	33.86	70.09	**45**	−24.13	27.09	56.08
46	56.76	66.16	136.95	**47**	34.98	55.64	115.17
48	−79.16	0.51	1.06	**49**	−6.34	35.68	73.86

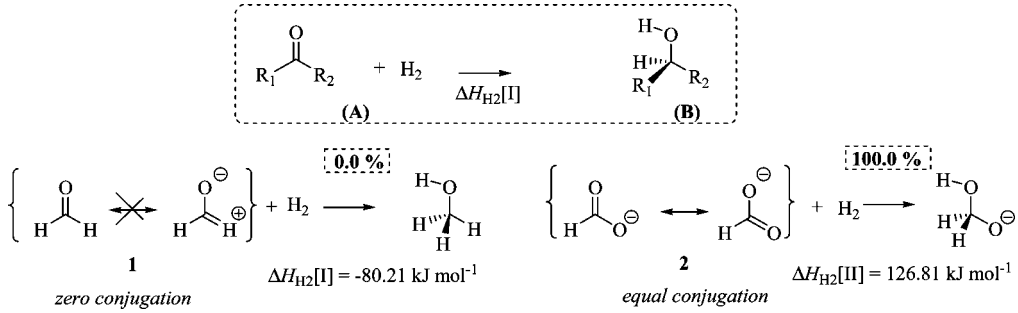
[a] By definition; [b] Fixed in its planar structure, [c,d,e,f]Modified by ring strain ΔH_{H2}*[I]; [c] $\Delta\Delta H_{H2}$(RS) = −20.10 kJ mol^{-1}; [d] $\Delta\Delta H_{H2}$(RS) = 5.55 kJ mol^{-1}; [e] $\Delta\Delta H_{H2}$(RS) = −1.04 kJ mol^{-1}; [f] $\Delta\Delta H_{H2}$(RS) = −4.20 kJ mol^{-1}. [g] Supposed that $\Delta\Delta H_{H2}$(RS) = 0 kJ mol^{-1}.

amide) is more resistant against attack by nucleophilic agents (e.g., HO^-, H_2O, amines, metal hydrides), whereas a carbonyl bond with a weaker conjugation (e.g., aldehyde or ketone) is correspondingly more reactive.[22] In many biological or pharmaceutical applications, "Mother Nature" or the practicing chemist must find the appropriate balance between reactivity and stability of the carbonyl bond, in order to efficiently and selectively form new chemical functionalities.

2. Methods

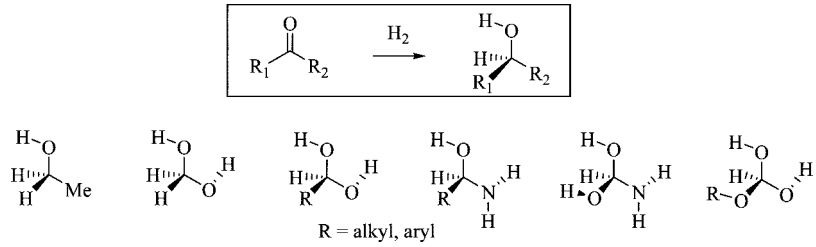
2.1. Computational Methods. All computations were carried out using the Gaussian03 (G03) program package.[23] Geometry optimizations and subsequent frequency analyses were carried out on selected carbonyl-containing systems from which enthalpy of hydrogenation (ΔH_{H2}) values were extracted. Computations were carried out at differing levels of theory, labeled as follows: A, HF/3-21G; B, HF/6-31G(d); C, B3LYP/6-

SCHEME 2: Definition of Carbonylicity Percentage via Enthalpy of Hydrogenation (ΔH_{H2}) of the Carbonyl Group[a]

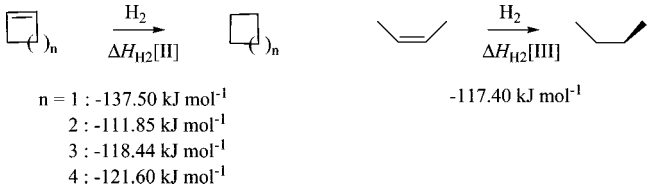


[a] Values were obtained from the geometry-optimized and frequency-confirmed structures, computed at the B3LYP/6-31G(d,p) level of theory. In structure **B**, the H−O−C−R_2 dihedral angle is in the anti orientation.

SCHEME 3: Illustrative Examples for Structure B



SCHEME 4: Reference Compounds Helping To Correct for Ring Strain (RS) of Endocyclic Carbonyl Compounds



31G(d);[24] D, B3LYP/6-31G(d,p); E, B3LYP/6-311++G(2d,2p), F, MP2(fc)/6-31G(d);[25] G, CCSD/6-31G(d);[26] H, G3MP2B3 (Tables 1 and 2 and Table S1 in Supporting Information).[27] Basis sets were chosen for their reliability in the characterization of aromaticity,[28−32] and amidicity (amidity)[9,21,33] in recently established works. Analytical frequencies were computed at the same levels of theory as used for geometry optimization, in order to properly confirm all structures as residing at minima on their associated potential energy hypersurfaces (PEHS). Thermodynamic functions (*U*, *H*, *G*, and *S*, listed in Tables S3 and S4 in Supporting Information) were computed at 298.15 K by use of the quantum chemical (rather than conventional) thermodynamic scale.

2.2. The Concept of Carbonylicity. A protocol has been developed to quantify the extent of conjugation of the substituted carbonyl group (-COX). The parameter thus obtained is termed "carbonylicity" in analogy to the terms "aromaticity"[28] and "amidicity".[21] To measure the stability and reactivity of a general carbonyl compound, an in silico hydrogenation reaction (**A** → **B**) was carried out (Scheme 2). In computing ΔH_{H2}, a given stable conformation and configuration of the products was chosen, exemplified in Scheme 3, in which no significant intramolecular interaction could be identified, potentially perturbing the system.

The following is a general set of rules to select the conformer for structure **B**:

(1) The conformation and configuration of structure **B** should be as close to structure **A** as possible.

(2) Neither formation nor annihilation of hydrogen bonds os allowed.

(3) The following arbitrary order of priority between R_1 and R_2 substituents was defined: NH_2 > NHR > OH > OR > PR_2 > SH > SR > R > H, differing from the Cahn−Ingold−Prelog priority rule.[34]

(4) The newly formed OH group must be in anti conformation relative to the heteroatom (R_2) chosen by the order of priority as defined in point 3.

The ΔH_{H2}[I] value (eq 1) of formaldehyde (**1**) was taken as being completely devoid of conjugation between the carbonyl and the H atom (0% conjugation), and the ΔH_{H2}[II] value of formate (**2**) was defined as being completely conjugated carbonyl group (100%). In the case of **1**, delocalization is not possible due to the lack of an occupied atomic orbital (i.e., lone pair) with the appropriate symmetry. Analogously to the amidicity percentage, measurement of ΔH_{H2} or determination of the enthalpy of formation allows for obtaining "experimental" percentage carbonylicity (eq 2).[21] It should perhaps be emphasized that, in choosing these standards (compounds **1** and **2**), care was taken to pick structural similarity and simplicity, since both compounds **1** and **2** correspond to nonstrained and sterically nonhindered structures.

$$\Delta H_{H2}[I] = H_B - H_A \quad (1)$$

$$(\text{carbonylicity } \%) = m\Delta H_{H2}[I] + (\text{carbonylicity } \%)_0 \quad (2)$$

This methodology, as with amidicity,[21] separates the effect of the internal enthalpy (ΔH) and the entropy changes (ΔS), opening the way to study independently the two critical elements of thermochemistry.

Resonance energy (RE, ΔH_{RE}) of the carbonyl bond, together with the steric effect and ring-strain energy, is the basic characteristic of the conjugation. From the carbonylicity percentage, one may define the resonance energy by eq 3e, analogous to that for amidicity:[21]

$$(\text{carbonylicity }\%)(\mathbf{X}) = m\Delta H_{\mathrm{H2}}[\mathrm{I}](\mathbf{X}) + (\text{carbonylicity }\%)_0 \quad (3a)$$

$$(\text{carbonylicity }\%)(\mathbf{1}) = m\Delta H_{\mathrm{H2}}[\mathrm{I}](\mathbf{1}) + (\text{carbonylicity }\%)_0 \quad (3b)$$

$$(\text{carbonylicity }\%)(\mathbf{X}) - (\text{carbonylicity }\%)(\mathbf{1}) = m\{\Delta H_{\mathrm{H2}}[\mathrm{I}](\mathbf{X}) - \Delta H_{\mathrm{H2}}[\mathrm{I}](\mathbf{1})\} \quad (3c)$$

Since (carbonylicity %)(**1**) ≡ 0, and $\Delta H_{\mathrm{H2}}[\mathrm{I}](\mathbf{X}) - \Delta H_{\mathrm{H2}}[\mathrm{I}](\mathbf{1}) = \Delta H_{\mathrm{RE}}(\mathbf{X})$, therefore

$$(\text{carbonylicity }\%)(\mathbf{X}) = m\Delta H_{\mathrm{RE}}(\mathbf{X}) \quad (3d)$$

or

$$\Delta H_{\mathrm{RE}}(\mathbf{X}) = (\text{carbonylicity }\%)(\mathbf{X})/m \quad (3e)$$

In order to obtain accurate values for ring structures **26**−**37**, one should consider the change in ring strain upon hydrogenation. Here we applied the same procedure as used in the determination of amidicity.[9,21] For this reason, reference reactions were considered for each of the lactam- and lactone-containing systems, where cycloalkenes of similar ring size were hydrogenated to the corresponding cycloalkane (ΔH_{H2}[II], Scheme 4). These values were compared with the corresponding ΔH_{H2} of *cis*-2-butene changing to *gauche*-butane (ΔH_{H2}[III]; eq 4), thereby obtaining, for the estimated ring strain (RS), the $\Delta\Delta H_{\mathrm{H2}}$(RS) values for each reaction. One may correct the ΔH_{H2}[I] values of compounds **26**−**37** with the calculated $\Delta\Delta H_{\mathrm{H2}}$(RS), yielding $\Delta H^{*}_{\mathrm{H2}}$[I] values (eq 5, Table S1). The final step is to convert $\Delta H^{*}_{\mathrm{H2}}$[I] to carbonylicity % by use of eq 2. Ring-strain energy is set to 0 in the case of open-chain compounds.[21]

$$\Delta\Delta H_{\mathrm{H2}}(\mathrm{RS}) = \Delta H_{\mathrm{H2}}[\mathrm{II}] - \Delta H_{\mathrm{H2}}[\mathrm{III}] \quad (4)$$

$$\Delta H^{*}_{\mathrm{H2}}[\mathrm{I}] = \Delta H_{\mathrm{H2}}[\mathrm{I}] - \Delta\Delta H_{\mathrm{H2}}(\mathrm{RS}) \quad (5)$$

2.3. Method Independence. The extent of method dependence of this protocol is first examined by calculating ΔH_{H2} values at the B3LYP/6-31G(d,p) level of theory and subsequently converting to carbonylicity percentages for a selected 19 carbonyl compounds of the 49 studied (Tables 1 and S1), analogously to amidicity.[21]

These were then compared to results obtained at various levels of theory (Tables 1 and S1). The correlation between ΔH_{H2} values, computed at differing levels, exhibited a modest method dependence ($R^2 = 0.9586$; Figure 1A). However, by converting all ΔH_{H2} values to carbonylicity percentages, one obtains a rather good fit with an $R^2 = 0.9891$ (Figure 1B). Additionally, all min−max and standard deviation values of the carbonylicity percentages are significantly smaller than the corresponding values of ΔH_{H2} (Table S1). The calculated average values of ΔH_{H2} and carbonylicity are very close to the values obtained by method D [B3LYP/6−31G(d,p)], therefore all further discussion is based on the use of method D. Conversely, the calculated carbonylicity percentages for the same compound are in the same range, irrespective of the theoretical method applied. Consequently, the percentage carbonylicity scale is practically method-independent. This methodology, therefore, may be considered as a quasi-rigorous method-independent technique. It must be emphasized that there is no limitation to the theoretical method to be employed and one may use as high or as low a level of computational theory as desired, clearly within reason. This quasi method-independence of the protocol is once again similar to that of amidicity[21] and aromaticity.[28]

2.4. Relationship between Amidicity and Carbonylicity Scales. The definition of the amidicity scale, where compounds **52** and **53** were selected as references, can be considered as a special case of the carbonylicity scale, where X = NR_1R_2 (Scheme 5).[21] Consequently, the amidicity scale is defined as part of the whole carbonylicity scale as shown in Figures 2 and 3.

3. Results and Discussion

In order to develop a quantitative carbonylicity scale (eq 2), a wide variety of carbonyl compounds (**3**−**49**) was investigated (Scheme 6, Tables 1 and 2, as well as Figure 4), in addition to the reference compounds (**1** and **2**). A total of 49 very different model compounds (**1**−**49**) were classified into four groups, representing different structural features (Scheme 6).

Compounds **1** and **3**−**25**, corresponding to the *first group*, were used to study the electronic effects of the X substituent attached to the functional groups from the periodic system and the simplest groups, with and without a net charge (Scheme 6). The role of ring strain (*second group*) was also studied from four- to seven-membered rings by use of model compounds such as small lactams **26**−**29** and lactones **30**−**33**. Among these, one finds the four-membered model **26**, as found in penicillin-type antibiotics, which exhibits a rather high reactivity toward nucleophiles. In the *third group*, lactam and lactone compounds were chosen to account and calibrate for aromatic stabilization and antiaromatic destabilization (**34**−**37**). In compounds **34** and **36**, one may presume that aromaticity and carbonylicity synergistically strengthen one another, meaning stronger conjugation yields higher aromaticity. In contrast, aromaticity and carbonylicity are in competition for compounds **35** and **37**. Therein the stronger conjugation manifests itself as stronger

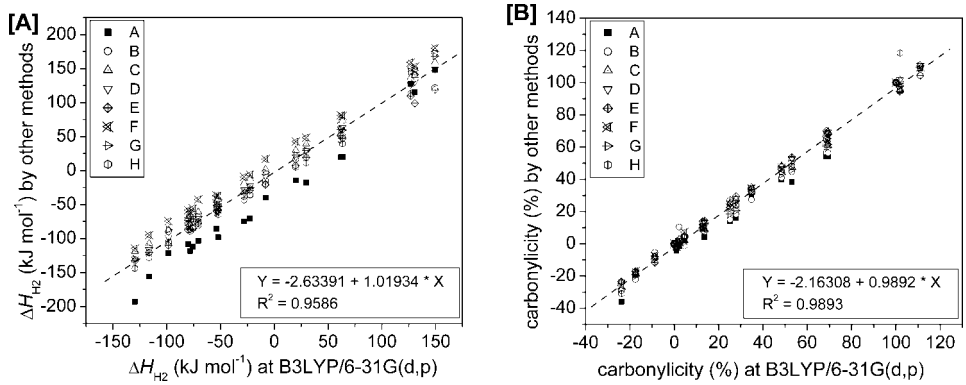
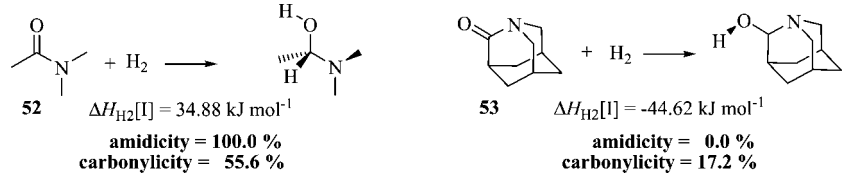


Figure 1. Correlation of (A) ΔH_{H2} (kilojoules per mole) and (B) carbonylicity (percent) values obtained by various methods against the results obtained by B3LYP/6-31G(d,p) (method D) and those of obtained other methods (methods A−C and E−H).

SCHEME 5: Definition of Amidicity Percentage via Enthalpy of Hydrogenation (ΔH_{H2}) of the Carbonyl Group[a]



[a] Values were obtained from geometry-optimized structures, computed at the B3LYP/6-31G(d,p) level of theory.

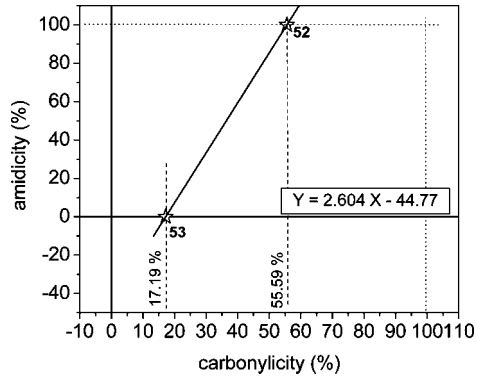


Figure 2. Correlation between carbonylicity and amidicity scales.

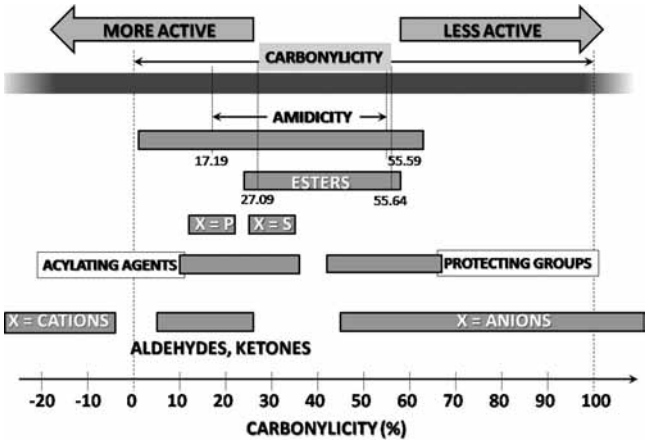


Figure 3. Division of the carbonylicity scale.

antiaromaticity, destabilizing the system. Ultimately equilibrium is attained, where stabilization of carbonylicity and destabilization of antiaromaticity are at an optimum value. A *fourth group*, conjugated models (**38**−**49**), sees the carbonyl conjugation competing with another type of conjugation, potentially coupled to and therefore modifying the carbonylicity values of these compounds. These four groups of simple model compounds cover a wide variety of carbonyl types, ensuring a practically complete study.

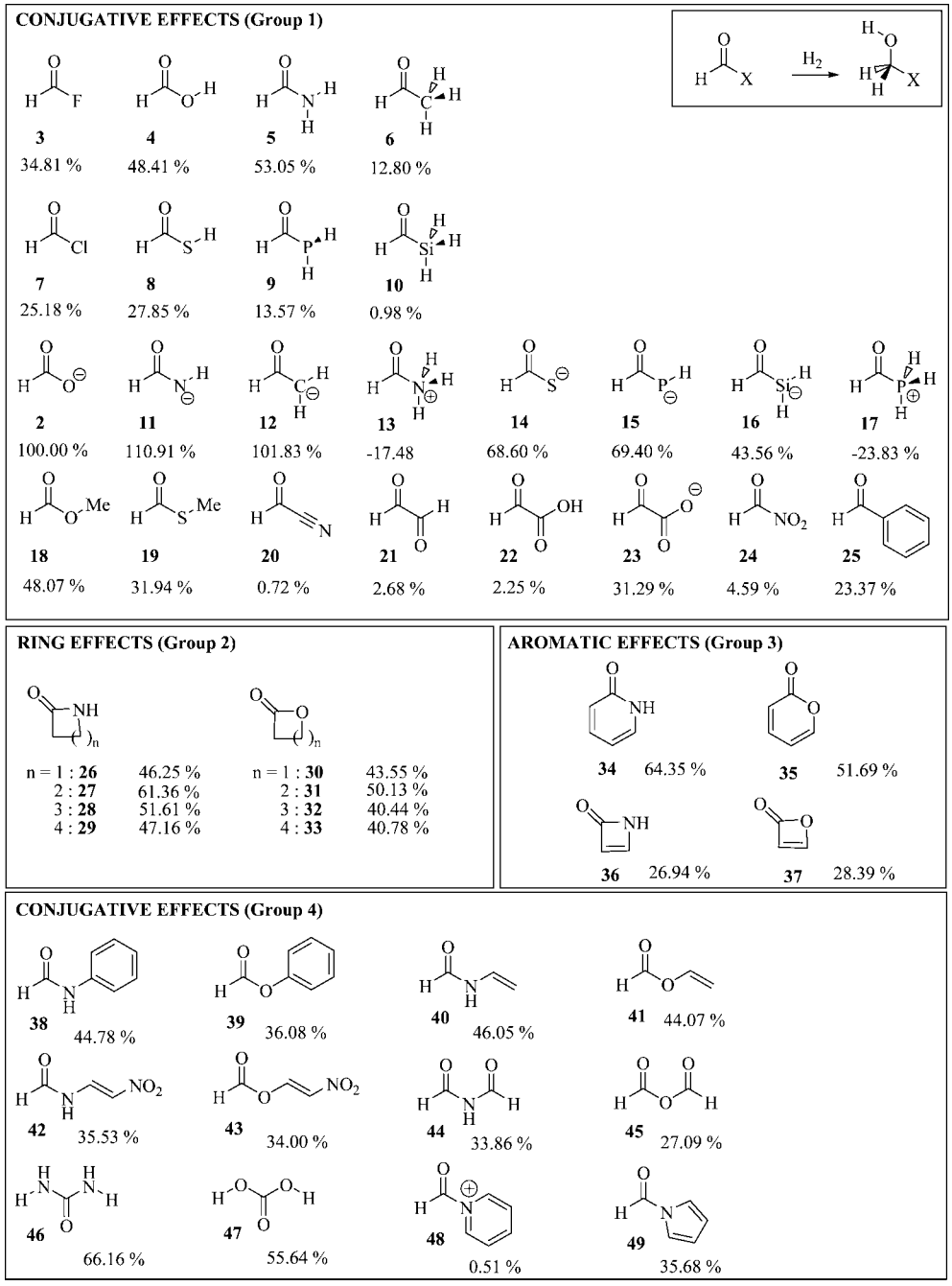
The 49 compounds can be subdivided into four groups as shown in Scheme 6 and also into four conjugation classes as shown in Scheme 7. The results obtained meet general chemical expectations. The carbonyls linked to electron-donating groups [EDG; for example, X = OH (**4**) or NH_2 (**5**)] exhibit higher carbonylicity percentages than carbonyls linked to nonconjugative or weakly conjugative groups [X = CH_3 (**6**), SiH_3 (**9**), or Ph (**25**)] or electron-withdrawing groups (EWG; for example, X = CN (**20**) or NO_2 (**24**)]. Deprotonated models (**1**, **11**, **12**, and **14**−**16**) show a very high degree of carbonylicity, in sharp contrast to the protonated species (**13** and **17**), which have strong electron-withdrawing effects. Although not aromatic systems, nevertheless carbonylicity measures the electron-donating and -withdrawing effect of substituent X, just like Hammett's σ-values. Consequently, an attempt to correlate the carbonylicity values obtained with their experimental Hammett σ(para) parameters is merited, as successfully applied to phosphorus compounds.[31] The attempt is quantified and presented in Figure 5, with noticeable scattering (R^2 = 0.693).

When the *second group* (effect of lactam and lactone ring size on the carbonylicity percentages) is considered, the carbonylicity of five-membered rings (compounds **26**−**29** and **30**−**33**) exhibits maximum value (Figure 6). As discussed, among small lactam rings, five-membered systems (**27**) possess the highest amidity values, and this is also the case for their (high) carbonylicity values.[21] Additionally, such values are higher than those of *trans*- (**50trans**; amidicity = 101.6%, carbonylicity = 56.22%) and *cis*-*N*-methylacetamide (**50cis**; amidicity = 96.5%, carbonylicity = 54.3%),[21] which mimics the ring-opened form of lactams. This uniquely high value explains its exceptional stability against nucleophilic attack. All other lactams of different ring size (**26**, **28**, and **29**) present lower amidicity and carbonylicity values than their corresponding ring-opened forms (**50trans** and **50cis**), indicating a lower resistance to nucleophilic attack. Similarly shaped curves describe the cases of lactones of small ring size (**30**−**33**), although they take place at lower carbonylicity values. The highest value is found in the five-membered lactone (**31**). In the case of lactones, in contrast to lactams, even the highest carbonylicity value of **31** is lower than that of the open-chain analogue *trans*-methylacetate (**51trans**), implying that a ring-opening process with alcohol is thermodynamically preferred in all cases. When the carbonylicity value of **51** in the cis arrangement (**51cis**) is considered, the geometrical structure is analogous to that of lactones with small ring size. It can therefore be concluded that the five-membered ring (**31**) presents a substantially higher carbonylicity value than **51cis**. The theoretical observation for the lower stability of small-ring lactones can no doubt be supported by empirical determinations.

In the *third group* (**34**−**37**), very large carbonylicity values were obtained for compounds **34** (the less stable tautomeric form of 2-hydroxypyridine)[21] and **35**, attributed to the extensive aromatic character of these compounds,[21,28] subsequently eliminated through a hydrogenation reaction. An inverse effect was found in the case of unsaturated four-membered lactam **36** and lactone **37**, where the unusually low carbonylicity values originate from the antiaromatic character of these compounds as discussed.[21,28]

Finally, in the *fourth group* (**38**−**49**), carbonyl compounds with differing degrees of conjugation were considered, to characterize the competition for the lone pair of the N and O atom between the neighboring carbonyl group and the unsaturated R-group attached to the N or O atom, outlined in Scheme 8. As expected, the less conjugated groups [phenyl (**38** and **39**) and vinyl (**40** and **41**)] do not significantly disturb the degree of conjugation. Somewhat stronger competition was attributed to the pyrrole (**49**) and nitrovinyl (**42** and **43**) groups, where strong competition again was found between the carbonyl group and the unsaturated R group for the lone pair of the N or O

SCHEME 6: List of Enthalpy of Hydrogenation (ΔH_{H2}) Values for Model Compounds, Measuring the Conjugation of the Carbonyl Bond[a]



[a] Numerical values under the structures represent the carbonylicity % values, determined at the B3LYP/6-31G(d,p) level of theory (method D).

atom, resulting in lowered carbonylicity percentages. In compound **48**, the positive, quaternary N atom does not exhibit conjugation with the carbonyl group; therefore a near-zero value of carbonylicity was measured (0.5%). Bisacyl compounds, such as diamides (**44**) and acid anhydride (**45**), are generally considerably less stable than their amide and acid counterparts, attributed to the competition between the two carbonyl groups. They exhibit roughly half the carbonylicity per CO group, in comparison to the amide (**5**) or acid (**4**), indicating that both carbonyl groups equally contribute to the conjugation. In the case of the carbamide and carbon acid structures (**46** and **47**), the carbonyl group is able to conjugate with either two N or two O atoms, significantly increasing their carbonylicity values.

3.1. Correlation between Carbonylicity and Computed Proton Affinity and Reactivity. It has been known for some time that, in formamide, the gas-phase basicity of the oxygen lone pair is greater than that of the nitrogen lone pair.[35] This has often been attributed to the conjugative stabilization of the carbonyl linkage. When the wide range of X functionalities attached to the CO group is taken into consideration, a relatively good correlation was observed between the PA and the carbonylicity values. A stronger conjugation should therefore exhibit lower affinity toward protonation, and in fact the calculated ΔH_{PA} values reveal this (Figure 7A). However, the PA may depend on many parameters, such as the relative steric hindrance and the character of the electron-withdrawing group attached to the X atom; thus only a qualitative trend is manifested ($R^2 = 0.712$). In the case of **23**, the original geometry

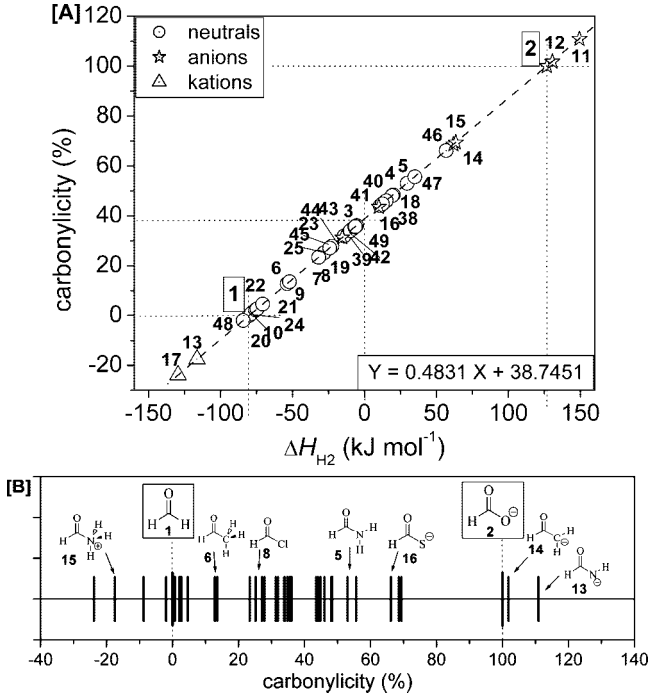


Figure 4. (A) Theoretical carbonylicity scale. The percentage value of carbonylicity based on the ΔH_{H2} value of a given compound computed at the B3LYP/6-31G(d,p) level of theory is shown. For the description of each compound, see Table 2 as well as Scheme 6. (B) Carbonylicity spectrum.

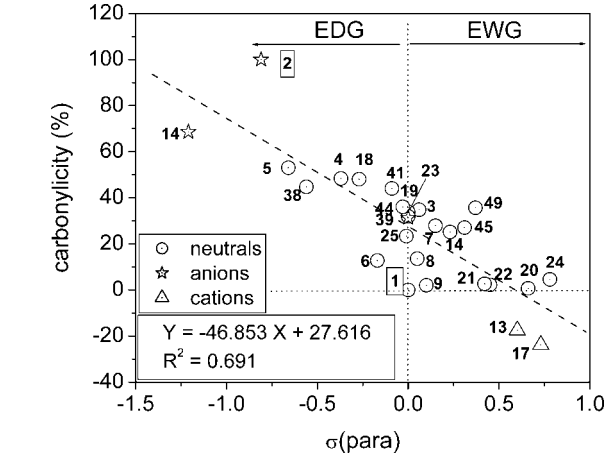


Figure 5. Correlation between Hammett σ(para) parameter and carbonylicity values calculated for model compounds **1**−**49**.

changes; therefore, it is omitted from the fitting. Once again, the correlation is improved considerably when the points are treated as three clusters corresponding to negative, neutral, and positive X substituents. One may observe that strongly conjugative groups considerably lower the PA, making the process more exothermic, with corresponding increases in carbonylicity; explained in terms of their resonance structures (Scheme 1).

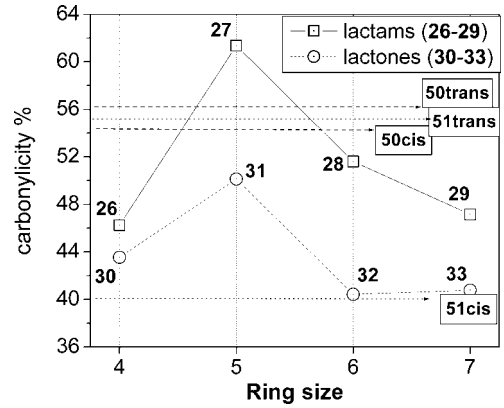


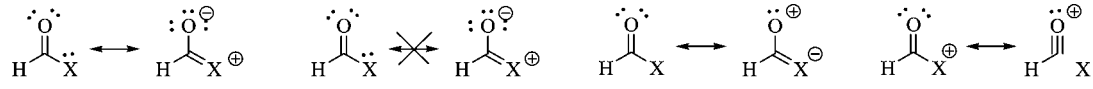
Figure 6. Correlation between ring size and carbonylicity percentage in the case of saturated lactam and lactone compounds. Carbonylicity values of cis and trans isomers of **50** (MeCO-NHMe) as well as those of **51** (MeCO-OMe) are also shown.

One of the aims of this work is to estimate, at least semiquantitavely, the reactivity of a carbonyl compound toward nucleophiles by a simple theoretical method, such as the carbonylicity percentage scale. The reactivity of a carbonyl compound is composed of the primary effect, neglecting steric hindrance, solvent effects, and other secondary effects. The first major effect is the intrinsic reactivity of the carbonyl group, controlled by the conjugation and electronic effect of the X group, while the second major effect is the leaving ability of the X group. As carbonylicity is only able to measure the former (intrinsic reactivity), direct correlation between the two was characterized by use of the reactivity of the carbonyl compounds **1**−**25** and **38**−**49** toward OH^- ions in the gas phase, as previously applied to amides.[21] The mechanism of the nucleophilic addition is composed of one step involving a tetrahedral adduct (**C** in Scheme 9), where the effect of the leaving ability of X has a reduced influence. The reactivity is measured and quantified here by use of the ΔH_{react} value defined by eq 6. In the cases where X is a very good leaving group, the adduct is not an intermediate and, after the first, low-barrier transition state (**TS-A**), leads to the corresponding acid (**D** or **4**) and X^- as products (Scheme 9). In cases where the adduct was not a minimum (**1**, **7**−**9**, **10**, **11**, **13**, **14**, **16**, **17**, **19**, **24**, **43**, **48**, and **45**), the compounds are removed from the fitting. In agreement with this rationale, the energy level of intermediate **C** was used as a measure of reactivity, according to eq 6, with the resultant reactivity values summarized in Table 3.

$$\Delta H_{react} = H_C - H_A \quad (6)$$

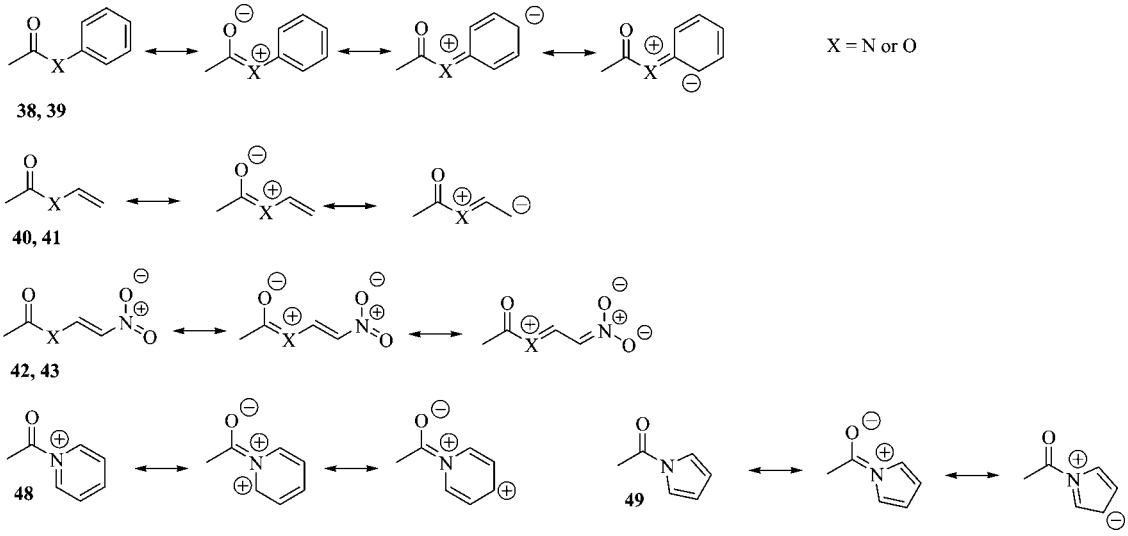
The correlation is not very good ($R^2 = 0.520$, Figure 7B) between the carbonylicity percentages and the reactivity (ΔH_{react}), but it indicates a trend, wherein a carbonyl compound having low carbonylicity is more active in an addition reaction than a compound with high carbonylicity. Anions have a steeper slope, while the tangent for the line fitted to neutral compounds

SCHEME 7: Possible Conjugative Structure of Various Classes of Carbonyl Compounds as a Function of the Electronic Nature of Substituents[a]



[a] Electron-donating, electron-withdrawing, and strongly electron-withdrawing groups (EDG, EWG, and strong EWG, respectively) are distinguished from nonconjugative groups.

SCHEME 8: Selected Representative Resonance Structures of 38−43, 48, and 49



indicates less sensitive dependence. This is in agreement with the general chemical picture that acyl halogenides (e.g., X = F; **3**) possessing low carbonylicity are more active and readily take part in addition and acyl exchange reactions (ΔH_{react} is large and negative). In contrast, carbonyl compounds possessing high carbonylicity values (amides and esters) exhibit low affinity to partaking in acylation reactions. There are, however, some known compounds (e.g., **1** and **6**) that have low carbonylicity values and are not acylation agents, due to the poor leaving ability of the X group, yet readily take part in a A_N-type addition reaction, as is well-known. For this reason, it is stressed again that the reactivity of the addition reaction is not the same as the reactivity of the acyl transfer reaction (Scheme 9), which is clearly the consequence of acyl transfers being two-step processes: addition followed by elimination. However, the reactivity itself may also require more complex considerations, where not only the strength of the acylic conjugation but also steric hindrance around the carbonyl group may influence ΔH_{react} values.

Similar correlations can be observed between carbonylicity values and NBO charges as well as carbonyl IR frequencies (see Table S2 and Figures S1 and S2 in Supporting Information).

3.2. Carbonylicity across the Periodic Table. It is known that the chemical characteristics of X strongly determine the extent of conjugation between the C═O group and its substituent X. Because carbonylicity is able to quantify the degree of conjugation, it is worth examining the trend of the extent of conjugation for all elements belonging to periodic columns 4−7 and rows 2−5. Figure 8A shows that the degree of conjugation decreases monotonically along the periodic rows, but the largest decrease can be seen between the second and the third row.

The trend is, however, more informative when the extent of conjugation is represented as a function of the periodic column. As shown in Figure 8B, the largest conjugation is exhibited by the elements in the second row (CH_3, NH_2, OH, F). The degree of conjugation of the elements in the second row is approximately double (or more than) that of the corresponding elements belonging to the same column. Exclusive of the second

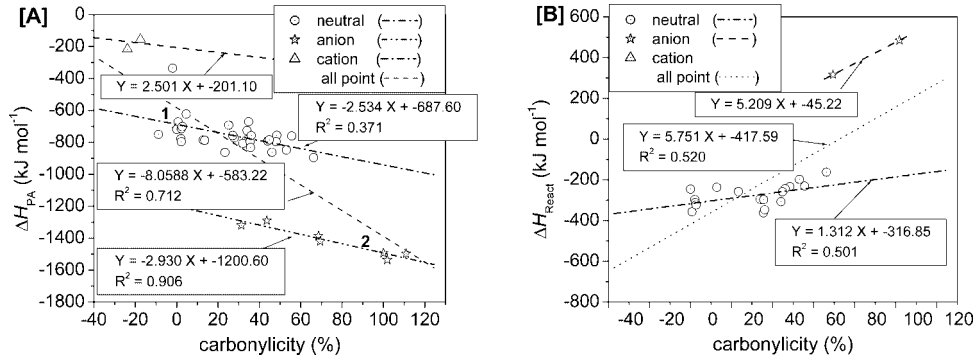
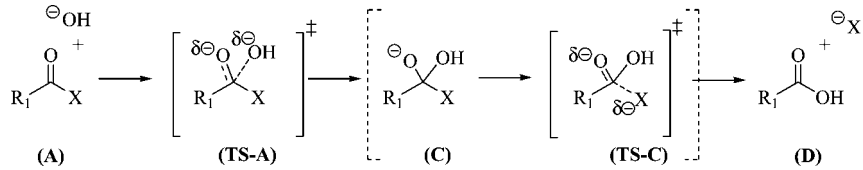


Figure 7. (A) Correlation between calculated Carbonylicity percentage and the proton affinity of each carbonyl (ΔH_{PA}). Compound **23** was omitted from the fitting. (B) Correlation between calculated carbonylicity percentage and the reactivity of amide (ΔH_{React}). Compounds **7**−**9**, **11**, **13**, **14**, **16**−**19**, **23**, **24**, **43**, **45**, and **48** are omitted from the fitting, since the structures did not correspond to energetic minima.

SCHEME 9: Mechanism of Hydrolysis of a Carbonyl Compound by OH^- Ion, Showing Consecutive Addition and Elimination[a]



[a] Note that **C** and **TS-C** may not occur if X is a very good leaving group, such as Cl.

TABLE 3: Computed ΔH_{PA} and ΔH_{react} Values for Compounds 1−25 and 38−49

	carbonylicity (%)	ΔH_{PA}	ΔH_{react}		carbonylicity (%)	ΔH_{PA}	ΔH_{react}
1	*0.00*	−718.3	−245.64	**2**	*100.00*	−1493.6	
3	34.81	−670.8	−297.32	**4**	48.41	−756.7	−233.50
5	53.05	−847.9	−197.63	**6**	12.80	−785.8	−236.83
7	25.18	−692.2		**8**	27.85	−771.9	
9	13.57	−787.0		**10**	0.98	−777.7	−297.13
11	110.90	−1497.3		**12**	101.83	−1536.3	485.16
13	−17.48	−155.2		**14**	68.60	−1385.8	
15	69.40	−1420.7	316.25	**16**	43.56	−1389.7	
17	−23.83	−216.4		**18**	48.07	−795.3	
19	31.94	−806.7		**20**	0.72	−671.6	−356.80
21	2.68	−701.1	−323.59	**22**	2.25	−714.0	−311.96
23	31.29	−1320.0		**24**	4.59	−622.4	
25	23.37	−862.7	−257.70				
38	44.78	−784.8	−258.49	**39**	36.08	−757.0	−346.78
40	46.05	−862.2	−243.81	**41**	44.07	−791.5	−307.64
42	35.53	−795.0	−361.86	**43**	34.00	−726.2	
44	33.86	−784.8	−295.02	**45**	27.09	−757.0	
46	66.16	−895.5	−162.27	**47**	55.64	−759.4	−230.72
48	0.51	−335.0		**49**	35.68	−832.5	−297.38

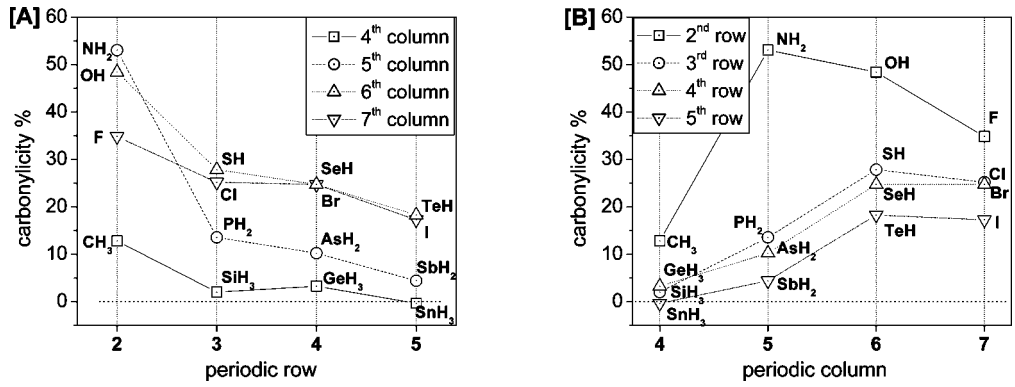


Figure 8. Trend of the carbonylicity curve of H−C(=O)−X along the periodic rows (A) and columns (B).

row, all rows exhibit a maximum conjugation with the overall maximum in the sixth column. In the second row, the maximum is at the fifth column, at the N atom exhibiting the highest conjugation among all elements. This suggests unique structures being attributed to the amide group, more specifically to the peptide bond.

3.3. Carbonylicity as a Driving Force for Acyl Transfer Reactions. Acyl transfer reactions are of significant interest from preparative and biological points of view, with simple acyl halogenides and acyl anhydrides being widely used in synthesis. Here we introduce Δ(carbonylicity %) value, which represent the difference between the carbonylicity values of the reactant and product systems:

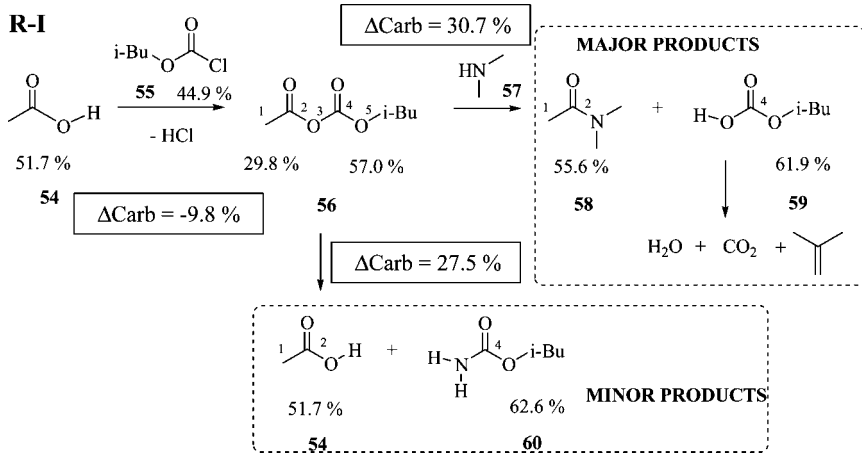
$$\Delta(\text{carbonylicity \%}) = \sum \text{carbonylicity}_{\text{products}} - \sum \text{carbonylicity}_{\text{reactants}} \quad (7)$$

If the resultant carbonylicity value is positive, then the reaction is intrinsically favored from the carbonylicity point of view. Steric hindrance, kinetic consequences, and side reactions also contribute to reactivity; therefore a positive carbonylicity value does not mean automatically a proceeding reaction. Nevertheless, Δ(carbonylicity) represents a thermodynamic driving force in acyl transfer reactions, analogous to the role of amidity in the case of the transamidation reactions.[9] In the following section, this new methodology is applied to the field of peptide chemistry, especially in peptide bond formation.

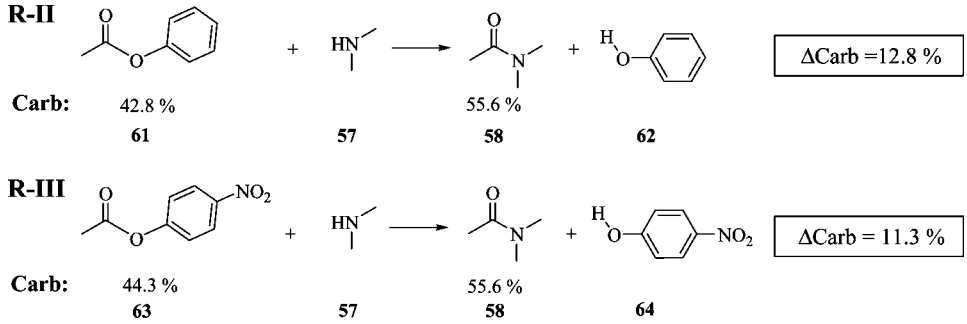
A peptide bond can be formed by different means, each beginning with activation of the acid reactant, followed by nucleophilic attack of the amine reactant. Three differing activation methods are considered here: anhydride (**R-I**),[36] active ester (**R-II**, **R-III**, and **R-IV**),[37] and activation by dicyclohexylcarbodiimide (DCC; **R-V**).[38] From the carbonylicity point of view, the reaction between an acid (such as **54**) and an amine (such as **55**) is thermodynamically advantageous, with the reaction exhibiting Δ(carbonylicity) of +3.9%, corresponding to $\Delta(\text{carbonylicity})/m = 3.9/0.4830 = 8.1$ kJ mol^{-1} increase in resonance energy. In all of the activation methods, the relatively high initial carbonylicity value of the acid reagent (**54**, 51.7%) is significantly lowered; consequently the reactivity of the acid is enhanced by an activation reagent.

In the case of peptide bond formation via mixed anhydrides (**R-I**), the acid (**54**) is reacted with isobutyl chloroformate (**55** in Scheme 10),[39] resulting in a mixed anhydride (**56**) with a relatively low carbonylicity value on the original carbonyl functionality (29.8%). This active species may easily react with an amine (**57**), leading to the desired product **58** (55.6%) and side product **59**, which subsequently decomposes to isobutylene, CO_2, and H_2O. Despite the change in the carbonylicity value being negative but small (−4.4%) in the activation step (**54** + **55** → **56**), the associated HCl elimination and salt formation with the applied base together provide a strong driving force. The active mixed-anhydride reagent exhibits low carbonylicity at C2 (29.8%), indicating significant reactivity toward the amine **57**; however, C4 atoms possess a combined larger carbonylicity (57.0%; decreased reactivity). Therefore, products **58** and **59** form exclusively and not **54** and **60**; the latter route is neither thermodynamically nor kinetically preferred.

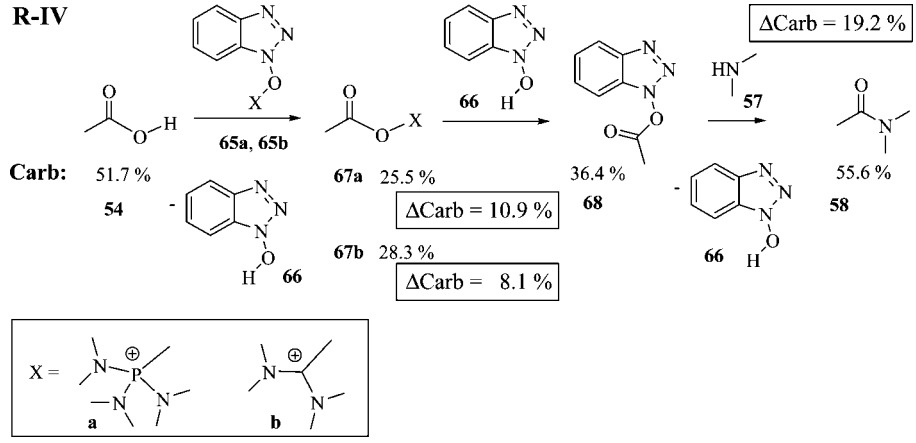
SCHEME 10



SCHEME 11



SCHEME 12

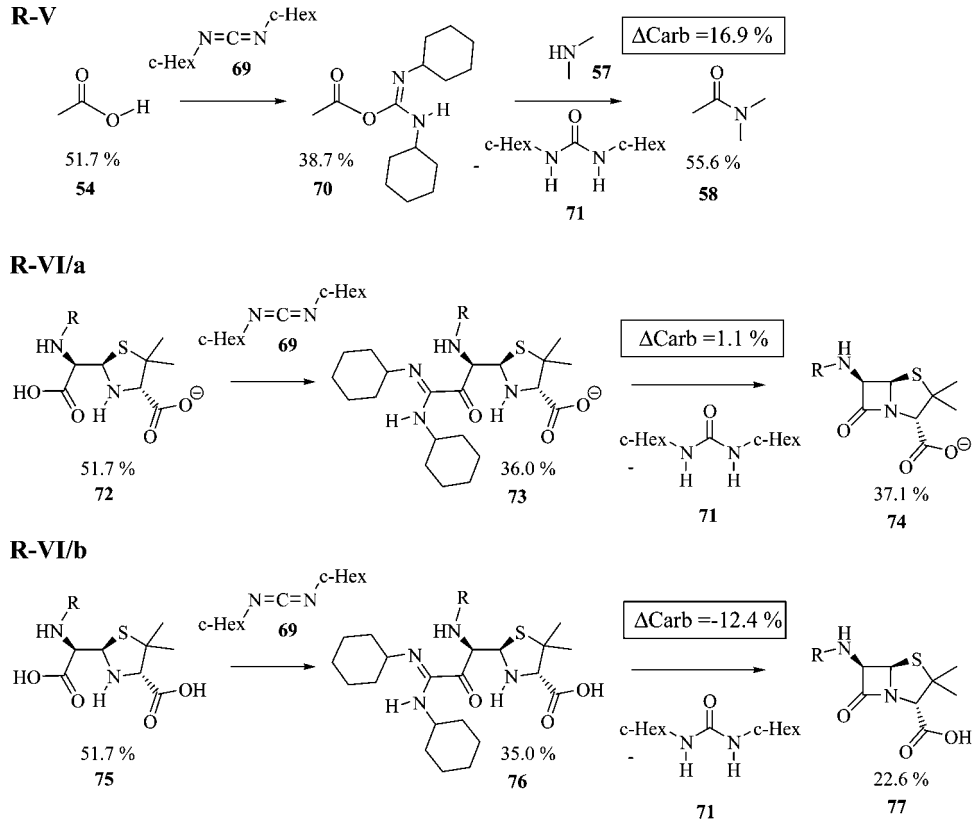


For an ester to be able to transform to the corresponding amide, the reaction requires an unusually high temperature or a Lewis acid catalyst (e.g., $AlMe_3$) in order to proceed, due to the high carbonylicity value of the original ester and the small change in Δ(carbonylicity). Active esters, which are usually aryl esters,[40,41] exhibit lower carbonylicity values, however, allowing for relative ease of reaction in suitable conditions. In **R-II** and **R-III** (Scheme 11), two known coupling procedures are presented, used earlier to prepare peptide bonds. In both cases, the significant increase in carbonylicity values predicts relative ease of reaction for the aryl ester (**61** and **63**) with **57**, resulting in **58** as the desired product as well as **62** and **64** as side products.

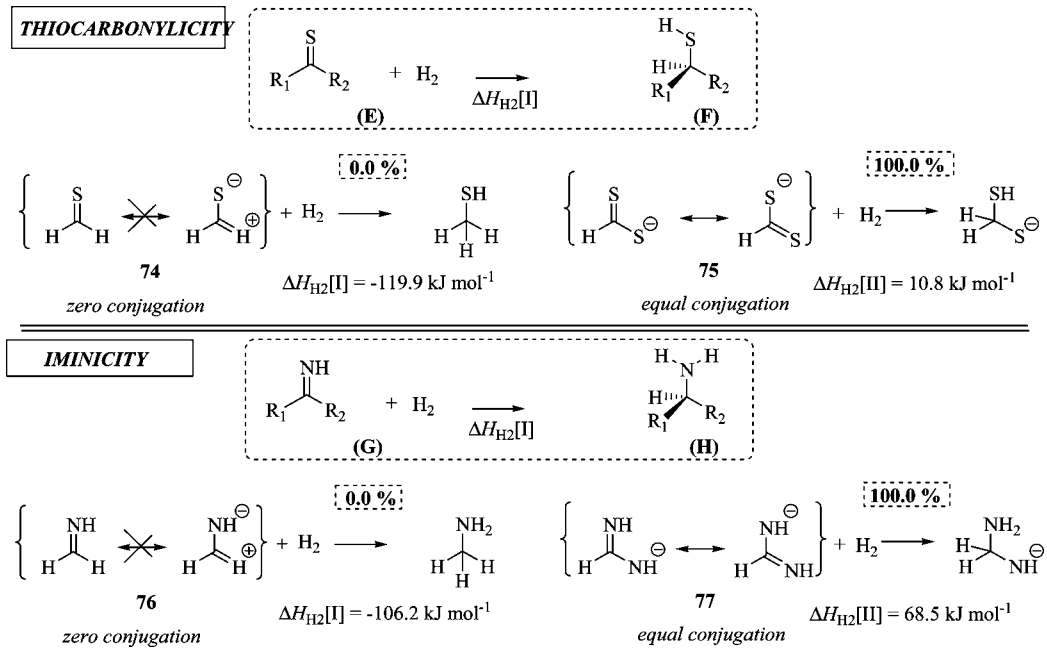
However, these active esters proved not to be so efficient due to the relatively high reaction temperature and long reaction time, attributed to insignificant changes in carbonylicity. More modern coupling reagents used in peptide chemistry, such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP; **65a**, **R-IVa** in Scheme 12)[42] and *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU; **65b**, **R-IVb**)[43] facilitate rapid peptide bond formation in optimized conditions. In both cases, the first step is elimination of the 1-hydroxybenzotriazole moiety (**66**) from the reagent, leading to very active acylating agents **67a** (25.5%) and **67b** (28.3%), which react with **66**, forming the less, yet sufficiently, active intermediate **68** (36.4%).[43] This intermediate then participates in an acyl-exchange reaction with **57**, forming the new peptide bond in **58**. Due to the higher carbonylicity change during reaction, the rate is accelerated even at room temperature. The corresponding carbonylicity values for **67a** and **67b** during reaction may explain the experimental observation that the BOP reagent (**65a**) is usually faster than HBTU (**65b**).

One of the most efficient reagents used in forming peptide bonds is *N*,*N*′-dicyclohexylcarbodiimide (DCC; **69**),[43,44] which

SCHEME 13



SCHEME 14: Definition of Thiocarbonylicity and Iminicity Percentages via Enthalpy of Hydrogenation (ΔH_{H2}) of Thiocarbonyl and Imine Groups, Respectively[a]



[a] Values were obtained from the geometry-optimized structures, computed at the B3LYP/6-31G(d,p) level of theory. In structures **F** and **H**, the H−O−C−R_2 dihedral angle is in the anti orientation.

readily reacts with the carboxylic acid (e.g., **54** in **R-V**) to form the very active species **70** (38.7%), as shown in Scheme 13. Subsequently, this intermediate initiates reaction with amines (e.g., **57**), while *N*,*N*′-dicyclohexylurea (DCU, **71**) leaves the molecule, yielding the amide **58**.

Most impressive is the use of DCC in synthesis of penicillin (Scheme 13, **R-VI/a**), where the final cyclization step is carried out with this reagent.[45−47] According to literature, cyclization of the open-chain monodeprotonated penicillin derivative (**72**) was successful only in basic conditions (aqueous KOH). After the reaction between **72** and DCC (**69**), the 51.7% carbonylicity value decreases to 36.0% in the resulting intermediate **73**. The higher carbonylicity value of the penicillin product **74** (37.1%) aids intermediate **73** in cyclizing. This marginally positive

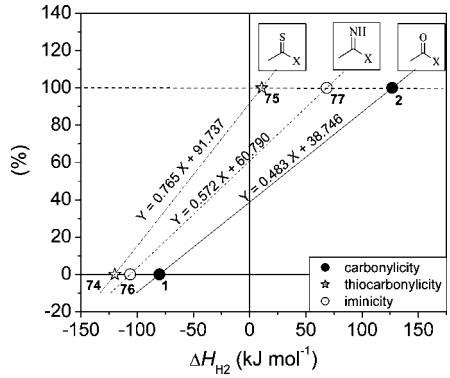


Figure 9. Comparison of ΔH_{H2} dependence of thiocarbonylicity and iminicity with carbonylicity.

difference in the carbonylicity (37.1% − 36.0% = +1.1%) is, however, not sufficient to provide the driving force to complete the reaction, helping to explain the low experimental yields (10−12%).

Many unsuccessful experiments were carried out in order to cyclize penicillin under neutral or slightly acidic conditions in hopes of improving yields (Scheme 13, **R-VI/b**).[46,47] In this case, the starting compound in neutral form (**75**) reacts with DCC, producing intermediate **76** (carbonylicity value = 35.0%), having a similar value to that obtained for **76**. However, here the penicillin product is neutral (**77**), exhibiting a reduced carbonylicity value (22.6%); the reaction is therefore inhibited due to the negative Δ(carbonylicity) value (22.6% − 35.0% = −12.4%).

3.4. Further Extension. Finally, one may define similar scales (e.g., thiocarbonylicity and iminicity values) analogously to carbonylicity (Scheme 14). With these, one is able to account for and characterize a large portion of the chemistry of conjugated compounds used in organic chemistry and biochemistry. Thiocarbonyls (**E**, including thioacids, thioketones, and thioesters], and imines (**G**; shift bases, amidines, cytosine, uracil, and thymine) represent very important molecular families not only in organic chemistry but also in biochemistry (e.g., lipid and peptide synthesis and DNA bases).

The three conjugativity scales (carbonylicity, thiocarbonylicity, and iminicity) are depicted in Figure 9. The two points (0% and 100%) that define the scale were arbitrarily chosen, yet the three lines have tangents that are similar in magnitude between 0.4 and 0.8.

4. Conclusions

A new linear scale, carbonylicity, has been defined to measure the extent of conjugation of substituted carbonyl compounds (−CO−X). The scale is based on the relative enthalpy values of hydrogenation reactions (ΔH_{H2}), with formaldehyde (**1**) arbitrarily chosen as 0% and formate ion as +100%. A representative set of 49 general carbonyl compounds were considered in the present study, and it was concluded that the ΔH_{H2} value may be a good measure of carbonylicity. Carbonylicity percentage was computed at eight differing levels of theory, from which it has been concluded that the methodology is quasi-method-independent. Alternatively, carbonylicity percentage may also be determined from experimental enthalpies of hydrogenation. A comparison has been made between the novel carbonylicity percentage values of the compounds examined and their calculated proton affinities, as well as their reactivity toward the nucleophilic OH^- ion; both cases exhibited linear relationships. For several reactions (e.g., acyl transfer), carbonylicity is shown to be a thermodynamic driving force of the reaction. The definition was extended to substituted thiocarbonyl and imino compounds.

Acknowledgment. CAFMaD (Wales, U.K.) and Project 985 (Beijing, China) for G.A.C. are acknowledged.

Supporting Information Available: Method independence study; correlations between carbonylicity and computed NBO charges, C═O bond distance, and carbonyl IR frequency; and computed energies (E), zero-point energies (E_{ZPE}), internal energies (U), and enthalpies (H) in hartrees at various levels of theories for compounds **1**−**77**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Voet, D.; Voet, J. G.; Pratt, C. W. *Fundamentals of Biochemistry, Upgraded Edition*; John Wiley and Sons, Inc.: New York, 2002; pp 124−194.

(2) Jalbout, A. F.; Shipar, Md. A. H. *J. Chem. Sci.* **2008**, *120*, 329–337.

(3) de Leon, A.; Jalbout, A. F.; Basiuk, V. A. *Chem. Phys. Lett.* **2008**, *457*, 185–190.

(4) Jalbout, A. F. *Mol. Phys.* **2007**, *105*, 941–949.

(5) Brown, R. S. Studies in Amide Hydrolysis. In *The Amide Linkage*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley: New York, 2003; Vol. 85, p 114.

(6) Robb, M. A.; Csizmadia, I. G. *J. Phys. Chem.* **1969**, *50*, 1819–1829.

(7) Smith, R. M.; Hansen, D. E. *J. Am. Chem. Soc.* **1998**, *120*, 8910–8913.

(8) Solomons, G. T. W.; Fryhle, C. B. Aldehydes and Ketones I. In *Organic Chemistry*, 7th ed.; Wiley & Sons Inc.: New York, 2000; pp 704−876.

(9) Mucsi, Z.; Chass, G. A.; Csizmadia, I. G. *J. Phys. Chem. B* **2008**, *112*, 7885–7893.

(10) Gaylord, N. G. *Reduction with Complex Metal Hydrides*; Wiley: New York, 1956; p 322, and references therein.

(11) Giri, V. S.; Pakrashi, S. C. *Synthesis* **1987**, 1128–1130.

(12) Akabori, S.; Takanohashi, Z. *Chem. Lett.* **1990**, 251–253.

(13) Bonnat, M.; Hercourt, A.; Le Corre, M. *Synth. Commun.* **1991**, *21*, 1579–1582.

(14) Greenberg, A.; Venanzi, C. A. *J. Am. Chem. Soc.* **1993**, *115*, 6951–6957.

(15) Wiberg, K. B. Origin of the Amide Rotation Barrier. In *The Amide Linkage*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley: New York, 2003; pp 33−45.

(16) Greenberg, A.; Moore, D. T.; DuBois, T. D. *J. Am. Chem. Soc.* **1996**, *118*, 8658–8668.

(17) Liebman, J. F. Studies of Organic Molecules. In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH: New York, 1986; Vol. 3, pp 267−328.

(18) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261–4270, and references therein.

(19) Greenberg, A.; Liebman, J. F., In *Energetics of Organic Free Radicals*, Martinho Simões, J. A., Greenberg, A., Liebman, J. F., Eds.; Chapman and Hall: London, 1996; pp 196−201.

(20) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.

(21) Mucsi, Z.; Tsai, A.; Szori, M.; Chass, G. A.; Viskolcz, B.; Csizmadia, I. G. *J. Phys. Chem. A* **2007**, *111*, 13245–13254.

(22) Greenberg, A.; Moore, D. T.; DuBois, T. D. *J. Am. Chem. Soc.* **1996**, *118*, 8658–8668.

(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Stratmann, R. E., Jr.; Burant, J. C., Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K., Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; NanayakkaraA.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 03*, Revision 6.0; Gaussian Inc.: Pittsburgh, PA, 2003.

(24) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(25) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503–506.
(26) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910.
(27) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650.
(28) Mucsi, Z.; Viskolcz, B.; Csizmadia, I. G. *J. Phys. Chem A* **2007**, *111*, 1123–1132.
(29) Mucsi, Z.; Csizmadia, I. G. *Curr. Org. Chem.* **2008**, *12*, 83–96.
(30) Mucsi, Z.; Körtvélyesi, T.; Viskolcz, B.; Csizmadia, I. G.; Novák, T.; Keglevich, G. *Eur. J. Org. Chem.* **2007**, 1759–1767.
(31) Mucsi, Z.; Viskolcz, B.; Hermecz, I.; Csizmadia, I. G.; Keglevich, G. *Tetrahedron* **2008**, *64*, 1868–1878.
(32) Mucsi, Z.; Keglevich, G. *Eur. J. Org. Chem.* **2007**, 4765–4771.
(33) Pilipecz, M.; Mucsi, Z.; Varga, T.; Scheiber, P.; Nemes, P. *Tetrahedron* **2008**, *64*, 5545–5550.
(34) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385–415.
(35) Hopkinson, A. C.; Csizmadia, I. G. *Can. J. Chem.* **1973**, *51*, 1432–4134.
(36) Yamashiro, D. *Int. J. Pept. Protein Res.* **1987**, *30*, 9.
(37) Bodanszky, M. In *The Peptides: Analysis, Synthesis, Biology. Volume 1: Major Methods of Peptide Bond Formation*; Gross, E., Meienhoffer, J., Eds.; Academic Press: New York, 1979; p 105, and references therein.
(38) Sheeman, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957**, *79*, 1262–1263.
(39) Stavropolous, G.; Karagiannis, K.; Anagnostides, S.; Ministrouski, I.; Selinger, Z.; Chorev, M. *Int. J. Pept. Protein Res.* **1996**, *45*, 508.
(40) Menger, F.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824–3829.
(41) Castro, B.; Dormoy, J.-R.; Evin, G.; Selve, C. *J. Chem. Res. (S)* **1977**, 182–185.
(42) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927–1930.
(43) Campagne, J.-M.; Coste, J.; Joutin, P. *J. Org. Chem.* **1995**, *60*, 5214–5223.
(44) Sheeman, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 3089–3094.
(45) For review: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; Wiley−VCH: Weinheim, Germany, 2003; Chapt. 3, pp 41−53, and references therein.
(46) Sheeman, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067–1068.
(47) Sheeman, J. C.; Goodman, M.; Hess, G. P. *J. Am. Chem. Soc.* **1956**, *78*, 1367–1369.

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