A Quantitative Scale for the Extent of Conjugation of the Amide Bond. Amidity Percentage as a Chemical Driving Force

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The amide bond may be considered as one of the most important chemical building blocks, playing an important role not only in living organisms but in organic chemistry as well. The exact description and precise quantification of the amide bond strength is difficult, requiring a particular type of theoretical investigation. The present paper suggests a novel, yet simple, method toward quantifying amide bond strength on a linear scale, defined as the "amidity scale". This is achieved using the computed enthalpy of hydrogenation (ΔH_{H2}) of the compound examined. In the present conceptual work, the ΔH_{H2} value for dimethylacetamide is used to define perfect amidic character (amidity = +100%), while azaadamantane-2-on represents complete absence of amidic character (amidity = 0%). The component ΔH_{H2} values were computed at differing levels of theory, providing a computational and quasi-"method-independent" measure of amidity. A total of 29 well-known amides were examined to demonstrate the "scoring" accuracy of this methodology. For the compounds examined, a correlation has been made between the computed amidity percentage and their common COSNAR resonance energy values, proton affinities, and reactivity in a nucleophilic addition reaction. Selected chemical reactions were also studied. It has been shown that the change of the amidity value, during acyl transfer reactions, represents a thermodynamic driving force for the reaction.

1. Introduction

Amide bonds may be considered as one of the most important chemical moieties in biological organisms, commonly found in peptides/proteins and lipids/membranes and other biochemical systems. Amides also play an important role in selected biologically active compounds, such as penicillin-like antibiotics, drugs, and toxins.[1] They are characterized as being very stable[2] chemical bonds, with half-lives in neutral aqueous solution exceeding hundreds of years.[3]

In contrast to their general resistance to reactivity, there are numerous examples in the fields of organic and biochemistry where the amide bond undergoes nucleophilic reaction. Examples include the spontaneous or enzymatic hydrolysis of the amide bond in peptides and proteins.[4] Perhaps the most well-known small biogen amides are the penicillin-like antibiotics,[5] which inhibit penicillin binding proteins such as transpeptidase and carboxylpeptidase through an acylation of a serine residue.[6−8] In this way, the bacterial cell wall synthesis stops, leading to higher susceptibility to osmotic effect[9] and cell rupture.

The reduction of the amide bond by complex metal hydrides has significant synthetic importance for obtaining various amines.[10−13] Some amide compounds are able to react with amines, known as an acyl transfer or transamidation reaction (Scheme 1). These processes represent very efficient transformations in synthetic organic chemistry towards selectively obtaining various amide structures from amino compounds. The most notable application is the Traube synthesis of heterocycles.[14−18]

The large variability in the chemical reactivity of the amide bond may be attributed to the potential for fine-tuning of its bond strength, facilitated by the attached substituent groups. The bond strength of a general amide compound, as illustrated by its associated resonance structures (**A-I** and **A-II** in Scheme 1),[19,20] determines its specific chemical reactivity, essential to the biological activity of biochemical compounds. A stronger amide bond is more resistant to attack by nucleophilic agents (e.g., HO^-, H_2O, amines, metal hydrides, or the hydroxyl groups of serine proteases), whereas a weaker amide bond is correspondingly more reactive.[21] For a stronger amide bond, the conjugation between N and the C of the carbonyl group is more extensive, meaning that the contributions of the two most significant resonance structures (**A-I** and **A-II**) are more closely balanced between than they are in a weaker amide bond. In the case where there is no significant conjugation, the preferred resonance structure is **A-I**. In many biological or pharmaceutical cases Mother Nature, or the practicing chemist, must find the appropriate balance between the reactivity and stability of the amide bond. If the amide bond is too reactive, it may have an increased activity, but it may also be metabolized prior to reaching its intended target (the enzyme). If, however, the amide bond is less reactive, with an increased stability in aqueous

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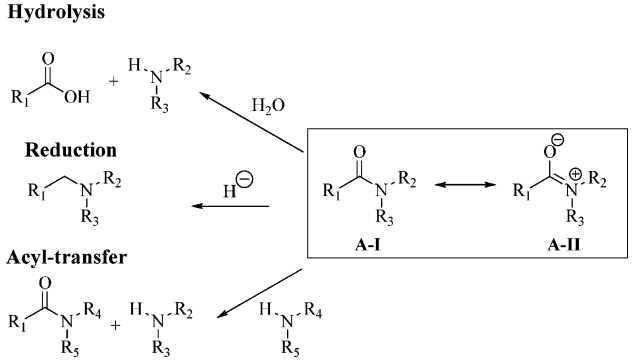
SCHEME 1: The Two Predominant Resonance Structures (A-I and A-II) of the Amide Moiety and Some Selected Typical Reactions



solutions and bodily fluids, it will be difficult for such a compound to react with efficacy when it encounters the target (the enzyme). The penicillin-like antibiotic[5] presents a good example for the above-mentioned natural design; the β-lactam ring is highly reactive due to its strained four-membered ring, which may open easily in the presence of nucleophilic reagents, such as the hydroxyl group of an enzyme side chain. The reactivity of the amide bond can be fine-tuned by using different substituents, obtaining an appropriate molecule, which both survives the aqueous body fluid and finds the targeted enzyme.

2. Methods

All computations were carried out using the Gaussian03 program package.[22] Geometry optimizations and subsequent frequency analyses were carried out on selected amide-containing systems from which the 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/6-31G(d),[23] **D** B3LYP/6-31G(d,p), **E** B3LYP/6-311++G(2d,2p), **F** B3LYP/aug-ccVTZ//B3LYP/6-311++G(2d,2p), **G** B3LYP/aug-ccVQZ//B3LYP/6-311++G-(2d,2p), **H** MP2(fc)/6-31G(d),[24] **I** CCSD/6-31G(d)//MP2(fc)/6-31G(d),[25] **J** CCSD(T)/6-31G(d)//MP2(fc)/6-31G(d),[26] **K** CCSD/6-31G(d), and **L** CCSD(T)/6-311G(d,p)//CCSD/6-31G(d) (Tables 2 and 3).[26] Basis sets were chosen for their reliability in the characterization of aromaticity, in agreement with recently established works.[27] The vibrational frequencies were computed at the same levels of theory as that used for geometry optimization in order to properly confirm all structures as residing at minima on their potential energy hypersurfaces (PEHSs). For the scaling of the thermodynamic parameters for levels **F**, and **G**, as well as **I**, **J**, **K**, and **L**, we made use of the scaling factors employed in methods **E** and **H**, respectively. Thermodynamic parameters (*U*, *H*, *G*, and *S*, listed in the Supporting Information, Table S1−S40) were computed at 298.15 K, using the quantum chemical, rather than the conventional, thermodynamic reference state.

3. Results and Discussion

3.1. The Concept. A protocol has been developed to quantify the extent of conjugation of the amide bond. The parameter, thus obtained, is termed "amidity", in analogy to the term "aromaticity".[27] To measure the reactivity and strength of a general amide compound, an in silico hydrogenation reaction was carried out (Scheme 2). In computing the ΔH_{H2}, a given stable conformation and configuration of the products was chosen in which no significant intermolecular interaction was identified, which may perturb the system.

TABLE 1: Computed ΔH_{H2} Values (kJ mol^{-1}) and Amidity % for Model Compounds (1−29) Geometry-Optimized at the B3LYP/6-31G(d,p) Level of Theory

	ΔH_{H2}[I]	Amidity (%)		ΔH_{H2}[I]	Amidity (%)
1	34.88	100.0[a]	**2**	−44.62	0.0[a]
3	29.62	92.4	**4**	36.18	101.6
5	32.97	97.6	**6**	33.70	98.5
7	20.50	82.0	**8**	0.89	57.3
9	28.13	91.5	**10**	39.87	106.3
11	35.63[b]	75.7	**12**	37.31[b]	77.8
13	41.27[c]	115.0	**14**	46.82[b]	121.9
15	27.66[d]	90.9	**16**	29.55[b]	93.3
17	−33.80[e]	13.6			
18	54.05[e]	124.1	**19**	59.15[e]	130.5
20	−4.35[d]	25.4	**21**	−3.63[d]	26.3
22	−68.59	−30.2	**23**	2.26	59.0
24	20.34	81.7	**25**	25.22	87.7
26	4.17	61.4	**27**	−1.95	53.7
28	56.76	127.5	**29**	41.06	107.8

[a] By definition. [b] Modified by ring strain ΔH_{H2}*[I]; $\Delta\Delta H_{H2}$(RS)= −20.10 kJ mol^{-1}. [c] Modified by ring strain ΔH_{H2}*[I]; $\Delta\Delta H_{H2}$(RS)= 5.55 kJ mol^{-1}. [d] Modified by ring strain ΔH_{H2}*[I]; $\Delta\Delta H_{H2}$(RS)= −1.04 kJ mol^{-1}. [e] Modified by ring strain ΔH_{H2}*[I]; supposing that $\Delta\Delta H_{H2}$(RS)= 0 kJ mol^{-1}.

The ΔH_{H2}[I] value (eq 1) of N,N-disubstituted or tertiary amide **1** was defined as a full or complete amide bond (100%), and the ΔH_{H2}[I] value of compound **2** was taken as being completely devoid of amidic bonding (0%), with negligible ring strain. In the case of **2**, delocalization is completely blocked due to the 3D structure, where the nonbonding electron pair is forced to be in a nonconjugative orientation.[28−31] Therefore, **2** behaves as a nonstrained tertiary amine rather than a disubstituted amide. The trimethyl homologues of **2** have also been prepared and reported.[32,33] Similar to percentage aromaticity,[27] measuring the ΔH_{H2} or determining the enthalpy of formation opens the way to obtaining experimental percentage amidity (eq 2a and 2b). It should perhaps be emphasized that in the choice of these standards (compounds **1** and **2**), care was taken to pick structural similarities since both compounds **1** and **2** correspond to disubstituted amides, like for structure **A**, as specified in Scheme 2. Also, the choice of compound **2** seemed appropriate as the adamantane-type structure is expected to have no ring strain

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

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

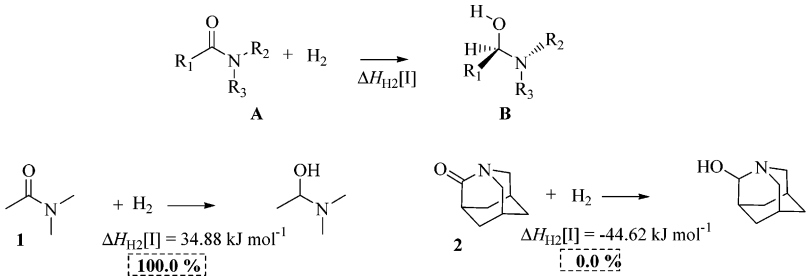
$$[\text{relative amidity \%}] = [\text{amidity \%}] - [\text{amidity \%}]_0 = m\Delta H_{H2}[\mathrm{I}] \quad (2b)$$

In order to design a quantitative amidity scale (eq 2a), a wide variety of amides (**3**−**29**) were investigated and discussed (Scheme 3, Table 1, and Figure 1), in addition to the reference compounds (**1** and **2**). The 27 widely different types of model compounds (**3**−**29**) were classified into 4 groups, representing illustrative amide types (Scheme 3). Compounds (**1** and **3**−**10**), corresponding to the first group, were used to study the steric and inductive effects of the alkyl and cycloalkyl groups. The increasing volume of the N substituents decreased the conjugation between the carbonyl and the N atom due to steric hindrance. The role of ring strain (second group) was also studied for four- to six-membered ring sizes, using model compounds **11**−**17**. Among these well-known small lactams, the four-membered structures **11** and **12** were used to model penicillin-type antibiotics, which exhibit large reactivity toward

TABLE 2: Parameters for the Linear Scale of Amidity Percentage, Calculated from Theoretical ΔH_{H2} Values (kJ mol^{-1}) Obtained for 1 and 2, According to eq 2a

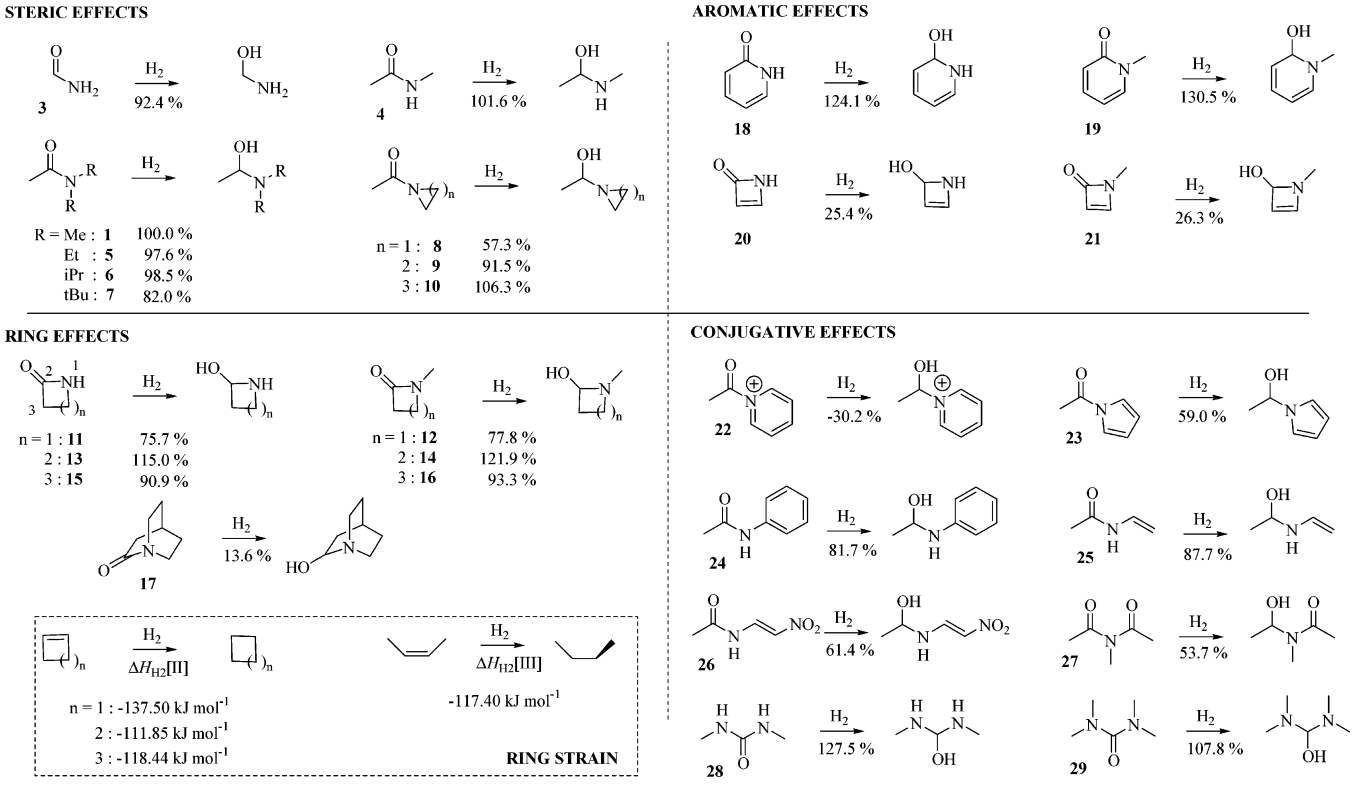
	method	ΔH_{H2}(1) 100%	ΔH_{H2}(2) 0%	*m*	[amidity%]0
A	HF/6-31G(d)	14.38	−68.75	1.203	82.705
B	HF/6-31G(d)	33.50	−40.03	1.360	54.441
C	B3LYP/6-31G(d)	29.97	−34.21	1.558	43.301
D	B3LYP/6-31G(d,p)	34.88	−44.62	1.258	56.126
E	B3LYP/6-311++G(2d,2p)	29.01	−45.28	1.346	60.948
F	B3LYP/aug-ccVTZ//B3LYP/6-311++G(2d,2p)	31.01	−44.59	1.323	58.982
G	B3LYP/aug-ccVQZ//B3LYP/6-311++G(2d,2p)	31.56	−43.29	1.336	57.836
H	MP2(fc)/6-31G(d)	43.14	−33.88	1.298	43.984
I	CCSD/6-31G(d)//MP2(fc)/6-31G(d)	33.21	−39.87	1.368	54.552
J	CCSD(T)/6-31G(d)//MP2(fc)/6-31G(d)	41.94	−31.68	1.358	43.029
K	CCSD/6-31G(d)	26.51	−46.92	1.362	63.903
L	CCSD(T)/6-311G(d,p)//CCSD/6-31G(d)	12.46	−54.80	1.487	81.471
	average	30.13	−43.99	1.355	58.440
	S.Dev.	9.19	10.11	0.0935	13.0319

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



[a] Values were obtained from the geometry-optimized structures, computed at the B3LYP/6-31G(d,p) Level of Theory. In structure B, the O−C−N−R_3 and H−O−C−N dihedral angles are in the anti orientation.

SCHEME 3: A Method to Determine the Enthalpy of Hydrogenation (ΔH_{H2}) Value for Model Compounds (1, 3−29), Measuring the Conjugation of the Amide Bond[a]



[a] Reference compounds, helping to correct for ring strain (RS) of cyclic amides, are shown in the dashed box (lower left-hand side). The numerical values below each arrow represent the amidity % values at the B3LYP/6-31G(d,p) level of theory.

nucleophiles. In the third group, amide compounds were chosen to account and calibrate for aromatic stabilization and antiaromatic destabilization (**18**−**21**). In compounds **18** and **19**, one may suppose that the aromaticity and amidity promoted one other, meaning a stronger amide bond resulted in higher aromaticity. In contrast to the previously mentioned compounds,

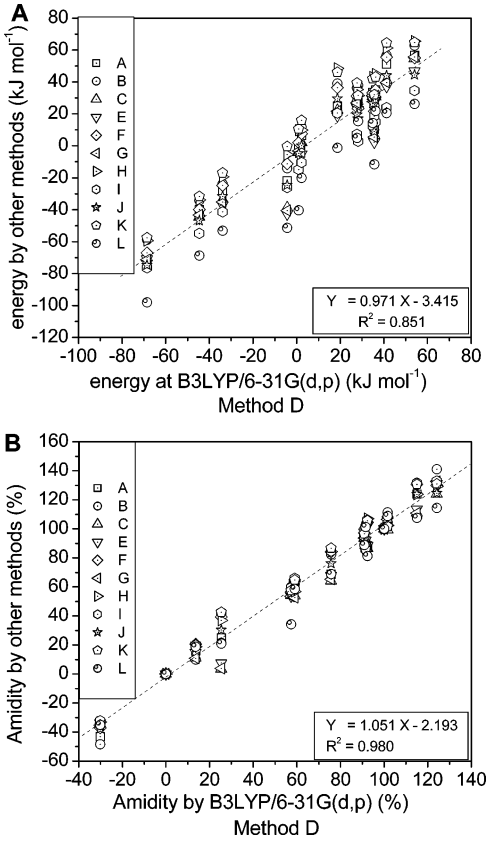


Figure 1. Correlation of ΔH_{H2} (A) in kJ mol^{-1} and amidity % (B) values obtained by various methods against the results obtained by B3LYP/6-31G(d,p) (method **D**) and those of obtained other methods (methods **A**−**C** and **E**−**L**).

in the case of compounds **20** and **21**, the aromaticity and amidity were competing with one other; here, the stronger amide group would result in stronger antiaromaticity, which destabilizes the system. Once an equilibrium is attained, the stabilization of the amidity and corresponding destabilization of the antiaromaticity showed balanced values. Selected conjugated amides were subsequently considered towards characterizing the π-electronic effect of conjugated model molecules. In these cases, the amide conjugation was expected to compete with another type of conjugation, changing the amidity values of these compounds. We thought that these simple model compounds covered almost all possible amide types and led to a well balanced study.

In order to obtain accurate values for ring structures (**11**−**17**), one should consider the change of the ring strain in the hydrogenation reaction process, where an sp^2-hybridized C atom (with ∼120° bond angle) may distort towards sp^3 hybridization (with ∼109° bond angles). For this reason, reference reactions were considered for each of the lactam-containing systems, where the cycloalkene with a similar ring size was hydrogenated to the appropriate cycloalkane (ΔH_{H2}[II], Scheme 3). These values were compared with the corresponding ΔH_{H2} of *cis*-2-butene changing to gauche butane (ΔH_{H2}[III]; eq 3), thereby obtaining, for the estimated ring strain (RS), the $\Delta\Delta H_{H2}$(RS) values for each reaction. One may correct the ΔH_{H2}[I] values of compounds **11**−**17**, **20**, and **21** with the calculated $\Delta\Delta H_{H2}$-(RS), yielding ΔH_{H2}*[I] values (eq 4, **Table S1**). The final step is to convert the ΔH_{H2}*[I] to amidity %, using eq 2. By definition, ring strain energy is zero in the cases of the open chain compounds

$$\Delta\Delta H_{H2}(\mathrm{RS}) = \Delta H_{H2}[\mathrm{II}] - \Delta H_{H2}[\mathrm{III}] \quad (3)$$

$$\Delta H_{H2}^{*}[\mathrm{I}] = \Delta H_{H2}[\mathrm{I}] - \Delta\Delta H_{H2}(\mathrm{RS}) \quad (4)$$

The corresponding chemical equations and enthalpy values for II and III are shown in the lower left-hand corner of Scheme 3.

3.2. Method Independence. The method dependence of this methodology was examined by calculating the ΔH_{H2} values at

TABLE 3: The Computed ΔH_{H2} Values (kJ mol^{-1}) and Calculated Amidity % at Differing Levels of Theory for 12 Selected Compounds

		method[a]														
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	average	MAX − MIN	S Dev.
3	ΔH_{H2}	−1.20	24.90	38.97	18.62	18.89	22.25	21.75	48.58	36.51	46.02	29.50	20.62	27.12	49.78	13.80
	%	**81.3**	**88.3**	**104.0**	**92.4**	**86.4**	**88.4**	**86.9**	**107.1**	**104.5**	**105.5**	**104.08**	**106.2**	**96.26**	**25.80**	**9.72**
4	ΔH_{H2}	21.78	35.02	43.40	36.18	28.50	30.73	31.38	44.88	34.96	43.14	28.83	14.95	32.81	29.93	8.88
	%	**108.9**	**102.1**	**111.3**	**101.6**	**99.3**	**106.2**	**106.4**	**102.3**	**102.4**	**101.6**	**103.17**	**103.7**	**104.08**	**12.00**	**3.45**
8	ΔH_{H2}	−40.36	0.77	10.75	0.89	−4.96	−4.03	−3.17	9.66	2.09	10.59	−4.74	−14.88	−3.12	51.11	13.93
	%	**34.2**	**55.5**	**60.0**	**57.3**	**54.3**	**53.7**	**53.6**	**56.5**	**56.4**	**57.4**	**57.45**	**59.4**	**54.65**	**25.80**	**6.75**
9	ΔH_{H2}	15.45	27.25	37.93	28.13	22.75	25.00	25.51	31.46	23.52	31.56	17.01	2.82	24.03	35.11	9.10
	%	**101.3**	**91.5**	**102.4**	**91.5**	**91.6**	**92.0**	**91.9**	**84.8**	**86.7**	**85.9**	**87.08**	**85.7**	**91.03**	**17.60**	**5.76**
11[b]	ΔH_{H2}	−11.50	10.45	25.05	35.63	2.41	6.59	5.52	31.05	21.66	32.07	8.96	18.50	15.53	47.13	14.17
	%	**68.9**	**68.7**	**82.3**	**75.7**	**64.2**	**67.7**	**65.2**	**84.3**	**84.19**	**86.6**	**76.10**	**84.6**	**75.71**	**22.40**	**8.47**
13[b]	ΔH_{H2}	20.61	51.16	56.78	41.27	37.20	41.26	39.74	61.40	55.62	64.44	44.03	23.91	44.79	43.83	13.79
	%	**107.5**	**124.0**	**131.8**	**115.0**	**111.0**	**113.6**	**110.9**	**123.7**	**130.7**	**130.6**	**123.87**	**131.6**	**121.19**	**24.30**	**9.12**
15[b]	ΔH_{H2}	5.03	28.29	36.26	27.66	24.28	29.30	26.86	35.30	31.15	39.36	19.37	7.23	25.84	34.33	10.68
	%	**88.8**	**92.9**	**99.8**	**90.9**	**93.6**	**97.7**	**93.7**	**89.8**	**97.2**	**96.5**	**90.28**	**94.9**	**93.84**	**11.00**	**3.49**
17[b]	ΔH_{H2}	−53.21	−28.42	−23.87	−33.90	−37.11	−33.50	−35.18	−19.39	−24.79	−16.97	−31.68	−41.34	−31.61	36.24	9.97
	%	**18.7**	**15.8**	**9.9**	**13.6**	**11.0**	**14.7**	**10.8**	**18.8**	**20.6**	**19.9**	**20.75**	**20.0**	**16.21**	**10.85**	**4.11**
18	ΔH_{H2}	26.35	56.72	62.72	54.05	46.84	54.62	55.73	65.54	55.08	64.75	44.51	34.64	51.80	39.19	11.91
	%	**114.4**	**131.6**	**141.0**	**124.1**	**124.0**	**131.2**	**132.7**	**129.1**	**129.9**	**131.0**	**124.52**	**133.0**	**128.88**	**26.60**	**6.55**
20	ΔH_{H2}	−51.42	−21.83	−14.03	−4.35	−42.65	−38.81	−40.52	−5.50	−11.18	−0.42	−24.64	−26.16	−23.46	51.00	16.91
	%	**20.9**	**24.8**	**21.4**	**25.4**	**3.5**	**7.6**	**3.7**	**36.9**	**39.3**	**42.5**	**30.34**	**42.6**	**24.91**	**39.10**	**14.27**
22	ΔH_{H2}	−98.00	−71.89	−58.85	−68.59	−70.94	−70.10	−71.30	−59.42	−67.07	−57.58	−74.75	−76.47	−70.41	40.42	10.68
	%	**−35.2**	**−43.3**	**−48.4**	**−30.2**	**−34.5**	**−33.8**	**−35.3**	**−33.2**	**−37.2**	**−35.2**	**−37.90**	**−32.2**	**−36.37**	**18.20**	**5.00**
23	ΔH_{H2}	−20.03	6.39	11.94	2.26	−5.24	2.06	−3.87	9.88	7.54	15.96	0.11	−10.43	1.38	35.99	10.14
	%	**58.6**	**63.1**	**62.2**	**59.0**	**53.9**	**61.7**	**52.7**	**56.8**	**64.9**	**64.7**	**64.1**	**66.0**	**60.64**	**13.30**	**4.42**

[a] **A** HF/3-21G; **B** HF/6-31G(d); **C** B3LYP/6-31G(d); **D** B3LYP/6-31G(d,p); **E** B3LYP/6-311++G(2d,2p); **F** B3LYP/aug-ccVTZ//B3LYP/6-311++G(2d,2p); **G** B3LYP/aug-ccVQZ//B3LYP/6-311++G(2d,2p); **H** MP2(fc)/6-31G(d); **I** CCSD/6-31G(d)//MP2(fc)/6-31G(d); **J** CCSD(T)/6-31G(d)//MP2(fc)/6-31G(d); **K** CCSD/6-31G(d), **L** CCSD(T)/6-311G(d,p)//CCSD/6-31G(d). [b] Modified by ring strain.

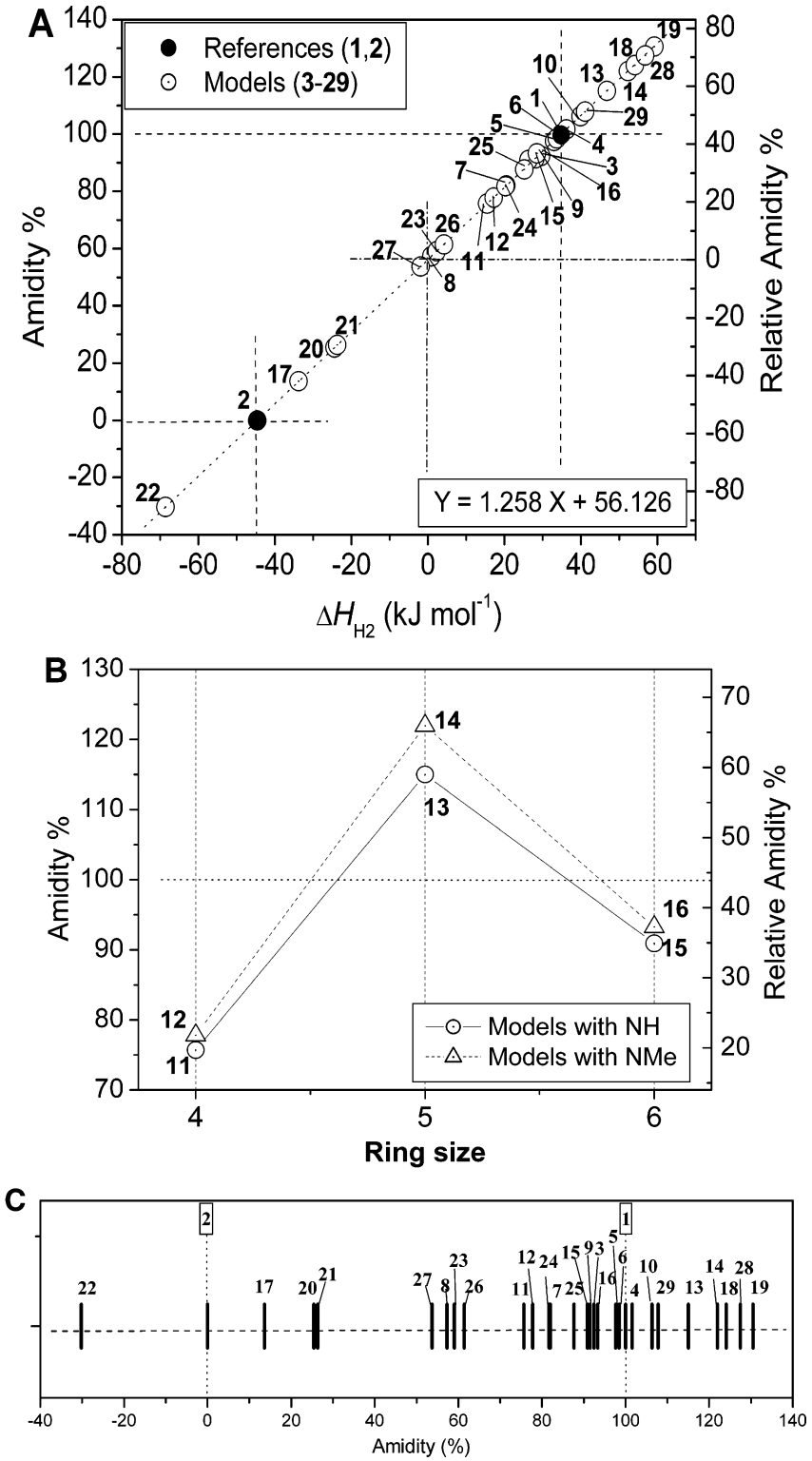
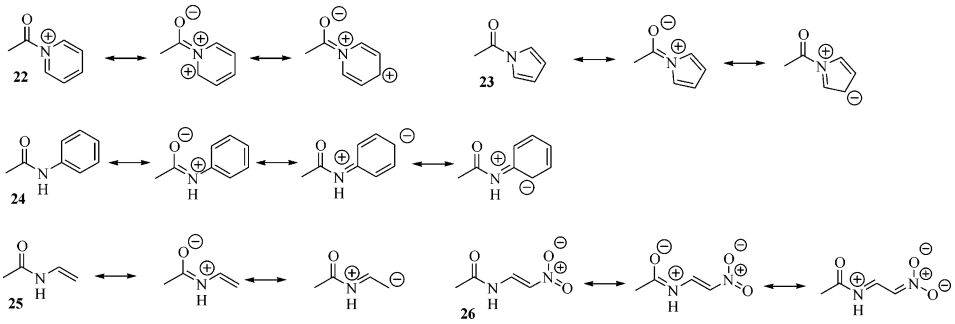


Figure 2. (A) The theoretical amidity scale. Shown are the percentage value of amidity based on the ΔH_{H2} value of a given compound computed at the B3LYP/6-31G(d,p) level of theory. For the description of each compound, see Table 1 as well as Scheme 3. (B) Correlation between the ring size and the amidity % in the case of compounds **11**−**17**. (C) "Amidity spectrum".

the B3LYP/6-31G(d,p) level of theory and subsequently converting it to amidity percentages for 12 selected amide compounds of the 29 studied (Table 1).

These were subsequently compared to results obtained at differing levels of theory (Tables 2 and 3). The correlations between the ΔH_{H2} values, computed at differing levels of theory, show significant method dependence ($R^2 = 0.851$; Figure 1A). However, by converting all ΔH_{H2} values to amidity percentages, one may find a fairly good fit according to the R^2 values obtained ($R^2 = 0.980$; Figure 1B). All MIN−MAX and standard deviation (S.Dev.) values of the amidity percentages are significantly smaller than the corresponding values of ΔH_{H2} (Table 3). In the exception of two cases (**13**, **22**), the calculated average values of ΔH_{H2} and the amidity are very close to the values obtained by method **D** [B3LYP/6-31G(d,p)]; therefore, the discussion is based on this method. Conversely, the calculated amidity percentages for similar compound are in the same range, irrespective of the theoretical method applied.

SCHEME 4: Selected Representative Resonance Structures of 22−26



Consequently, the percentage amidity scale is virtually method-independent. This methodology, therefore, may be considered as a quasi-rigorous method-independent technique. It must be emphasized, however, that there is no limitation in the theoretical method to be employed, meaning that one may use as high or as low a level of a computational theory as desired. The quasi-method independence of the protocol has previously been examined[27] in the case of aromaticity and antiaromaticity.

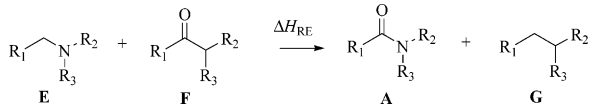
It should perhaps be emphasized that for relatively small molecules, such as those studied in this paper, method **D** may conveniently be used. However, even for oligopeptides, which have several amide bonds, only a lower level theory, such as method **A**, is practical at this time (2007). As the tangents (*m*) of the two lines are quite similar, 1.203 and 1.258 for methods **A** and **D**, respectively (c.f. Table 2), the quasi-method independence of the applied protocol is a great advantage.

3.3. Applications. As can be seen from Figure 2A, for the first group, the results obtained meet general chemical expectations, where the crowded amide (**7**) exhibits a lower amidity percentage than a noncrowded one (**1**). The results also point to the fact that the alkyl group has electron-donating ability, indicated by the lower amidity percentage, where the N atom is in an unsubstituted NH_2 form (**3**), in comparison to that of the disubstituted one (**1**). It should perhaps be emphasized at this point that the "relative amidity", calculated by eq 2b and calibrated on the right-hand side of Figure 2A, is proportional to the stabilization energy or stabilization enthalpy (ΔSE).

Considering the second group, the effect of lactam ring size on the amidity percentages calculated for compounds **11**−**17** exhibits a maximum (Figure 2B) at five-membered rings (**13**, **14**), followed by six-membered (**15**, **16**), and subsequently, by four-membered rings (**11**, **12**). Systems **13** and **14** exhibit higher amidity percentages than those of **15** and **16**, which may be explained by the $C^3-C^2-N^1-C^n$ dihedral angle (see $\chi_{C3-C2-N1-C^n}$ tabulated geometries in the Supporting Information). The largest deviation from planarity for this dihedral values (13.15°) is found in systems **15** and **16**, while in **13** and **14**, it is considerably smaller (5.51°). The nonplanarity of the amide group in the six-membered lactams is responsible for the lower amidity values. In the case of systems **11** and **12**, the stretched four-membered lactam rings prove to be "amidically unfavorable", even though the dihedral angles are nearly planar ($\chi_{C3-C2-N1-C^n} = 0°$), traditionally regarded as being related to high stability in the amide bond.

Compound **17** showed an extremely low amidity percentage, which was to be expected as its structure was analogous to that of **2**. This compound has recently been prepared,[28,31] together with its analogues.[28,34−38] These exhibited very large proton affinities (PA), determined both experimentally (964 kJ mol^{-1})[31] and theoretically (944.3 and 958.4 kJ mol^{-1}),[21,31] in comparison to established PAs of amides (880−900 kJ mol^{-1}).[39] The very large gas-phase basicities of the amide nitrogen lone pairs of such compounds fall into the range of the PAs of tertiary amines.

SCHEME 5: The Definition of COSNAR Resonance Energy (ΔH_{RE})



In the third group (**18**−**21**), the highest amidity values were obtained for compounds **18** (the less stable tautomeric form of 2-hydroxypyridine)[40] and its *N*-methyl derivative (**19**). These exceptionally high amidity percentage may be attributed to the extensive aromatic character of these compounds,[41,42] which is subsequently eliminated as a consequence of the hydrogenation reaction. An inverse effect was found in the cases of the unsaturated four-membered lactams **20** and **21**, where the unusually low amidity values originate from the antiaromatic character of these compounds.[43]

Finally, in the fourth group (**22**−**29**), some other amides with differing degrees of conjugation were considered in order to characterize the competition for the lone pair of the N atom, between the neighboring carbonyl group and the unsaturated R group attached to the amide nitrogen (Scheme 4). As expected, the less conjugated groups [phenyl and vinyl (**24**, **25**)] exhibited the highest amidity percentage. Somewhat stronger competition was attributed to the pyrrole (**23**) and nitrovinyl (**26**) groups, where strong competition was again found between the carbonyl group and the unsaturated R group for the lone pair of the N atom, resulting in a lowered amidity percentage. In compound **22**, the positive, quaternary N atom did not exhibit conjugation with the carbonyl group; therefore, a very low amidity value was measured in this case. Bisacyl compounds (**27**) are usually more unstable than their amide counterparts, which may be attributed to the two competing carbonyl groups, and exhibit ∼50% amidity per CO group, indicating that both carbonyl groups equally contribute to the conjugation. In the case of the carbamide structures (**28**, **29**), the carbonyl group was able to conjugate with two N atoms, increasing their amidity values.

3.4. Correlation between Amidity and Resonance Energy. The resonance energy (RE, ΔH_{RE})[19−21,44] of the amide bond, together with the steric effect and ring-strain energy, form the basic characteristic of amide conjugation. First, the RE was estimated by the amide bond rotation, introducing many uncertainties to the computations.[45] Three approaches were subsequently developed as follows: methyl-capping based on experimental data (MCE),[46] group increments (GI),[47] and carbonyl substitution nitrogen atom replacement (COSNAR),[21,44] each generating slightly different results. In this study, the COSNAR method (Scheme 5) was used for comparison, itself based on the use of isodesmic reactions. An attempt was made to correlate these values with the ΔH_{H2} value and amidity

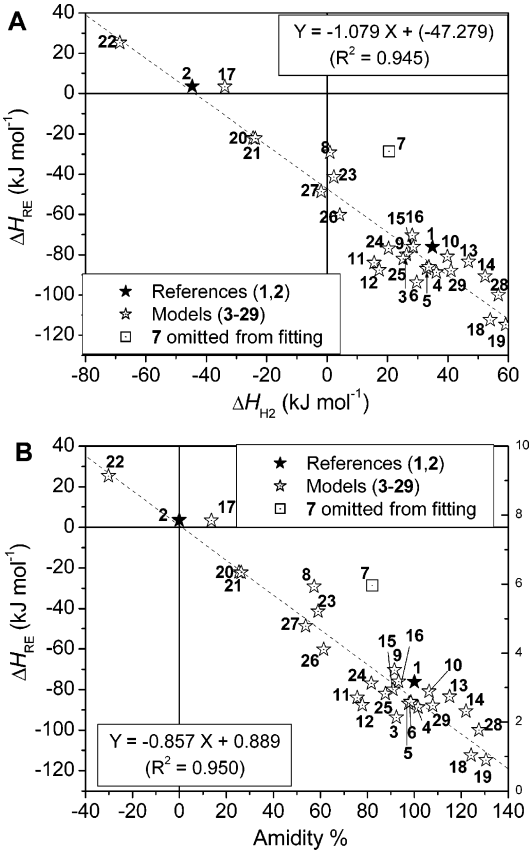


Figure 3. Correlation of the COSNAR resonance energy (ΔH_{RE}) with the computed ΔH_{H2} values (A) and the calculated amidity percentage (B). Compound **7** was omitted from the fitting.

percentage (Figure 3A and B). One may conclude that the linear fit on the correlated points is reasonably good due to the fact that those methods are evaluating the same basic phenomenon. A relatively good correlation coefficient in Figure 3A (R^2 = 0.945) and the nearly unit slope ($n = -1.079$) indicate that the hydrogenation reaction protocol measures the same resonance energy as that of the COSNAR isodesmic reaction method. However, the COSNAR method is considerably more complicated, requiring the computations of four compounds (Scheme 5) rather than two, each of which has the same size and complexity. It seems that our present protocol is a more tractable method.

$$\Delta H_{RE} = H_A + H_G - (H_E + H_F) \qquad (5)$$

3.5. Correlation between Amidity and Carbonyl IR Frequency, Proton Affinity, as well as Reactivity. The IR frequency of a carbonyl group is characteristic to its molecular properties; therefore, the correlation between the computed IR frequencies and the calculated amidity values of all model compounds (**1**−**29**) is studied here. When all model compounds (**1**−**29**) are considered (Figure 4A), the linear fitting exhibits a relatively poor R^2 value (R^2 = 0.453), but the trend is indisputable. Ignoring all ring amides and considering only the open chain primary and secondary amides (Figure 4B), the fitting is much better (R^2 = 0.840), indicating that the ring strain has an additional effect on the carbonyl frequencies.

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.[48] This has often been attributed to the conjugative stabilization of the amide linkage. Consequently, the PA of the N atom may also be expected to correlate with

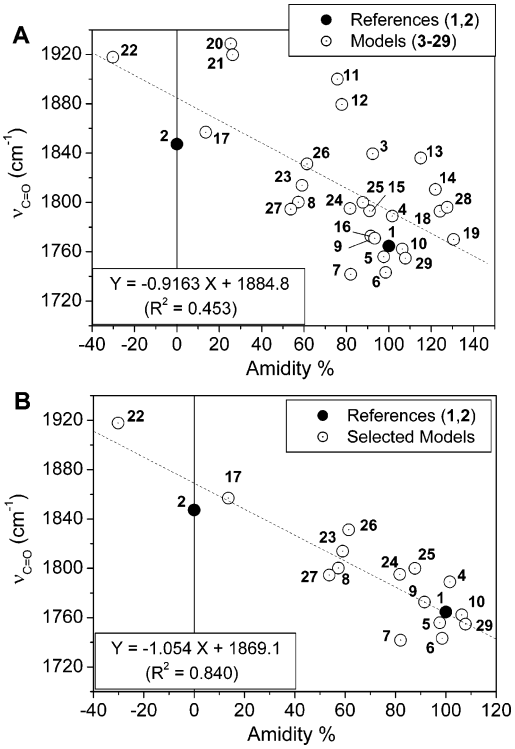


Figure 4. (A) Correlation between calculated amidity percentage and the carbonyl IR frequencies of the amide ($\nu_{C=O}$) for all model compounds (**1**−**29**). (B) Correlation between calculated amidity percentage and the carbonyl IR frequencies of the amide ($\nu_{C=O}$) for selected model compounds.

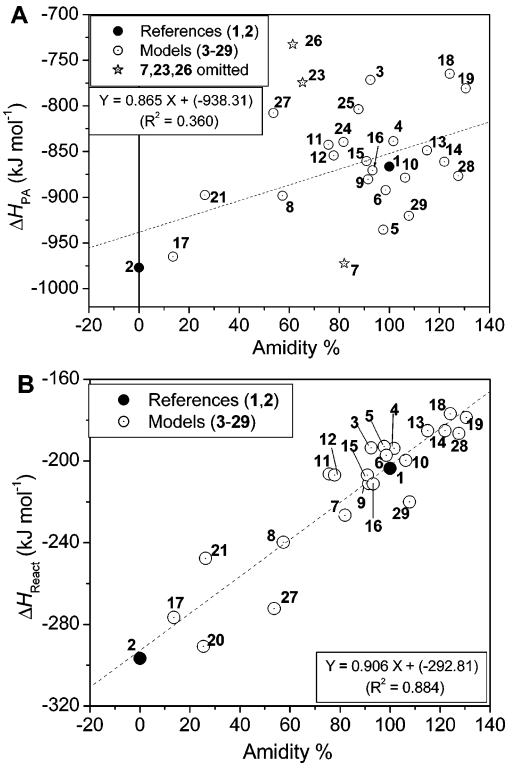


Figure 5. (A) Correlation between calculated amidity percentage and the proton affinity of each amide (ΔH_{PA}). Compounds **7**, **22**, **23**, and **26** are omitted from the fitting. (B) Correlation between calculated amidity percentage and the reactivity of amide (ΔH_{React}). Compounds **7**, **22**, **23**, and **26** are omitted from the fitting.

the amidity percentage. A stronger amide should therefore exhibit lower affinity toward protonation, and in fact, the

SCHEME 6: The Mechanism of the Hydrolysis of an Amide by a OH− Ion

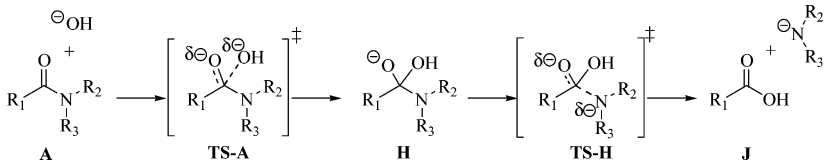
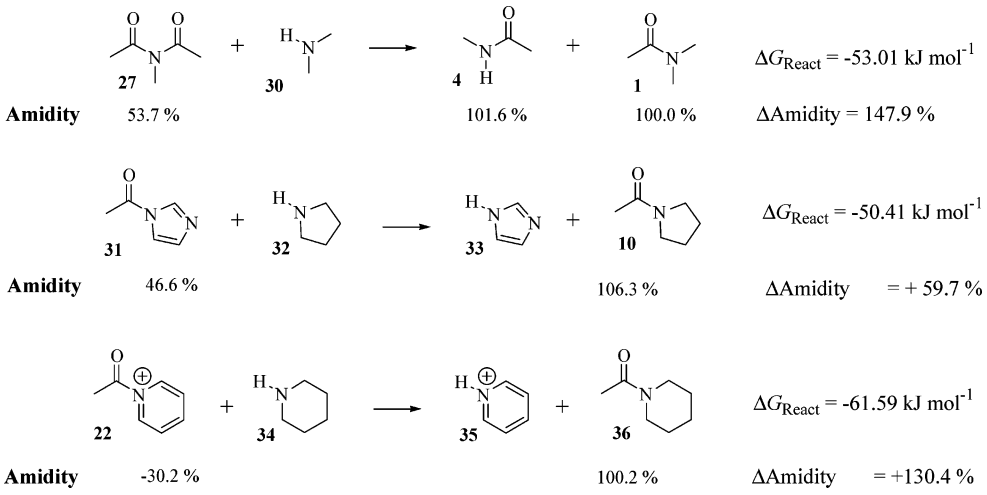


TABLE 4: Computed ΔH_{RE}, ΔH_{PA}, and ΔH_{React} Values, in kJ mol^{-1}, and $\nu_{C=O}$, in cm^{-1}, for the Compounds Examined (1−29), Obtained at the B3LYP/6-31G(d,p) Level of Theory

	ΔH_{RE}	ΔH_{PA}	ΔH_{React}	$\nu_{C=O}$		ΔH_{RE}	ΔH_{PA}	ΔH_{React}	$\nu_{C=O}$
1	−76.27	−866.36	−193.87	1764.64	**2**	3.51	−977.07	−296.61	1847.27
3	−93.83	−771.48	−193.83	1839.48	**4**	−88.74	−838.66	−193.87	1789.01
5	−87.03	−935.48	−192.88	1755.95	**6**	−86.21	−892.21	−197.15	1743.27
7	−28.96	−972.55	−226.57	1741.68	**8**	−29.23	−898.36	−239.81	1800.21
9	−70.37	−880.33	−211.10	1772.67	**10**	−80.98	−878.56	−199.70	1762.28
11	−84.10	−842.48	−206.33	1900.01	**12**	−87.65	−854.27	−206.94	1879.45
13	−83.55	−848.67	−185.12	1836.07	**14**	−90.73	−861.03	−185.14	1810.54
15	−79.95	−860.36	−206.86	1793.18	**16**	−76.09	−870.53	−211.25	1771.10
17	3.42	−965.03	−276.57	1856.93					
18	−112.39	−764.71	−176.96	1792.85	**19**	−114.82	−780.63	−178.69	1770.20
20	−22.06	−996.42[a]	−457.58[b]	1928.57	**21**	−22.17	−897.63	−467.41[b]	1919.76
22	25.18	*a*	−913.56[b]	1917.84	**23**	−41.48	−774.34	−290.77	1813.88
24	−76.90	−839.47	−247.72	1795.07	**25**	−82.11	−803.61	−235.19	1800.00
26	−60.21	−732.58	−349.28[b]	1831.23	**27**	−48.62	−807.70	−272.35	1794.55
28	−40.13[c]	−876.62	−186.43	1796.08	**29**	−26.83[c]	−920.33	−219.96	1754.76

[a] The protonated species does not exist. [b] The tetrahedral intermediate is not a minimum. [c] Value had to be doubled since there are two amide bonds in the molecule.

SCHEME 7: Selected Acyl Transfer Reactions



calculated ΔH_{PA} values revealed this trend (Figure 5A). However, the PA surely depend on other parameters, such as the order of the amide, the relative steric hindrance, and the identity of the electron-withdrawing group attached to the N atom; hence, as theorized, the fit is not reliable ($R^2 = 0.360$). One may observe that the disubstituted amides show more negative PA values (e.g., **1**, **4**, **12**, **14**, **16**, and **19**) than do secondary ones (e.g., **3**, **4**, **11**, **13**, **15**, and **18**). The electron-withdrawing and strongly conjugative group on the N atom (e.g., **23**, **25**, and **26**) considerably decreases the PA, in contrast with the amidity trend. This phenomenon can be explained in terms of their resonance structures (Scheme 1).

One of the aims of this paper is to estimate, at least semiquantitavely, the reactivity of an amide compound by a simple theoretical method, such as the amidity percentage scale. To show the direct correlation between amidity percentage and intrinsic reactivity, we studied the reactivity of the amides **1**−**29** toward OH^- ions in the gas phase. The mechanism of the amide hydrolysis is composed of at least two steps involving a tetrahedral intermediate (H) and two transition states (TS) (Scheme 6). Assuming that the rate-determining step includes the first TS (TS-A) rather than the second, the reactivity of the amide can be described by the energy level of TS-A, to a good degree of accuracy. However, in the first approximations, the activation energy may be replaced by the energy level of H. In agreement with this rational, the energy level of intermediate H was used as a measure of reactivity, according to eq 6, with the resultant reactivity values summarized in Table 4

$$\Delta H_{React} = H_H - H_A \quad (6)$$

In contrast to the proton affinity (Figure 5A), a relatively good correlation ($R^2 = 0.884$) was observed between the amidity percentages and the reactivity (ΔH_{React}) of the amides examined (Figure 5B). However, the reactivity itself may also require more complex considerations, where not only the strength of the amide bond but the steric hindrance around the carbonyl group may influence the ΔH_{React} values. In the case of compounds **20** and

21, the expected cyclic tetrahedral intermediates ring-open, while the intermediates of **22** and **27** dissociate. Consequently, for these compounds, the computed ΔH_{React} values deviate from the linear fit.

3.6. Amidity as a Driving Force for Acyl Transfer Reactions. Acyl transfer reactions have a significant interest from preparative and biological points of view. The active, amide-type acylating agents (such as **22** and **23**) may provide mild reaction conditions and exhibit large reactivity toward nucleophiles, as opposed to hard acylating agents, such as acyl halogenides and acyl anhydride; therefore, these compounds are widely used in synthesis.

Here, we introduce the Δamidity value, which represents the difference between the amidity values of the starting materials (reactants) and the products (eq 7)

$$\Delta\text{amidity} = \text{amidity(products)} - \text{amidity(reactants)} \quad (7)$$

If the resultant Δamidity value is positive, then the reaction is allowed from an "amidity point of view". Clearly, a reaction may have several other parameters determining whether or not it is allowed, including steric hindrance, kinetic consequences, or side-reaction; therefore, a positive Δamidity value does not automatically indicate that a reaction will proceed. Nevertheless, the Δamidity represents a thermodynamic driving force of an acyl transfer reaction.

The succinimid and phthalimide analogues behave as acyl transfer agents in the presence of amines, producing two amide groups.[49] Here, we report an analogue model reaction, where a bisacyl compound **27** reacts with dimethylamine (**30**), yielding two different amide compounds (**4** and **1**) under exothermic conditions. The Δamidity value, which is the difference between the amidity values of the starting molecules and the products, is quite large (147.9%), possibly providing a strong driving force.

Compound **31**[50,51] represent a mild acylating agent (Scheme 7), prepared from a carboxylic acid and carbonyldiimidazole [CDI], which is a commercially available, convenient starting material. Compound **31** readily takes part in acylation reactions with amines (e.g., **32**) in refluxing THF. The acylating properties of this molecule can be attributed to the competition between the aromatic ring and the amide group for the lone pair of the N atom. This strong competition decreases the amidity percentages of the acetylated imidazole ring (**31**), which significantly increases during the acylation reaction, representing one of the driving forces of these processes.

Compound **22** exhibits extremely low amidity percentage (−30.2%), making this molecule an excellent acylating agent, which can be prepared in situ from AcCl and pyridine.[52,53] Clearly, **22** reacts readily with amines (e.g., with **34**), where the reaction exhibits an extremely large Δamidity value.

4. Conclusion

A new linear scale, amidity, has been defined to measure the strength of an amide bond. The scale is based on the relative enthalpy values of hydrogenation reactions (ΔH_{H2}), arbitrarily choosing dimethylacetamide (**1**) as +100% and azaadamantane-2-on as 0%. It has been demonstrated that, apart from a constant shift, the ΔH_{H2} values are virtually equal to the COSNAR resonance energy (H_{RE}) values. A representative set of 29 general amide compounds were included in the present study, concluding that the ΔH_{H2} value may be a good measure of amidity. Amidity percentage was computed at 12 different levels of theory, from which it has been concluded that this methodology is quasi-method-independent. Alternatively, amidity percentage may also be determined using experimental enthalpies of hydrogenation. A comparison was also made between the novel amidity percentage values of the compounds examined and their calculated proton affinities, as well as their reactivity to OH^- ions, both cases exhibiting a linear relationship. For several reaction (e.g., acyl transfer), the amidity turned out to be a thermodynamic driving force of the reaction.

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Supporting Information Available: The full author list for ref 22. Tables S1, S2, and S4−S40 contain the computed energies (*E*), zero-point energies (E_{ZPE}), internal energies (*U*), and enthalpies (*H*) in hartree at various levels of theory for compounds **1**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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