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Energy Managements in the Chemical and Biochemical World, as It may be Understood from the Systems Chemistry Point of View

Zoltán Mucsi, Péter Ábrányi Balogh, Béla Viskolcz and Imre G. Csizmadia
University of Szeged
Hungary

1. Introduction

If anyone compares biochemical and industrial processes from energetic point of view, it may well be concluded that the bio-production of any living entity exhibits far greater energy efficiency than any human controlled industrial production. Most of the bio-reactions take place at the same cell at the same temperature, within a narrow range, without external heating or cooling system. In contrast to that, industrial chemical processes usually proceed separately at various reaction temperatures from –80 °C to +200 °C. Furthermore, these reactions require significantly larger energy input, which is taken in either as external heating or internal molecular energy of active reagents (high energy reagents, like acylhalogenides and $LiBH_4$), meanwhile the large excess of energy waste, released during the reaction, must be led away.

Behind the high efficacy of biological processes compared to man-made processes there are two energetic reasons. At first, biological reactions used to start from low energy intermediates and proceed by means of very well designed catalysts, such as enzymes, therefore activation energy gaps are low (**Figure 1**, green line), consequently reaction can be carried out at ambient temperature. Secondly, reagents used by living organism, like NAD^+, FAD, ATP and other bio-reagents are so effectives under enzymatic conditions, that they need to store only slightly more than the necessary energy within their structures to carry out the reaction, resulting low energy waste, or in other word, reagents balance the reaction energy by their internal molecular energy. Two non-catalyzed laboratory processes (black dashed and red lines) are compared with a enzyme catalyzed biological process (green line) schematically in **Figure 1** and **Table 1**. For any reaction to proceed, sufficient reagent has to be chosen, which at Gibbs free energy level is higher than the Gibbs free energy level of the product. The Gibbs free energy difference between the row material and product ($G_I \rightarrow G_F$) is called built-in energy. To prepare active reagent from row material, some energy needs to be invested ($G_I \rightarrow G_1$ and $G_I \rightarrow G_3$). Under laboratory conditions **I** (black, dashed line), instead of the addition of high energy and very active reagents, we react only low energy reagent (at G_1), therefore thermal energy *via* increased reaction temperature need to be input ($G_1 \rightarrow G_5$), consequently the waste energy is high. In laboratory condition **II** (red line), normally high energy and active reagent is reacted *via* low transition state ($G_3 \rightarrow G_4$), it does not require high reaction temperature. However, the overall waste energy remained

significant, due to the large investment energy to prepare active reagents from row materials. In contrast with the previous processes, biological system (green line) uses low energy reagents (at G_1) joint with effective enzyme catalyst ($G_I \rightarrow G_2$), therefore the resultant waste energy is minimal.

Processes	Type of the process	Invested energy	Transition state energy	Waste energy	Reaction rate	Product efficacy
Laboratory I (black dashed)	non-catalysed	**low** G_1–G_I	**high** G_5–G_1	**high** G_F–G_5	**low**	**low**
Laboratory II (red line)	non-catalysed	**high** G_3–G_I	**low** G_4–G_3	**high** G_F–G_4	**high**	**high**
Biological (green)	catalysed	**Low** G_1–G_I	**low** G_2–G_1	**low** G_F–G_2	**high**	**high**

Table 1. Summary of the comparison of two laboratory and a biological processes from energy management point of view, joining to **Figure 1**.

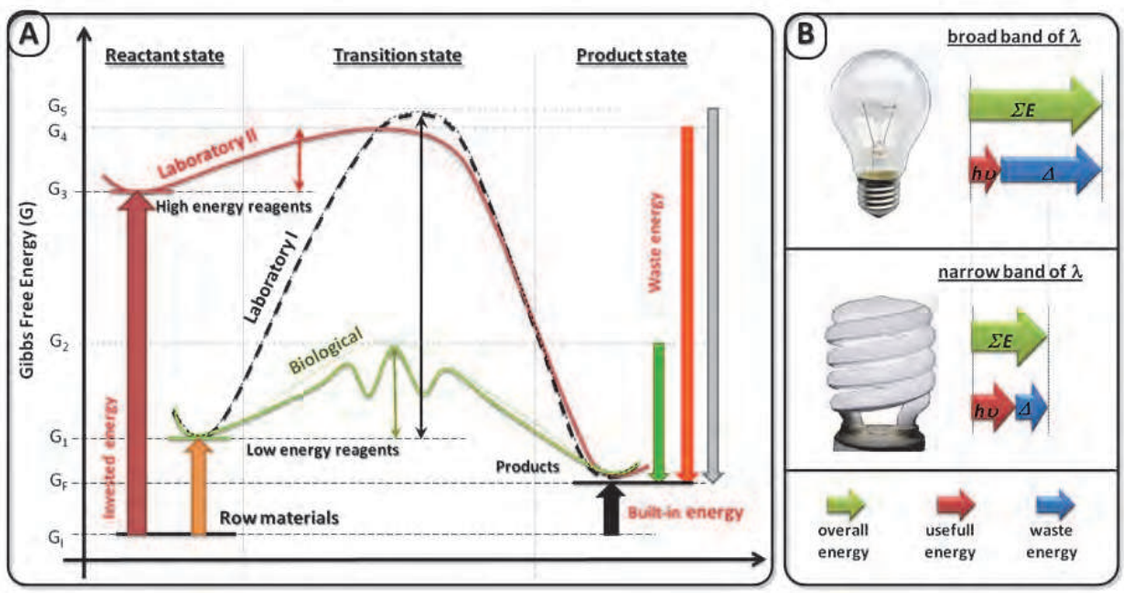

Fig. 1. (**A**) Relative Gibbs free energy profiles for a reaction carried out at laboratory I. (black dashed line, low energy reagent, non-catalyzed process, therefore high energy transition state and large energy waste), biological (green line, low energy reagent, enzymatic catalysis, therefore low energy transition state and low energy waste) and laboratory II. conditions (red line, high energy reagent, non-catalyzed process, but low energy transition state and high energy waste). The biological reaction is the most energy efficient due to the smallest invested and waste-energies. G_I = initial Gibbs free energy; G_F = final Gibbs free energy; from G_1 to G_5 = different Gibbs free energy levels. (**B**) A schematic comparison of an incandescent light bulb with a modern 'energy-saving bulbs' being in analogy with the manmade reaction and natural processes.

By symbolic analogy, one may compare the influence of structure on energy loss in many synthetic reactions to that of an incandescent light bulb; the latter losing (as 'side product' wavelengths and heat) ~70 % of energy input to produce the desired product 'white light' (**Figure 1B**). Yield of white light may be improved by optimizing each of the systemic components, where even shape contributes to efficient excitation of filament-gas to populate a narrow band of desired energy levels; as in modern 'energy-saving bulbs'.

Nowadays, in modern organic and medicinal chemistry a typical molecule may involve several analogous functional groups, which are able to react with a reagent dissimilarly, resulting in different products, therefore the fast determination or at least estimation of the reactivity of these functional groups is essential for planning synthetic routes. Nevertheless, in the case of theoretical methods, which can predict reactivities by modeling the reaction mechanism, it is typical that behind a seemingly simple chemical reaction, the real mechanism is quite complex, involving many species in each individual elementary step, like reactants, reagents, solvent molecules, catalysts, and acid or base as co-reagents [1–5]. All these species should be involved in the calculation to investigate the real and detailed mechanism, in order to obtain a correct and accurate view of the reaction taking place in a real media. In fact, determination of the minimal size of the appropriate chemical model (e.g. number of explicit solvent molecules necessary) is very difficult, time and resource consuming [1]. Moreover, an incorrect chemical model provides not only inaccurate energy values, but frequently absolutely wrong or opposite results, questioning the competence of theoretical methods in the applied science [1]. Reactions taking place in media usually require the consideration of a base or an acid as catalyst together with many solvent molecules in an appropriate 3D arrangement [1,2,5]. Taking into consideration of all of these criteria, it seems nearly impossible to model even a simple acylation reaction. It was demonstrated earlier that the computation of one or a few, easily and quickly computable quantum mechanical (QM) descriptors, such as aromaticity [6–9], amidicity [10–12], carbonylicity,[13,14] olefinicity,[15–17] and others can predict properly and somewhat quantitatively certain reactivity and selectivity issues. The global and complex view of these descriptors was defined as the concept of systems chemistry [18], wherein molecules are described as strategically located functional components within molecular frameworks, 'valued' at more than their components' sum, acting in unison to effect efficient energy management.

2. The concept and methodology of systems chemistry

2.1 General remarks

Every organic structure and their energy content can be modeled at three levels of organization. This deconvolution of the total energy into three components is illustrated by **Figure 2**. The first level takes into consideration only the σ skeleton of a molecule, the energy content of this level can be calculated by the sum of the average sigma bond type. The second level summarizes the π scaffold, summing up the π energy content of the double bonds (i.e. double bond energy – single bond energ). It is known that adjacent double bonds get into interactions by overlapping between their atomic orbitals. However, the estimation of the energy content of the resonance level is not trivial. In simpler cases, where the number and the types of the σ and the π-bonds do not change the resonance energy is turned out to be a reliable measure of the overall relative energetic of the process. In order to measure it, a novel concept and therefore a novel discipline was defined, wherein molecules are

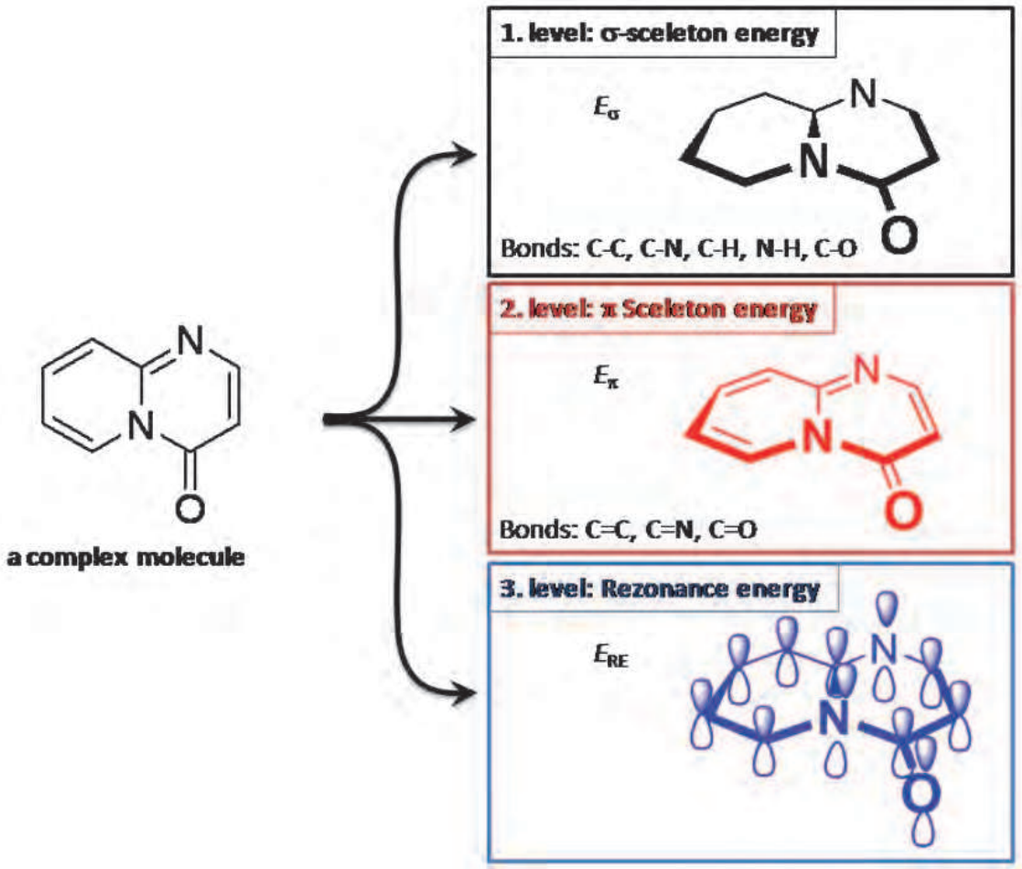

Fig. 2. A schematic illustration of how the internal molecular energy may be deconvoluted to σ, π and resonance energy.

described as frameworks of strategically located functional components within molecular frameworks, acting in unison to effect efficient energy management. The term 'Systems Chemistry' effectively serves to define the phenomena of an assembly of atoms and functional groups (a molecule) having systemic properties 'valued' at more than their component sum. Systems Chemistry focuses on the framework of component functional groups and atoms within a given molecule acting in unison to orchestrate a variety of chemical phenomena. Molecular properties, such as reactivity and stability, are a result of the relative spatial orientation(s) of constituent atoms, mediated by environmental and statistical factors (e.g. solvent and concentration/bulk, respectively). Systems Chemistry is a discipline wherein component functionalities are not segregated, in a reductionist fashion, but rather where they are considered as integrated parts of a whole system of interacting functional groups; yet, reductionist component resolution is retained.

This implies that functional molecular systems are more than just assemblies of atomic and functional components. To attain Nature's efficiency, one must approach chemical phenomena as systems rather than as single entities. Systems Chemistry has in-hand the types and locations of organic functional groups (*e.g. ortho*, *meta*, *para* substitutions, catalyst-ligand identities) and aims to quantifying their relationships and influence on one another. Coupling between components of a chemically or biologically important molecule, such as aromatic rings, amide groups, olefins, carbonyls and metal-ligands, are central to the

molecules' chemical efficiency. With the quantification of these couplings in mind, we recently introduced the molecular descriptors: aromaticity,[6] amidicity,[10] carbonylicity,[13] olefinicity,[15] each of which in a surrogate thermodynamic function, contributing to the characterization of the mechanisms by which Nature fine-tunes and stores reaction energies to attain hyper-efficiency.

2.2 Aromaticity

Chemical structures and transition states are often influenced by aromatic stabilizing or antiaromatic destabilizing effects, which are not easy to characterize either experimentally or theoretically. The exact description and precise quantification of the aromatic characteristics of ring structures is difficult and requires special theoretical investigation. A novel, yet simple method to quantify both aromatic and antiaromatic qualities on the same linear scale, by using the enthalpy of hydrogenation reaction of the compound has been examined. A reference hydrogenation reaction is also considered on a corresponding non-aromatic reference compound in order to cancel all secondary structure destabilization factors, such as ring strain or double bond strain. From these data the relative enthalpy of hydrogenation may easily be calculated [6]:

$$\Delta\Delta H_{H2} = \Delta H_{H2}(\text{examined}) - \Delta H_{H2}(\text{reference}). \quad (1)$$

In the present work concept, the $\Delta\Delta H_{H2}$ value of benzene defines the perfect or completely aromatic character (**+**100%), while the closed shell of the singlet cyclobutadiene represents maximum antiaromaticity (**–**100%).

Aromaticity and antiaromaticity are characterised by a common and universal linear scale based on the heat of hydrogenation (ΔH_{H2}(I), Eq. 2; **Figure 3**) when cyclobutadiene (**1**) and benzene (**2**) are considered as –100% and +100%, respectively. This methodology compares the hydrogenation reaction of the examined compound [**3**→**6**, ΔH_{H2}(I), Eq. 2] with that of a properly chosen reference reaction [**9**→**12**, ΔH_{H2}(II), Eq. 3]. The difference between the two enthalpy values [$\Delta\Delta H_{H2}$(AR), Eq. 4] is transformed to aromaticity percentage (AR %; Eq. 5), which is the basis of the calculation of the resonance enthalpy [H_{RE}(AR); Eq. 6]. Some aromatic compounds may exhibit larger aromaticity values, than 100%, meaning to a larger resonance enthalpy (RE) inside the system. Typical case is the double ring naphthalene and its analogues, where this larger value is the sum of the resonance enthalpies of the two rings.

$$\Delta H_{H2}(\text{I}) = H[\mathbf{6}] - \{H[\mathbf{3}] + H(H_2)\} \quad (2)$$

$$\Delta H_{H2}(\text{II}) = H[\mathbf{12}] - \{H[\mathbf{9}] + H(H_2)\} \quad (3)$$

$$\Delta\Delta H_{H2}(\text{AR}) = \Delta H_{H2}(\text{I}) - \Delta H_{H2}(\text{II}) \quad (4)$$

$$\text{AR \%} = m_{AR}\,\Delta\Delta H_{H2}(\text{AR}) + b_{AR} \quad (5)$$

$$H_{RE}(\text{AR}) = \text{AR \%} / m_{AR} \quad (6)$$

The various compounds for which aromaticity and antiaromaticity values were determine form a "spectra" of such aromatic/antiaromatic characters are illustrated by **Figure 4**.

Interesting examples can be found in phosphorous organic compounds [7–9,19], one of them is exemplified in **Figure 5**. The aromaticity of phospholes was questionable for a long time and the commonly accepted view was that they have a very weak aromatic character. The

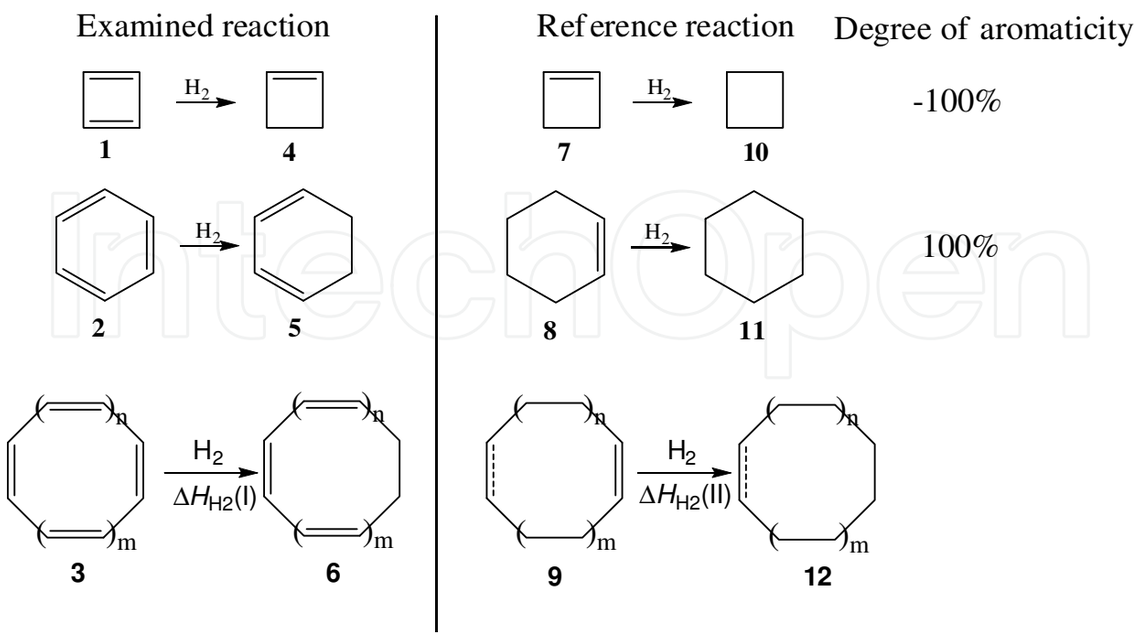

Fig. 3. ΔH_{H2} vales calculated for an antiaromatic and aromatic species.

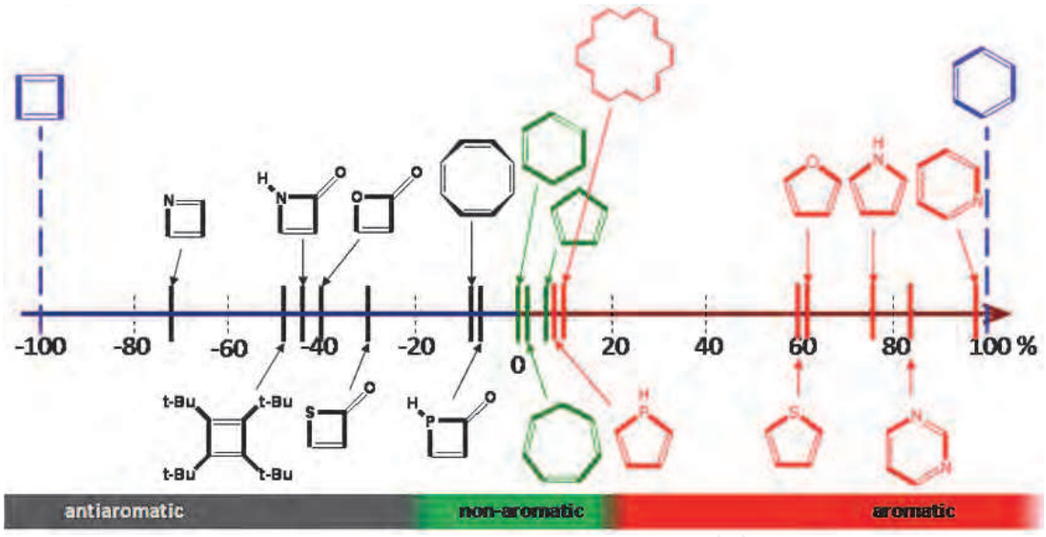

Fig. 4. Combined aromaticity and antiaromaticity spectrum with some representative compounds.

weak aromaticity may be due to the pyramidal geometry around the P atom since the lone electron pair cannot effectively participate in the delocalization. Several studies revealed that contrary to the stability of phosphole (**13**), phosphole oxide derivatives (**14**) exhibit an unusual instability. The phosphole oxides (**14**) obtained on oxidation of the phospholes (**13**), undergo a Diels-Alders type [4+2] dimerization reaction to afford **15** (upper line of **Figure 5**). Other experimental findings revealed that an other phosphole derivative **16** is stable for days, but their oxidized derivative **17** is unstable under the same conditions and is

rearranged to **18** (lower line of **Figure 5**). The instability of **17** was explained by the existing weak antiaromaticity [9,19].

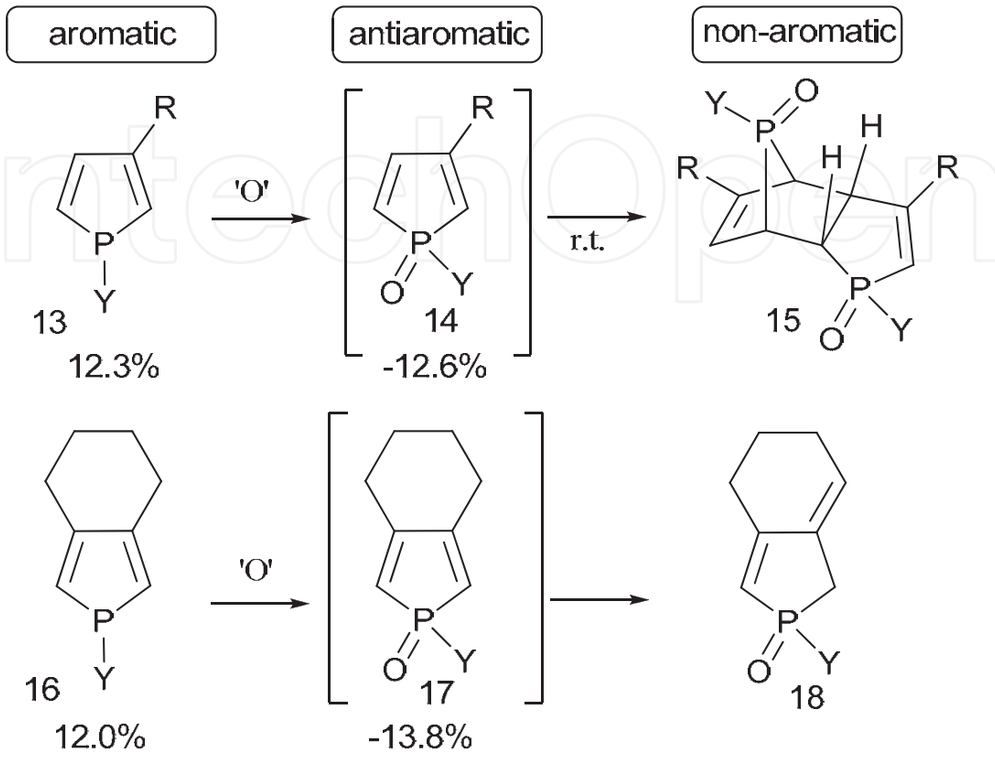

Fig. 5. ΔH_{H2} vales calculated for selected antiaromatic and aromatic species containing phosphorous.

2.3 Carbonylicity and amidicity

The carbonyl group is one of the most pervasive moieties in organic, bioorganic and industrial chemistry. Ketons, aldehydes as well as carboxylic acids, their halogenides, amides, esters, acyl anhydrides and other derivatives are also so-classified, commonly found in peptides/proteins, lipids/membranes and other biologically active compounds, such as Penicillin, drugs and toxins. They may be characterized as being very stable and resilient (amides, esters, acids), as well as very reactive systems (carboxyl acid halogenids, and thiol derivatives). There are numerous examples in the field of organic and biochemistry, where the carbonyl derivatives undergoes nucleophilic addition reaction, such as esterification, transesterification, amidation, transamidation, anhydride formation, aldol addition, among others. 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, amines and other compounds (**Figure 6**). 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, predetermines its specific chemical reactivity; analogous to the situation in amide systems [13].

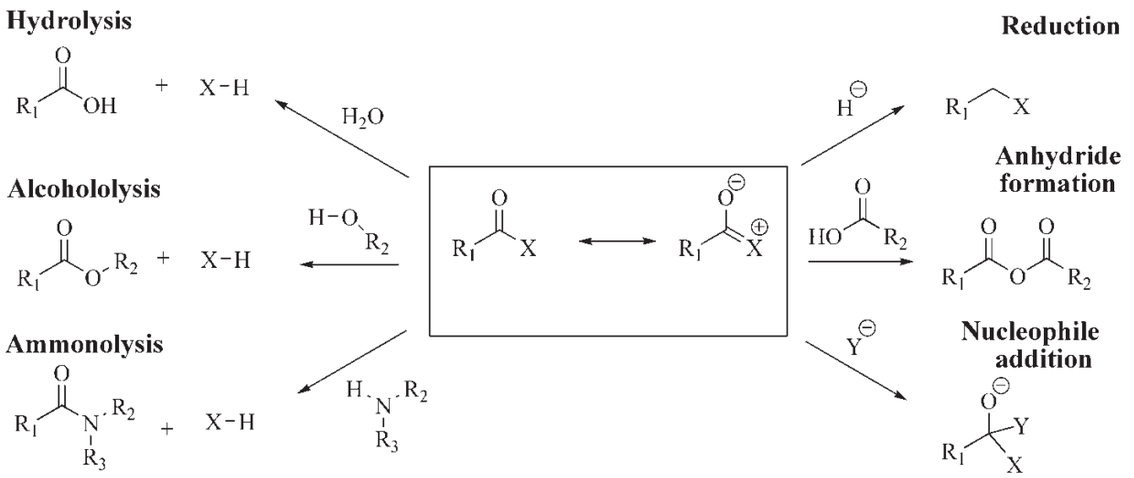

Fig. 6. A schematic illustration of the variety of reactions of carbonyl derivatives.

The large variability in the chemical reactivity of the amide bond may be attributed to the potential for fine-tuning of the bond strength, facilitated by the attached substituent groups. The amide bond strength of a general amide compound, as illustrated by its associated resonance structures, 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. For a stronger amide bond, the conjugation between N and the C of the carbonyl group is more extensive, meaning that the contribution of the two most significant resonance structures are more closely balanced between the two structures, than in a weaker amide bond. In the case where there is no significant conjugation, the preferred resonance structure is represented by the left structure in the box in Fig. 6. [10].

2.3.1 Amidicity and carbonylicity percentages and its resonance enthalpies (AM% and CA %):

The "amidicity scale", quantifying amide bond (**Figure 7**) strength on a linear scale, based on the computed enthalpy of hydrogenation [ΔH_{H2}(AM); Eq. 7; **Figure 8-TOP**] of the compound examined, comparing to reference compounds **19** and **20**. The ΔH_{H2}(AM) value for dimethylacetamide (**19**) is used to define perfect amidic character (Eq. 8.; AM % = +100%), while azaadamantane-2-on (**20**) represents complete absence of amidic character (AM % = 0%) [10]. The amidicity value is transformed to the resonance enthalpy [H_{RE}(AM); Eq. 9]. However, amidicity is not limited to the values between 0% and 100%. Some amide compounds exhibit extreme amidicity values, either below 0% or above 100%, and referring to the cases when the amide bond may be weaker than that in **20** or stronger than that in **19**, respectively.

$$\Delta H_{H2}(\mathrm{AM}) = H[\mathbf{22}] - \{H[\mathbf{21}] + H(H_2)\} \quad (7)$$

$$\mathrm{AM}\ \% = m_{AM}\,\Delta H_{H2}(\mathrm{AM}) + b_{AM} \quad (8)$$

$$H_{RE}(\mathrm{AM}) = \mathrm{AM}\ \% \,/\, m_{AM} \quad (9)$$

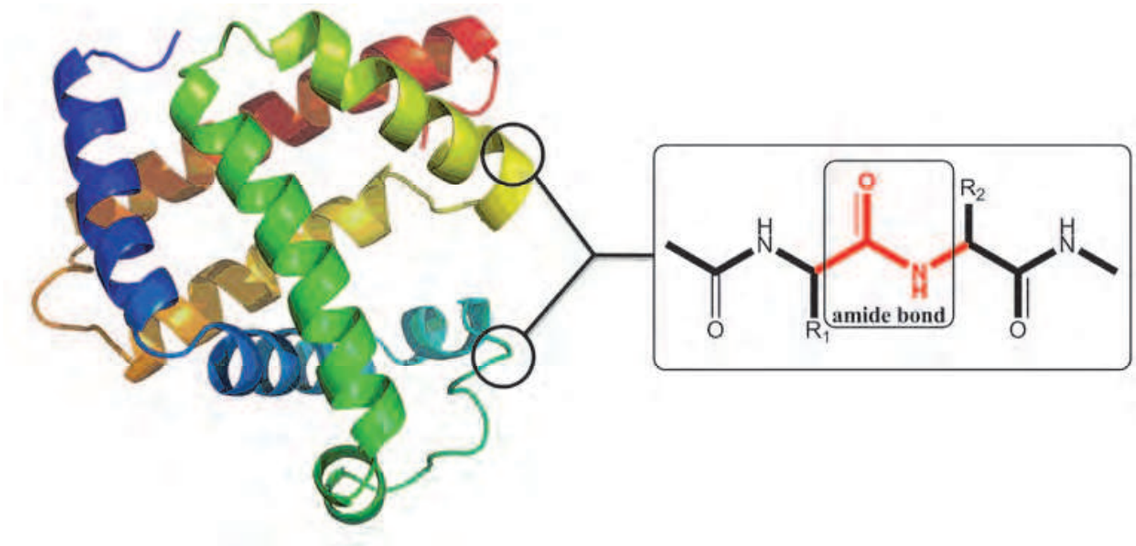

Fig. 7. A schematic illustration of the occurance of an amide bond within protein secondary structures.

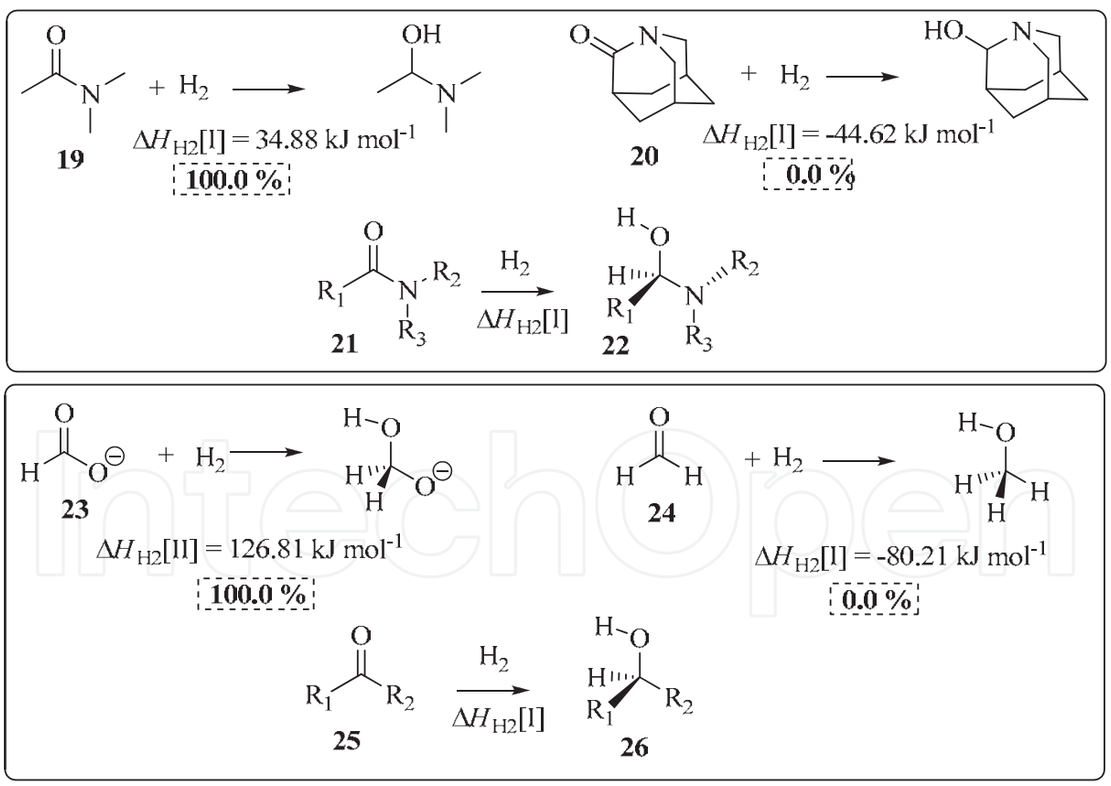

Fig. 8. The definition of the amidicity (**TOP**) and carbonylicity percentages (**BOTTOM**) based on the enthalpy of hydrogenation (ΔH_{H2}) of the carbonyl group. Values were obtained from the B3LYP/6-31G(d,p) geometry-optimized structures. In structure **22** and **26**, the O–C–X–R^3 and the H–O–C–X dihedral angles are chosen to be in the *anti* orientation.

Analogously, the "carbonylicity scale", quantifying carbonyl bond strength on a linear scale, based on the computed enthalpy of hydrogenation [ΔH_{H2}(CA); Eq. 10; **Figure 8-BOTTOM**] of the compound examined, comparing to reference compounds **23** and **24**. The ΔH_{H2}(CA) value for formiate anion (**23**) is used to define perfect conjugation (Eq. 11.; CA % = +100%), while formaldehyde (**24**) represents complete absence of a conjugation (CA % = 0%) [13]. To calculate the carbonylicity value of compound **25** can be calculated by the hydrogenation reaction to **26**, using Eq. 10–12. The carbonylicity value is transformed to the resonance enthalpy [H_{RE}(CA); Eq. 12]. Here the carbonylicity value is also not limited to the values between 0% and 100%.

$$\Delta H_{H2}(CA) = H[\mathbf{25}] - \{H[\mathbf{26}] + H(H_2)\} \quad (10)$$

$$CA\ \% = m_{CA}\, \Delta H_{H2}(CA) + b_{CA} \quad (11)$$

$$H_{RE}(CA) = CA\ \% \ / \ m_{CA} \quad (12)$$

Figure 9 shows, in a combined fashion the amidicity (**TOP**) and carbonylicity (**BOTTOM**) scale. Note that the two set of values represent different scales, than the amidicity is a special section of the carbonylicity scale.

Amidicity percentage for example is able to predict whether a transamidation reaction is taking place under the given conditions or not [10–12] and it can also point out the most reactive amide bond of a molecule. It was shown that carbonyl groups exhibiting a lower amidicity value are more reactive toward nucleophilic reagents (like amines) than carbonyl groups having a larger value. Moreover, when more products can be deduced it was demonstrated that the difference between the sum of amidicity percentages of products and the sum of those values in the reactants indicates the direction of a transamidation reaction. If this difference is positive, the reaction is energetically favored, while in the case of a negative value the reaction is disadvantageous from the driving force point of view. The reaction route, where the sum of amidicity percentages for products is larger than that for other possible reaction routes, is predicted to be the favorable one.

A very similar conclusion was drawn for acyl transfer reactions using carbonylicity as the descriptor [13]. It should be noted, however, that these simple views of the reaction do not consider the kinetic consequences, which sometimes perturb the simplest and quickest conclusion. For example, as presented in an earlier work [13], in acyl transfer reactions it is not enough to find the lowest carbonylicity value, but one of the carbonyl groups should also be a good leaving group.

2.4 Olefinicity

The olefinic group, illustrated in **Figure 10**, may be considered as one of the most important moieties in the organic and bioorganic chemistry. Substituted olefines, such as enamines, vinyl eters and other derivatives can be ranked among this category. Most of them are common in the field of the biochemistry such as proteins, lipids, nucleinic acids and other biologically active compounds like drugs and toxins. Their chemical reactivity may be characterised as very stable and resistant chemical systems, (simple olefines), as well as very active and reactive compounds (enamines, vinyl esters, etc.). There are numerous examples in the field of organic and biochemistry, where the olefinic derivatives undergo electrophilic or nucleophilic reactions [15].

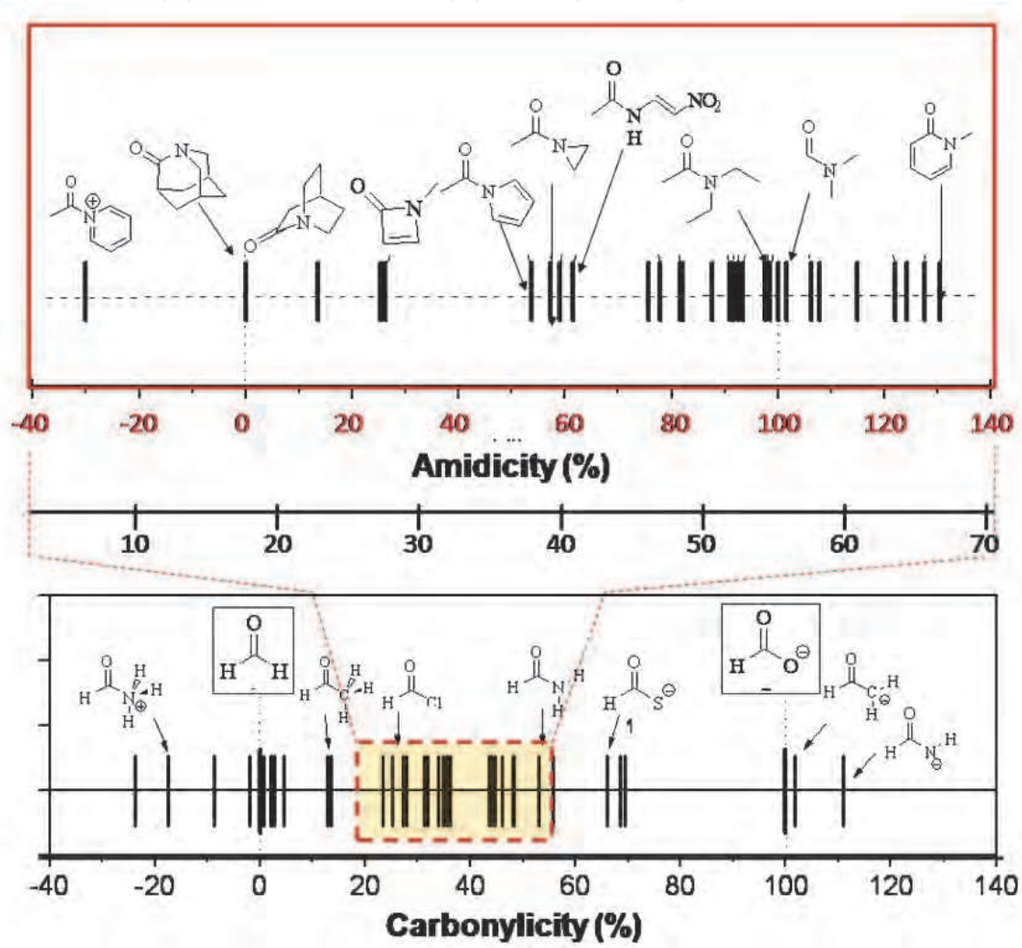

Fig. 9. A schematic representation of the theoretical amidicity and carbonylicity values of given compounds on the carbonylicity and amidicity spectrum, illustrating, that the amidicity spectrum is a small section of the carbonylicity spectrum.

The large variability in the chemical reactivity of the olefin group may be attributed to the potential fine-tuning ability of the bond conjugation, facilitated by the attached substituent groups. The extent of conjugation of a general olefin compound, as illustrated by its associated resonance structures (**Figure 10**), predetermines its specific chemical reactivity [15].

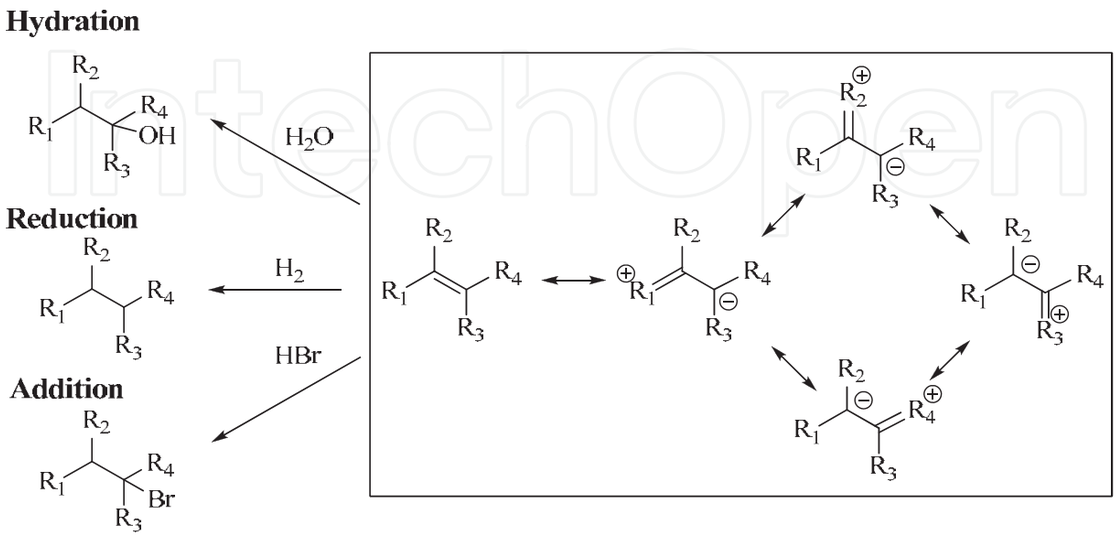

Fig. 10. Some selected typical reactions of the olefinic moiety.

2.4.1 Olefinicity percentage and its resonance enthalpy (OL %):

The "olefinicity scale", quantifying alkene bond strength (**Figure 11**) on a linear scale, based on the computed enthalpy of hydrogenation [ΔH_{H2}(OL); Eq. 13] of the compound examined (**29**), comparing to reference compounds **27** and **28** (Eq. 14) [15]. The ΔH_{H2}(OL) value for allyl anion (**27**) is used to define equivalent conjugation (OL % = +100%), while ethylene (**28**) represents complete absence of conjugation (OL % = 0%), by Eq. 15. This olefinicity value is transformed to resonance enthalpy [H_{RE}(OL); Eq. 15].

$$\Delta H_{H2}(\mathrm{OL}) = H[\mathbf{T}] - \{H[\mathbf{S}] + H(\mathrm{H_2})\} \quad (13)$$

$$\mathrm{OL\ \%} = m_{OL}\,\Delta H_{H2}(\mathrm{OL}) + b_{OL} \quad (14)$$

$$H_{RE}(\mathrm{OL}) = \mathrm{OL\ \%} / m_{OL} \quad (15)$$

3. Energetic study of industrial and biochemical reactions

Due to the enormously large variety of chemical reactions, in this chapter only acyl transfer reactions, including transamidation and reduction-oxidation reactions are exemplified, which are also essential both in industrial chemistry and biochemistry. In order to understand the energy flow and determine the direction of such reactions, thermodynamic selection rule and driving force should be clarified. Based on Systems Chemistry approach, measuring numerically the resonance energy of functional groups inside the molecule, a relatively simple protocol is provided for practicing organic chemists to predict the outcome of an experiment. The change of specific values over the course of a reaction made it

possible to see that the process is favorable or unfavorable. A series of examples are analyzed in the order of the complexity, from simple single value change to multi value changes.

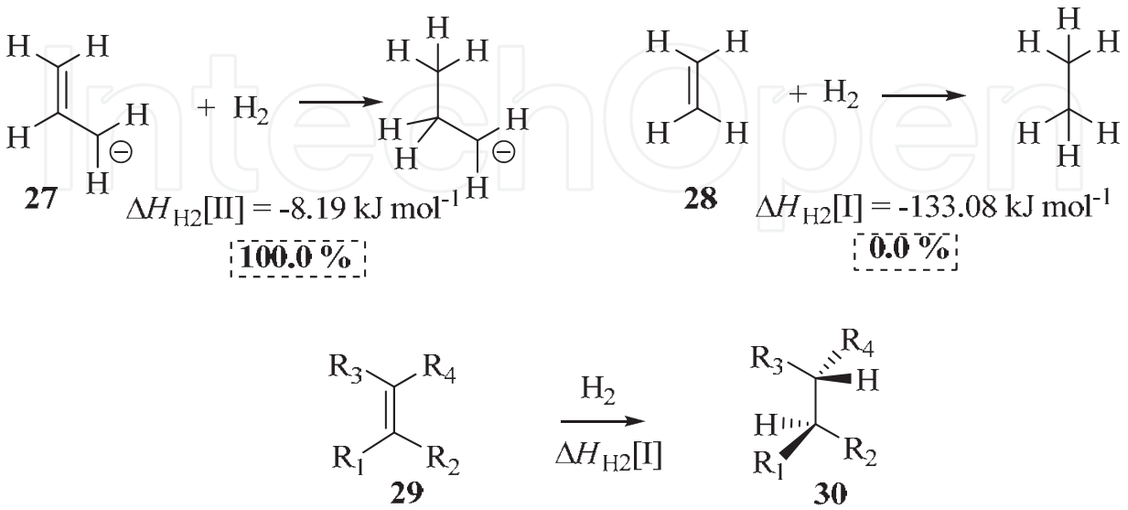

Fig. 11. The definition of the olefinicity percentage based on the enthalpy of hydrogenation (ΔH_{H2}) of the double bond. Values were obtained from the B3LYP/6-31G(d,p) geometry-optimized structures.

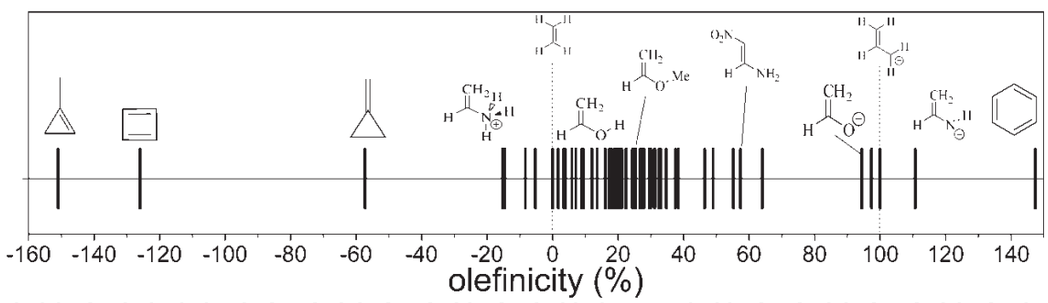

Fig. 12. A schematic representation of the theoretical olefinicity values of given compounds on the olefinicity spectrum.

3.1 General remarks for acyl transfer reactions

In the following paragraph, some very important acyl transfer processes are studied from energy management point of view comparing the human and biochemical solutions. The first studied reaction is a simple amide and ester formation from simple amine or alcohol as reactants *via* different ways. Acyl transfer reactions have a significant interest from preparative and biological points of view. For simple acyl halogenides and acyl anhydrides are widely used in common synthesis. Here we introduce Δcarbonylicity or ΔCA (%) value, which represent the difference between the carbonylicity values of the starting molecules and the products (Eq. 16), illustrated by **Figure 13** [13].

Fig. 13. A general acyl transfer reaction, where the active acyl reagent reacts with reactant Y, producing acyl product and X.

$$\Delta CA\ (\%) = CA\%(\text{product}) - CA\%(\text{starting material}) \quad (16)$$

If the resultant ΔCA value is positive, then the reaction is favored from the 'carbonylicity point of view'. Of course, a reaction may have several other parameters, which determine if a reaction is favored or not, such as steric hindrance, kinetic consequences, side-reaction; therefore a positive carbonylicity value does not mean automatically the occurance of a reaction. Nevertheless, the Δcarbonylicity represents a thermodynamic driving force of an acyl transfer reaction, analogously to the role of amidicity (AM%) in the case of the transamidation reactions (**Figure 14**). The change in the amidicity value gives information about the direction of a transamidation reaction, described by Eq. 17. In the following part, this new methodology is applied on the field of peptide chemistry, especially for the peptide bond formation [10].

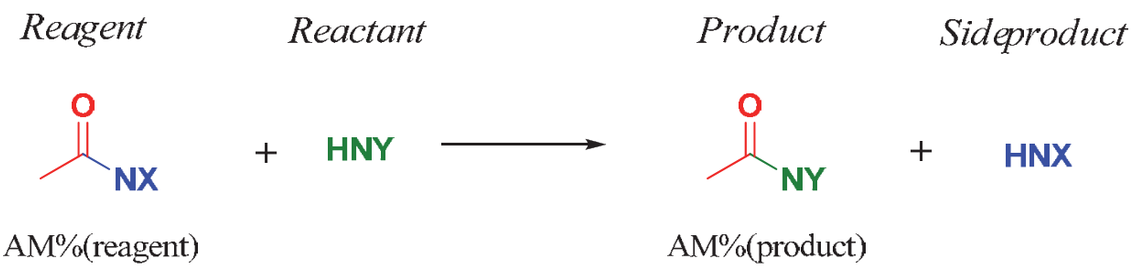

Fig. 14. A general transamidation reaction, where the active amide reagent reacts with amine reactant Y, producing amide product and X.

$$\Delta AM\ (\%) = AM\%(\text{product}) - AM\%(\text{starting material}) \quad (17)$$

As was mentioned, amide and ester functionalities play crucial role in chemistry constructing proteins, nucleic acids, polyhydrocarbons, vitamins, lipids, drugs, plastics and many other important materials. The simplest chemical reagent to form amide or ester bonds is carboxylic acides. However, carboxylic acids are typically not able to effectively form the desired amide product and the ester formation is also very slow under normal conditions. In this case the slow ester formation reaction can be explained by the low carbonylicity change.

The unproductive amide formation in the case of carboxylic acids is due to the deprotonation of the acid reagents to an unreactive reagent by the amine, being in an acid-base equilibrium. Carboxylate anion exhibits very large carbonylicity value (106%), which makes this reaction to very endothermic, consequently unsuccessful. From **Figure 15** it is

clear that in order to produce an ester or an amide the acid has to be activated or in other word has to prepare a high energy reagent. One of the simplest protocols for activation is the chlorine exchange of the hydroxyl group, but it can be done *via* different methods. The first method for reagent formation of **Figure 16** clearly indicates that the HCl molecule is not energetic enough to carry out the necessary activation. In the second method of **Figure 16**, where the high energy content phosphoryl chloride ($POCl_3$) is already sufficiently strong for activate the carboxylic acid. Finally, high energy active reagent, acid chloride can readily react with ammonia in an exothermic reaction.

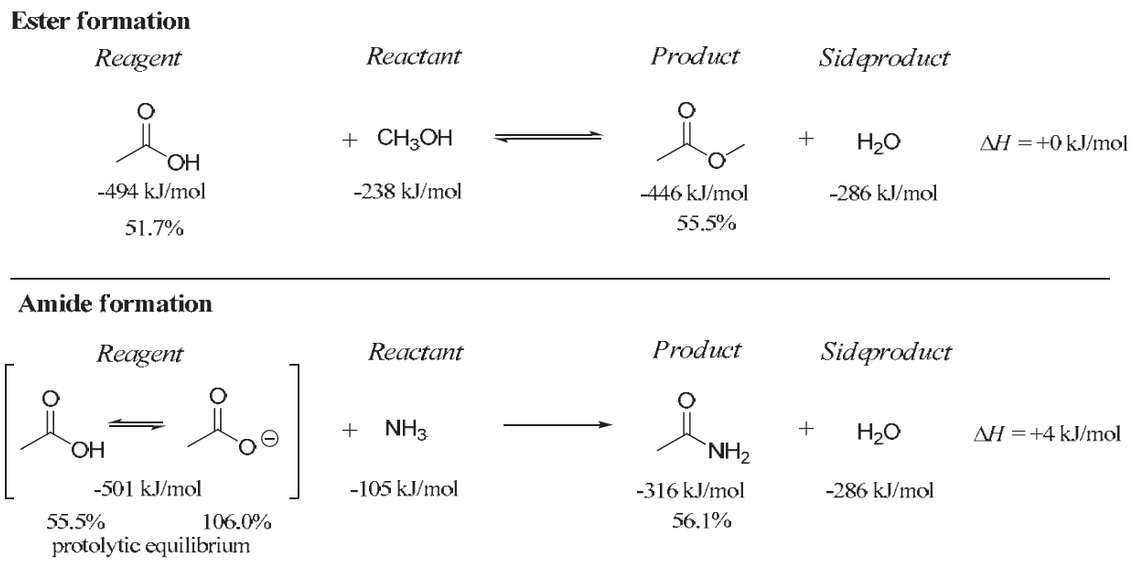

Fig. 15. Thermodynamics of simple ester and amide formation. Data were taken from the National Institute of Standards and Technology (NIST).

3.1.1 Acyltransfer reactions making amide bonds

An amide or peptide bond can be formed by different ways and each method starts with the activation of the acid reactant, followed by the nucleofil attack of the amine reactant. From the carbonylicity point of view, the reaction between an acid (*e.g.* **31**) and an amine (*e.g.* **34**) is thermodynamically advantageous, in the present example the reaction exhibit +3.9 % of Δcarbonylicity, which means Δcarbonylicity / m = 3.9 / 0.4830 = 8.1 kJ/mol increase in resonance energy. However, as was discussed before, an acid is not able to react with an amine due to the high carbonylicity value of the forming inactive carboxylate anion in the protonation-deprotonation equilibrium. To form amide **35**, the acid reagent need to be activated somewhat, that is to be transformed to a more active carbonyl reagent (**36**) having lower carbonylicity value. In all of the activation methods, this high carbonylicity value of **31** are lowered significantly, consequently the reactivity of the acid is enhanced [10–12].

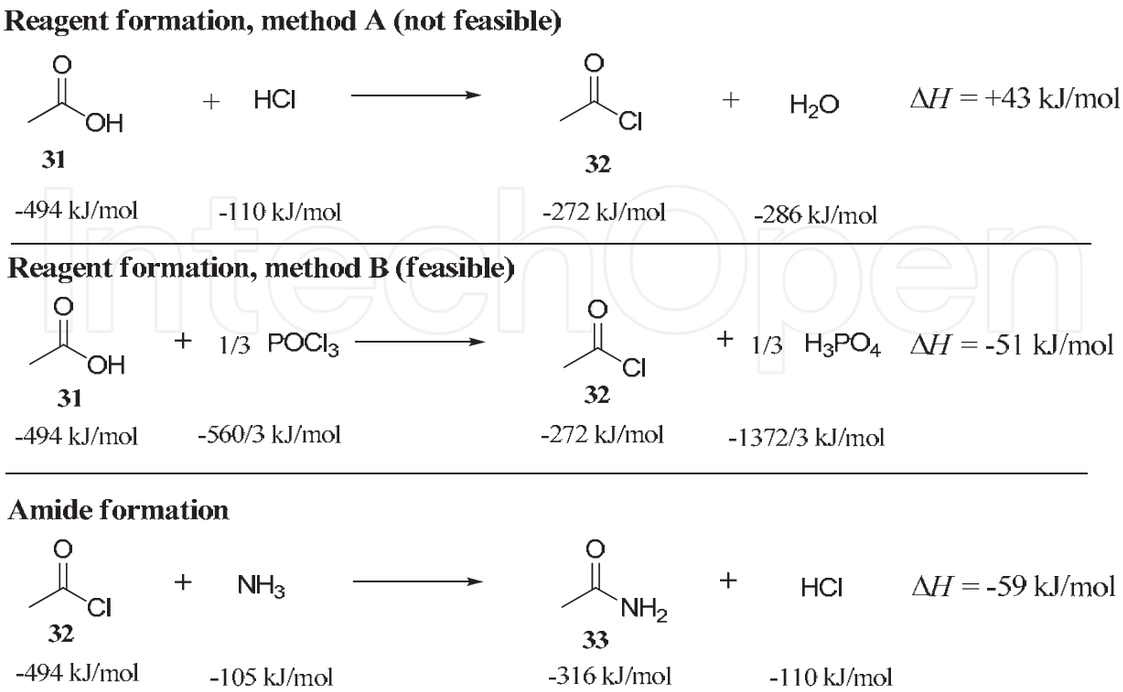

Fig. 16. Formation and utilization of an active (*i.e.* high energy) reagent. Data were taken from the National Institute of Standards and Technology (NIST).

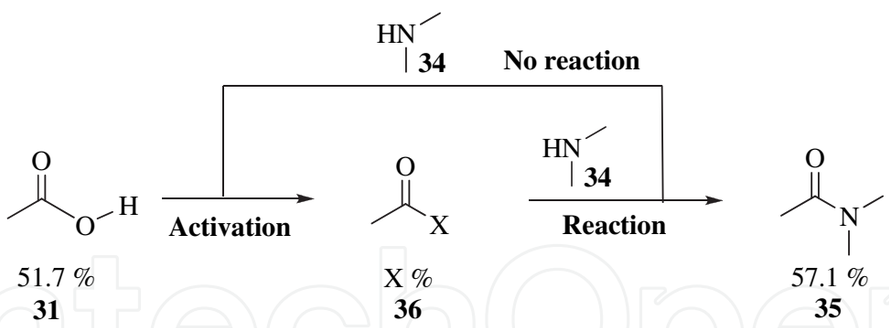

Fig. 17. Amide formation through reactant activation

Five different activation methods are considered and studied here; involving acylchloride (**R-I**), anhydride (**R-II**), active ester (**R-III**, **R-IV**, **R-V**). Also, activation by 1-hydroxy benztriazole derivatives (BOP and HBTU, **R-VI**) and by dicyclohexyl carbodiimide (DCC, **R-V**). The most widely known amide forming reagent is the acyl chloride (**R-I**; **37** in **Figure 18**) exhibiting as low carbonylicity value as 23.7 %. In the course of reaction with an amine (**34**), the change in carbonylicity is very significant (ΔCA = +33.4%), yielding **35** [10].

In the case of the peptide bond formation *via* mixed anhydrides (**R-II**), the acid (**31**) is reacted by isobutyl-chlorophormate (**38**, in **Figure 19**), resulting a mixed anhydride (**39**) with low carbonylicity value on the original carbonyl functionality (29.8 %). This active species may easily react with an amine (**34**), leading to the desired product **35** (57.1 %) and side-

product **40** (55.6 %), which decomposes to isobutylene, CO_2 and H_2O. Although, in the activation step (**31** + **38** → **39**) the change in the carbonylicity value is small, but negative but small (–4.4 %), the HCl elimination and the salt formation with the applied base provide a strong driving force. The active mixed anhydride reagent (**39**) exhibits low carbonylicity at C2, indicating a significant reactivity toward **34**, however C4 atom possesses a larger carbonylicity, which is not so reactive, therefore only products **35** and **40** form exclusively and not **41** and **42**, which route is not preferred from either thermodynamic and kinetic point of view [10].

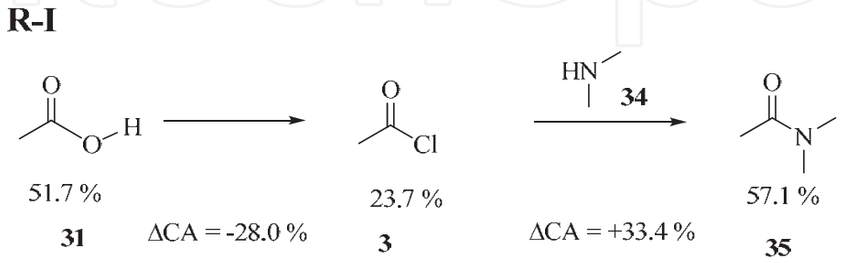

Fig. 18. Amide formation through activated acid chloride

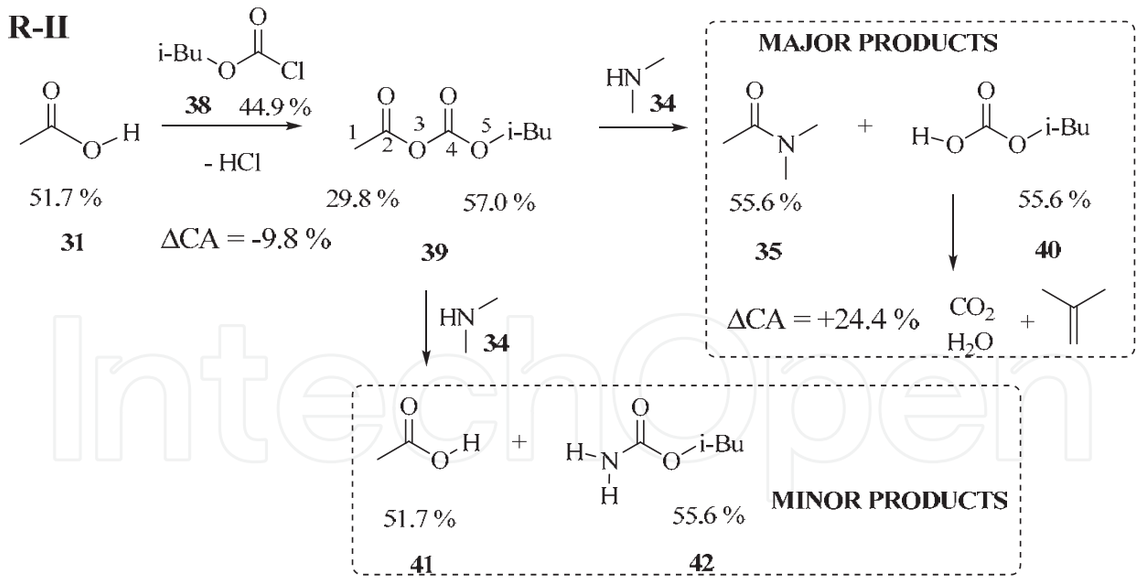

Fig. 19. Amide formation through activated mixed anhydride

Originally, an alkyl ester (**43**) is able to transform to the corresponding amide **35** and **44**, but due to the high carbonylicity value of the ester **43** and the small change in Δcarbonylicity in **R-III** (**Figure 20**), the reaction requires usually high temperature or Lewis acid catalyst (e.g. $AlMe_3$) to proceed. Active esters, which are usually aryl esters, however exhibit lower carbonylicity values, which allow a smooth reaction under convenient circumstances.

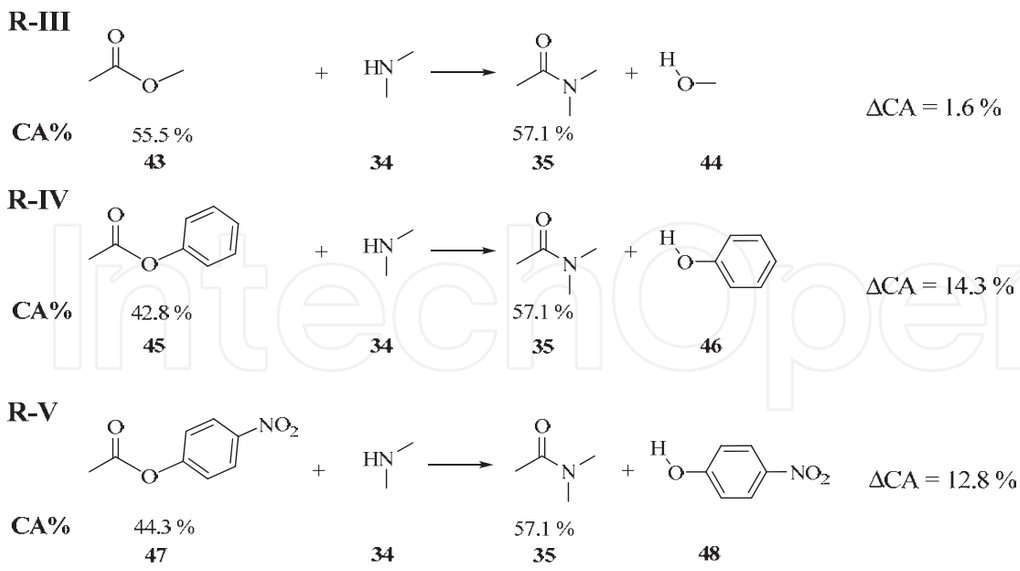

Fig. 20. Amide formation from various esters

In **R-IV** and **R-III** (**Figure 20**), two known coupling procedures are presented, which were used earlier to prepare peptide bond. In both cases, the significant increase in the carbonylicity values predicts a smooth reaction of the aryl ester (**45**, **47**) with **34**, resulting amide **35**, beside **46** and **48** as by-products [10].

However, these active esters proved to be not so efficient due to the relatively high reaction temperature and long reaction time, which may be attributed to the not too significant carbonylicity changes. More modern coupling reagents in the peptide chemistry, such as benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, **49a**, **R-VIa** in **Figure 21**) and *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluoro-phosphate (HBTU, **49b**, **R-VIb**) provide more rapid peptide bond formations in smooth conditions. In both cases, in the first step, is the elimination of the 1-hydroxy-benztriazole moiety (**50**) of the reagent, leading to a very active acylating agents **51a** (25.5 %), **51b** (28.3 %), which reacts with **50**, forming a common, less active, but active enough intermediate **52** (36.4 %). Finally, this intermediate **52** takes part in an acyl-exchange reaction with **34**, furnishing the formulation of a new peptide bond in **35**. Due to the higher carbonylicity change during the reaction, the reaction rate is faster even at room temperature. Moreover, the corresponding carbonylicity values for **51a**, **51b** during the reaction sequences may explain the experimental observation that the BOP reagent (**49a**) is usually provide faster reaction than HBTU (**49b**) [10].

The one of the most efficient peptide bond forming reagents is the *N*,*N*′-dicylclohexylcarbodiimide (DCC, **53**), which readily reacts with the carboxylic acid (e.g. **31**), forming a very active species **54** (38.7 %), as shown by **R-VII** in **Figure 22**. Subsequently, this intermediate furnishes a reaction with amines (**34**), meanwhile *N*,*N*′-dicyclohexylurea (DCU, **55**) leaves the molecule, yielding the amide **35**.

The most impressive usage of DCC may well be the synthesis of penicillin (**Figure 22**, **R-VIII/a**), where the last step of cyclization was carried out using this reagent. According to literature data, this cyclization of the open chain mono-deprotonated penicillin derivative (**56**) was successful only in basic condition (aqueous KOH). After the reaction between **56**

and DCC (**53**), the carbonylicity value 51.7 % decreases dramatically to 36.0 %, in the resulting intermediate **57**. Due to the slightly higher carbonylicity value of the penicillin product **58** (37.1 %), is the reason that intermediate **57** can in fact cyclize to form penicillin **58**. However, this small, but positive difference in the carbonylicity (37.1 % – 36.0 % = + 1.1 %) is not sufficient to provide enough driving force to complete the reaction, therefore the experimental yield is rather low (10–12%) [10].

Many unsuccessful experiments were carried out in order to cyclize penicillin in neutral or slightly more acidic conditions in the hope to improve the yield (**Figure 22**, **R-VIII/b**). In this case, the starting compound is in neutral form (**59**), which reacts with DCC, furnishing intermediate **60** (carbonyilicity value = 36.0 %), having the same value, than it was obtained for **57**. However, here the penicillin product is neutral (**61**), which exhibits much lower carbonylicity value (22.6 %), therefore the reaction is unable to proceed, due to the negative Δcarbonylicity value (22.6 % – 36.0 % = –13.4 %) [10].

In the triglyceride synthesis (**R-IX** in **Figure 23**) the starting fatty or oleic acid forms (**62**) an ester bond with a glycerin or its derivative (**67**). Living organism follow an analogue strategy as the human synthesis, namely acid (**62**) is activated by ATP (**63**) in the form of phosphorous anhydride (**64**), when the carbonylicity value of the carbonyl group is decrease to as low as 37.1%. This already active species presumably is in a too active form, it can hydrolyze in the aqueous media rapidly, therefore it is transformed to a somewhat stabilized reagent by means of CoA (**65**), yielding a little bit more stable a tioester derivative of fatty acid (**66**). This fatty acid derivative, finally can enter in an acyl transfer reaction by glycerine, providing the final product as glycerine ester **68** [10].

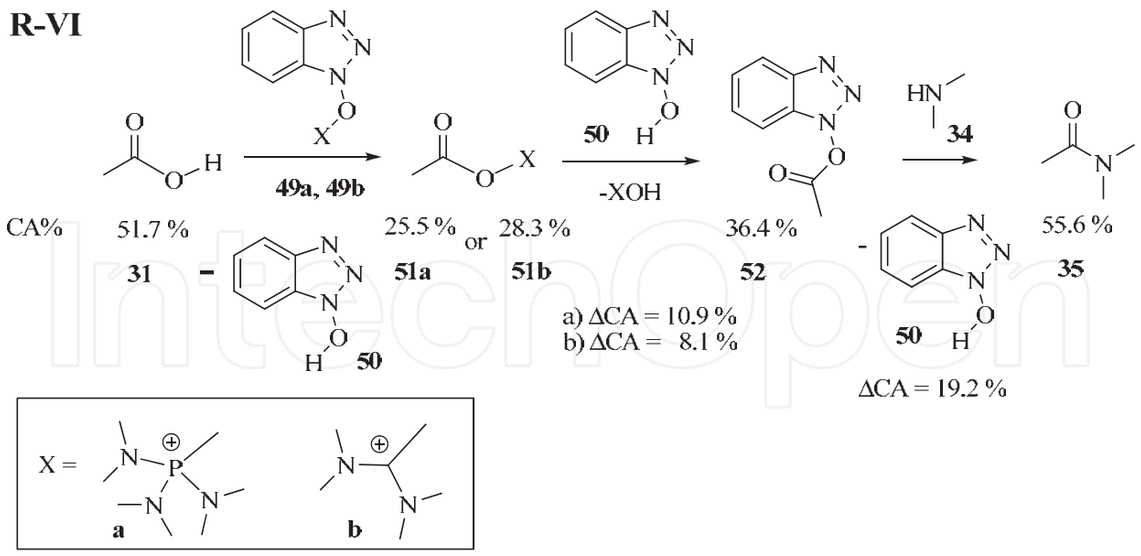

Fig. 21. Amide formation through carboxylic acid activation using 1-hydroxy-benztriazole derivative

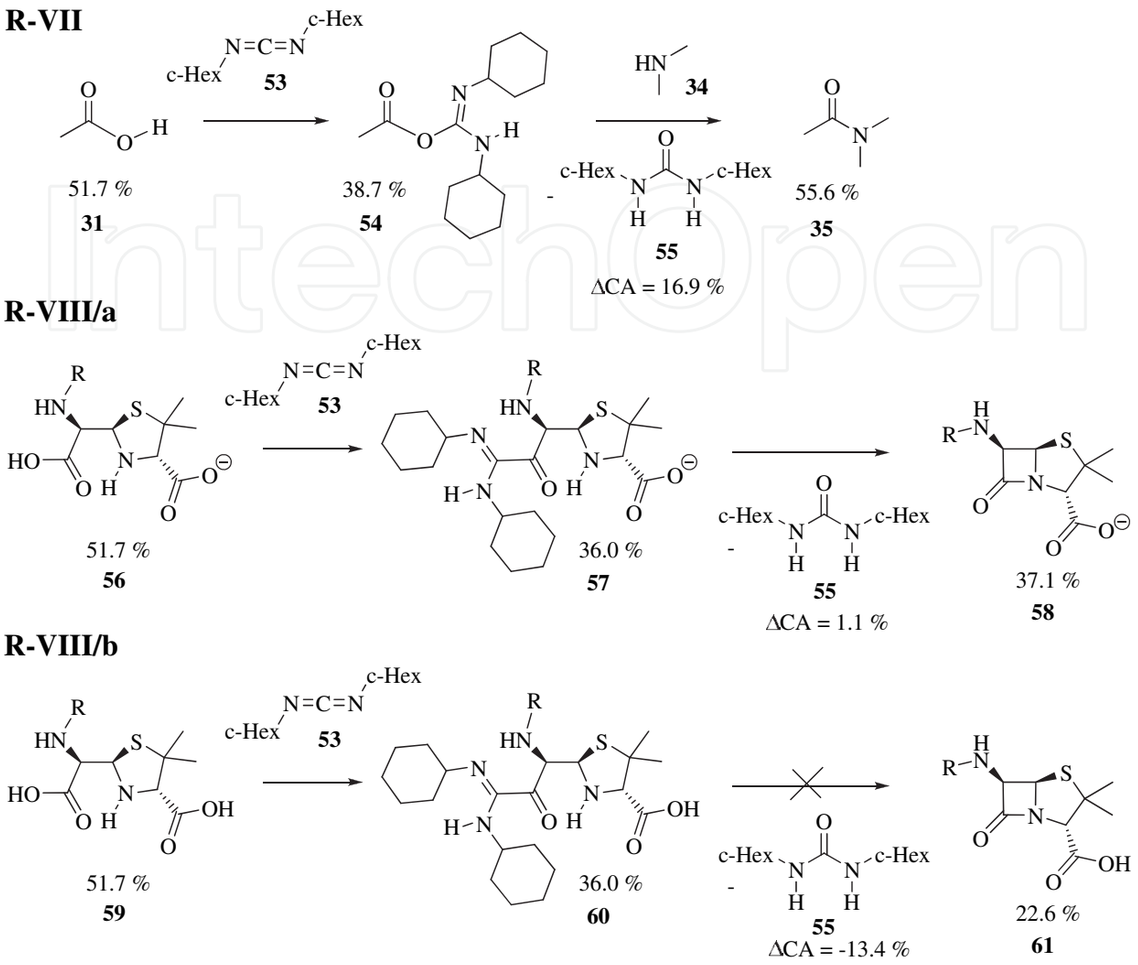

Fig. 22. Amide formation from carboxylic acid through activation by DCC

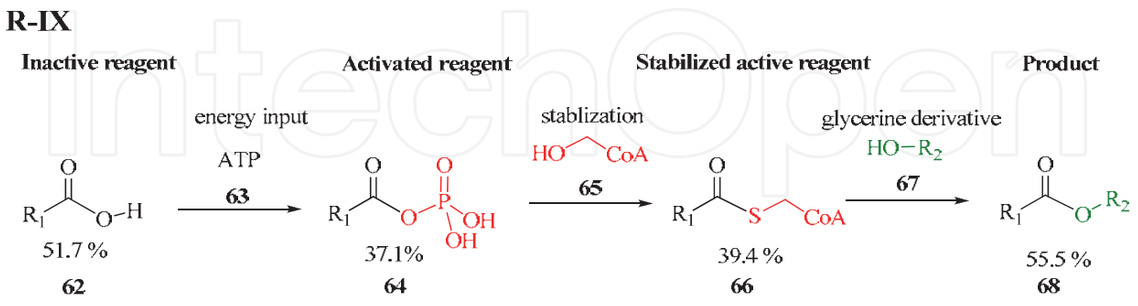

Fig. 23. Tri-gliceride formation from fatty acides *via* thioester activation.

From chemical point of view, the *in vivo* peptide or protein synthesis is based on similar strategy (**R-X** in **Figure 24**), where the free amino acid (**69**) is activated *via* analogous phosphorylation process (**69** → **70**) by means of ATP (**63**), resulting primary active reagent **70**, which reacts with a hydroxyl group on a well-defined site of tRNS (**71**), stabilizing the

active species in a less, but still active ester from (**72**). This AA-tRNS is the main active intermediate in this process, resulting finally the polypeptide chain (**74**) [10].

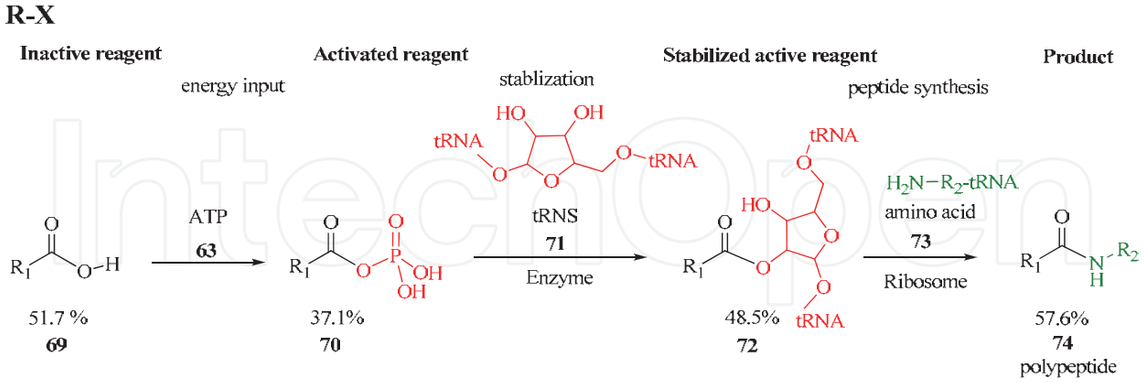

Fig. 24.

3.1.2 Transamidation reactions

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. Amide bonds may be considered as a one of the most important chemical moieties in biological organisms, common 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. They are characterised as being very stable chemical bonds, with half-lives in neutral aqueous solution exceeding hundreds of years.

In contrast to their general resistant to reactivity, there are numerous examples in the field of organic and biochemistry, where the amide bond undergoes nucleophilic reaction. Examples include the spontaneous or enzymatic hydrolysis of amide bond in peptides, proteins. Perhaps the most famous small biogen amides are the Penicillin-like antibiotics, which inhibit penicillin binding proteins such as transpeptidase and carboxylpeptidase through an acylation of a serine residue. In this way, the bacterial cell wall synthesis stops, leading to higher susceptibility to osmotic effect and cell burst.

The reduction of the amide bond by complex metal hydrides has significant synthetic importance to obtain various amines. Some amide compounds are able to react with amines, called as an acyl transfer or transamidation reaction. These processes represent very useful transformations in synthetic organic chemistry to obtain various amide structures from amino compounds, selectively. The most notable application is the Traube synthesis of heterocycles.

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 may also be metabolised prior to reaching its intended target (the enzyme)**.** If however, the amide bond is less reactive, with an increased stability in aqueous solutions and bodily fluids, it will be difficult for such a compound to react with efficacy when it encounters the target (the enzyme). The Penicilin-like antibiotics[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 survives the aqueous body fluid and finds the targeted enzyme.

Unsubstituted amides such as **75** and **33** exhibit a reduced value of amidicity (**Figure 21**) relative to mono-substituted or di-substituted ones, such as **77** and **35** (97–103 %); one may therefore predict a transamidation proceeding between them. Mono- and di-substituted amines (e.g. **34**) are shown to react readily with formamide (**75**, **R–XI**) and acetamide (**35**, **R–XII**) at RT or above, as used in the Traube synthesis. The formylation of benzylamine and *N*-methylbenzylamine furnished by **75** proceeded very smoothly, however, in the case of **33**, $AlCl_3$ was required in order to attain an acceptable rate, which is due to the high activation energy of the sterically hindered reaction center [10–12].

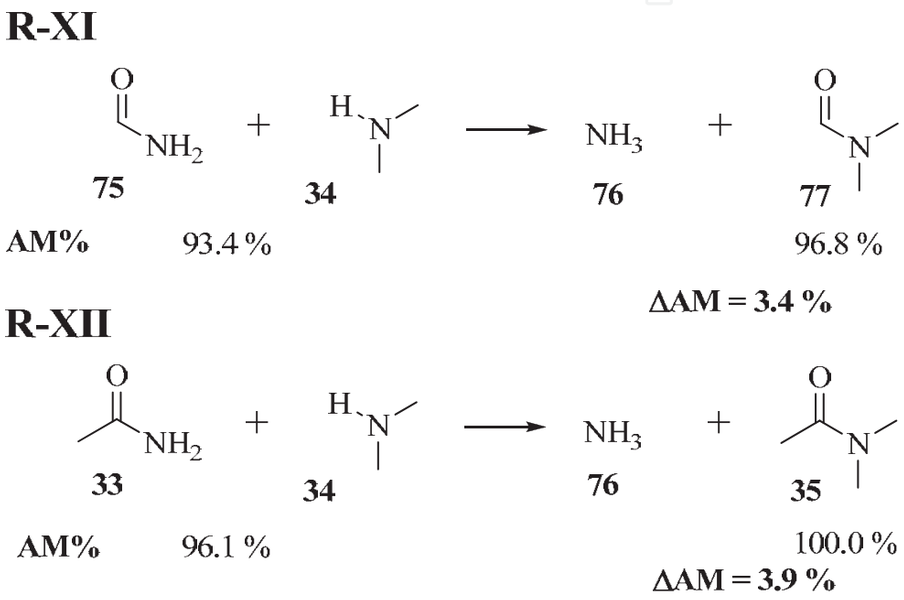

Fig. 21. Examples for transamidation involving secondary amine.

Compounds **78** and **82** represent mild acylating agents (**Figure 22**) taking part in transamidation reactions with amines (*e.g.* **79** for **R-XIII** and **R-XIV**), forming amide **81** and **80** and **83** as side-products. The acylating properties of these compounds can be attributed to the competition between the aromatic ring and the amide group of the N atom lone pair, which decreases both the amidicity and aromaticity percentages of the **78** and **82**. The main driving force of these reactions is the significant increase of the amidicity value during the acylation reaction. Compound **84** in **R-XV** (**Figure 22**) exhibits an extremely low amidicity percentage (–30.2 %), making this molecule an excellent acylating agent, prepared *in situ* from AcCl and pyridine. Thus, **84** readily reacts with amines (*e.g.* **85** for **R-XV**), with an extremely large ΔAM value (**Figure 22**) even at low temperature. In **R-XVI**, the acetanilide derivatives (*e.g.* **88**) with lowered amidicity values are also shown to be acylating compounds, transferring their acyl group to alkyl amines (*e.g.* **34** in **Figure 22**). The not too high ΔAM value may be one of the underlying reasons that these types of reactions are not often referred to in the literature. The reaction between **88** and **34** is very slow, even in the presence of $AlCl_3$ at high temperature, but it may be due to the larger steric hindrance of the carbonyl group in **82** [10–12].

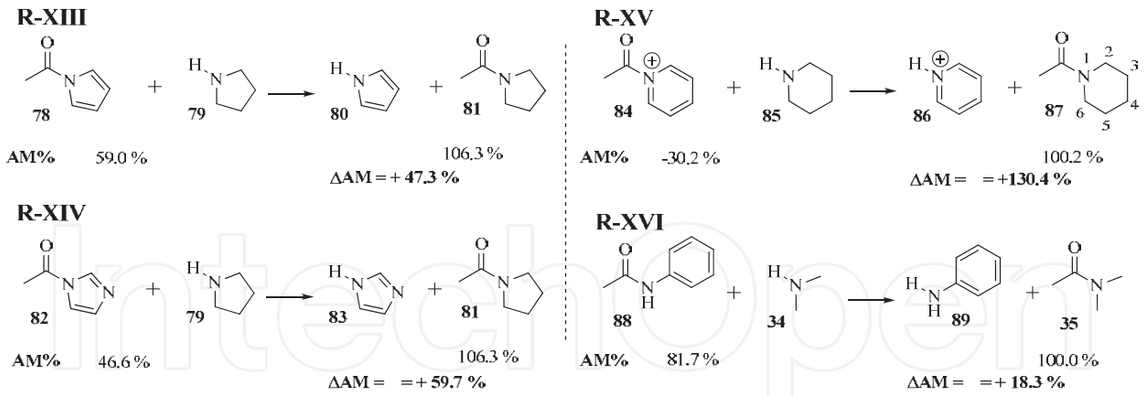

Fig. 22. Example for transamidation involving cyclic secondary amines

Using amidicity values, one may explain the inactivity of some commonly used organic amide-type solvents, such as *N,N*-dimethylformamide (**77**, DMF, **R–XVII** in **Figure 23**) and *N*-methylpirrolydinone (**91**, NMP, **R–XVII**, **Figure 23**). In both cases the ΔAM values are negative, making the reaction 'amidically unfavorable', therefore no reaction can be observed between **77** or **91** with **85** or **34**, even at 180° and in the presence of $AlCl_3$ as catalyst [10–12].

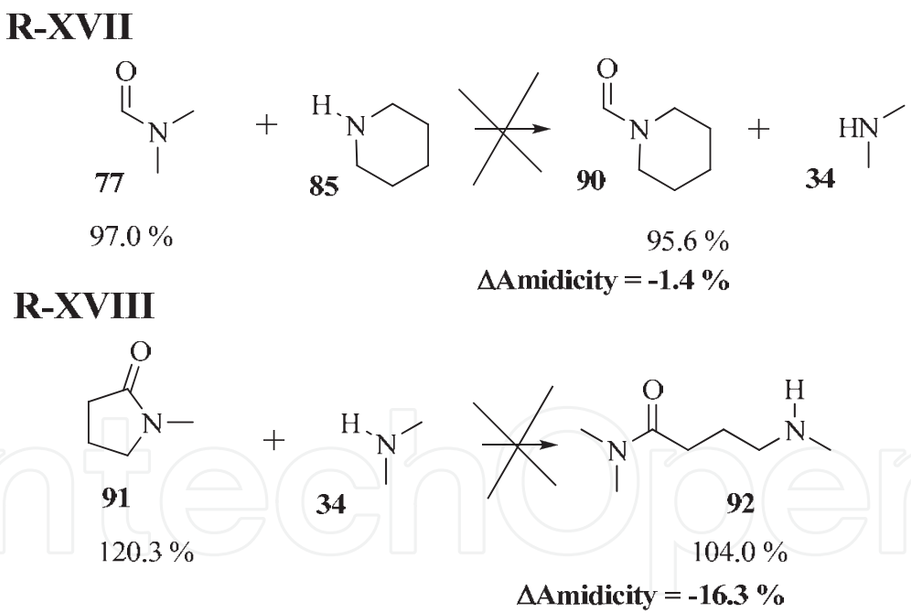

Fig. 23. Attempted transamidation reactions involving fully substituted amides and secondary amines

The use of the amidicity change or the change in stabilization enthalpy leads to a thermodynamic selection rule, allowing for the reactions to be categorized as being either thermodynamically favorable or unfavorable. This principle was illustrated as being operative in cases of differing reactions. Such a thermodynamic selection rule may be used to predict the selectivity of reactions in the presence of competing functional groups. The selectivity of the transamidation reactions was applied to molecular systems having an

additional, but another type of amino group (**93**). Molecule **93** has two opportunities for acylation, where in principle it could have yielded two types of mono-amide compounds (**94–95** and **96–97**) or a single diamide compound (**98 or 99**) as represented in **Figure 24**. As the amidicity change (ΔAM) indicated, only the alkyl amine group could react with **75** and **33**, therefore only compounds **94** and **95** were formed, whereas **96** and **97** as well as **98** and **99** were not produced, even in traces amounts [10–12].

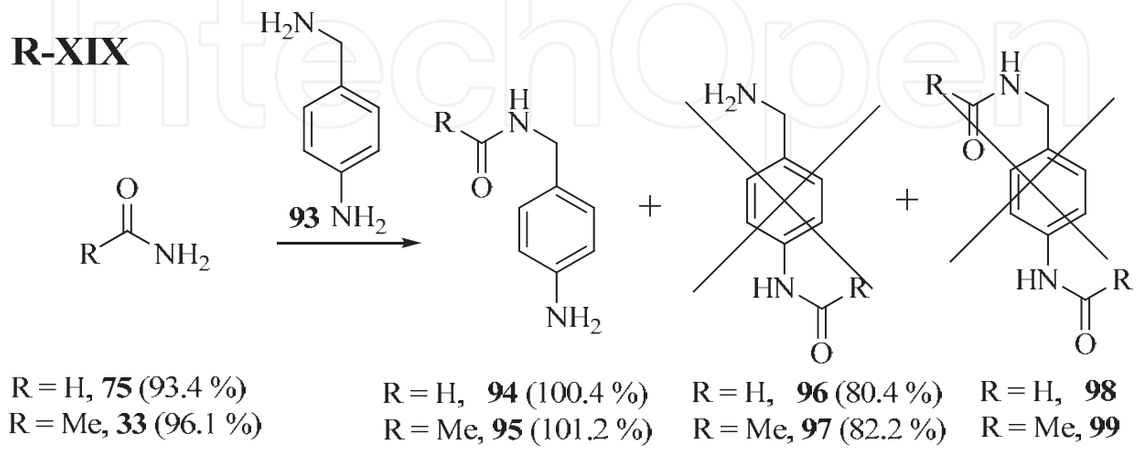

Fig. 24. Selectivity of transamidation reactions

From the numerous biochemical processes, involving transamidation reaction, only few, but very representative examples are presented here. The first example is taken from the multistep process of the blood clotting. In the last thirteenth step (**R-XX** in **Figure 25**) of the process, the two final protein intermediates **100** and **101** are jointed to each other through forming a side-chain amide bond. This process is spontaneous, therefore does not require external energy input. From system chemistry point of view, it is due to the positive ΔAM value of the process, where the initial 96.0% is increased to 101%. This small change provides a driving force for this reaction, but it is not enough to exhibit high reaction rate, therefore it is catalyzed by an enzyme transamidinaze [21].

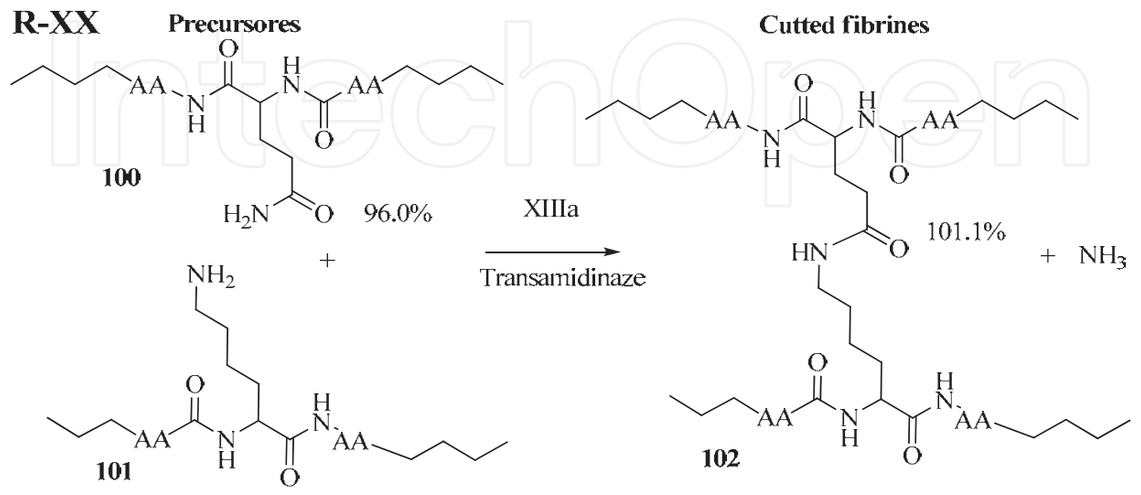

Fig. 25.

The intein-mediated protein splicing (**R-XXI**) is, relatively speaking, a newly discovered biological process (**Figure 26**) [21]. In this case however two amides are involved in transamidation process rather than me amide and one amine as before. Protein splicing is so rapid that the precursor protein is rarely observed in native systems. The intein peptide sequence usually contains no sufficient information and it is supposed to be originated from a virus, which inserted into the original DNA sequence producing the protein. The original broken protein sequence is named as extein. The intein plus the first C-extein residue contain sufficient information for splicing in foreign proteins, which involves four basic chemical steps. For the sake of simplicity, here we have presented only the starting and the ending states of the reaction and the amidicity values of the amide bonds were calculated for the functional groups in question.

R-XXI

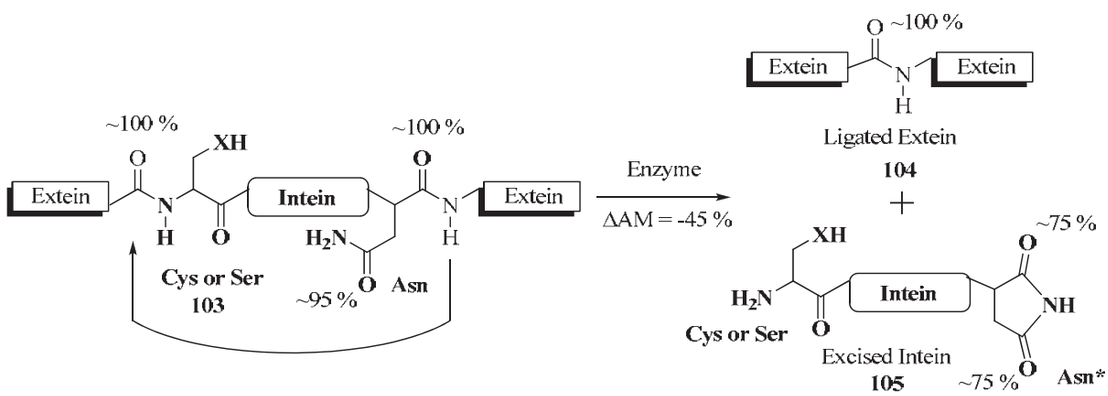

Fig. 26. Protein splicing as a special type of transamidation reaction.

The overall process exhibits large negative ΔAM value (–45 %), which may result an endothermic reaction. However, the folding of the spliced protein supposed to be more favorable, than that of the original, intein containing protein, which may provide an other driving force covering the energy demand of the overall process.

3.2 Complex analysis: Comparison of redox reactions of NAD and FAD with human made redox reaction [18]

Biochemical reactions are exceptionally energy-efficient relative to laboratory synthetic processes. Liberation and subsequent loss of heat in exothermic reactions (*e.g.* redox processes) is a mismanagement of energy and would be biologically detrimental as are highly endothermic ones, thus are avoided in nature. To support such a hypothesis, laboratory redox reactions were compared to those occurring in biological organisms. Evidently, Nature is able to store reactive potential within the molecular system, in carefully designed chemical structures which act as reversible energy carriers; effectively *molecular free-energy capacitors*. This *modus operandi* of Nature implies that during the evolutionary process, only those molecular that fulfilled near *thermo-neutral* requirements were retained. In an oxygen-containing atmosphere the development of aerobic life required appropriate reducing/oxidising agents. Thus, long ago Nature implemented the coenzymes dinucleotides Nicotinamide Adenine Dinucleotide (NAD^+, **106**) and Flavin Adenine Dinucleotide (FAD, **107**; for full structures see **Figure 27**, where the R groups later are

simplified to Me) together with their respective redox pairs NADH and $FADH_2$ to mediate the redox processes in all known living cells. These bioreagents play crucial energy storage roles, which act as 'energy catalysts', storing reductive potential until required.

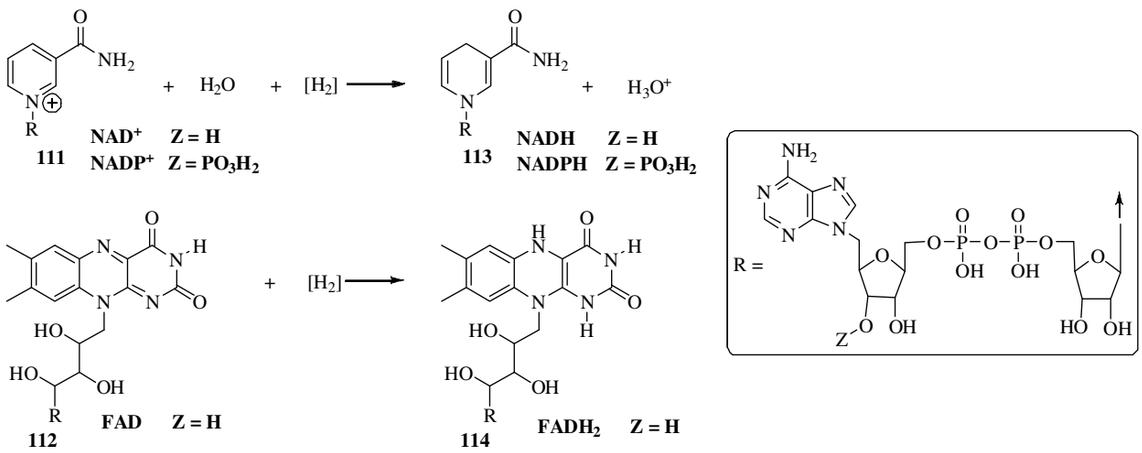

Fig. 27. The complete structures and reactions of NAD^+ (**111**) and FAD (**112**). The apostrophises at the compound numbers are emphasizing that these are the full structures rather than the model compounds on which the computations were performed.

These typical examples were selected, due to their published enthalpy of formation data. The preparation of reagent H_2 requires high amount of external energy (enthalpy), usually via electrolysis (**R-XXII/a** in **Figure 28**), while the reduction of pyruvate (**108**) to lactate (**109**) releases or waste also the same order of magnitude enthalpy (c.a. –200 kJ/mol; **R-XXII/b** in **Figure 28**). Other human applied reductive reagents, like $NaBH_4$ also serves analogues examples, where both the preparation and the usage of these reagents are not very energy efficient.

In the Nature side, the same reduction of pyruvate (**108**) to lactate (**109**) by using NADH (**108**) as bioreagent wastes only c.a. 30 kJ/mol enthalpy (**R-XXIII/b** in **Figure 28**). Moreover, the preparation of this active reducing reagent NADH (**108**) from NAD^+ (**111**) by means of maleate (**110**) and oxalacetate (**111**) redox equilibrium (**R-XXIII/a** in **Figure 28**).

Comparing these human- (**R-XXII**) and bioprocesses (**R-XXIII**), both the preparation (**a**) and reaction (**b**) of the NADH (bio)reagent proceed with $1/10^{th}$ the enthalpy change observed in the laboratory exercise, consequently this bioprocess can avoid the large endo- and exothermic changes in the course of the reaction, does not requiring intense external heating or cooling of the living organism. Such systemic chemical principles may be universally applied in all life-related processes. Coupling between components of a chemically or biologically important molecule, such as aromatic rings, amide groups, olefins, carbonyls and metal-ligands, are central to the molecules' chemical efficiency.

The reduction of NAD^+ and FAD is complimented by an enthalpy transfer between organic functional components (aromatic ring, amide and olefinic functionalities), yet, the sum of the overall energy values (the total system) remains nearly constant irrespective of what direction the redox reaction proceeds. From this aspect, both NAD^+ and FAD operate as real chemical systems of atoms and functional groups, working together within the individual molecules to store the reaction enthalpy as resonance enthalpy, rather than manifesting it as emitted or absorbed heat. In this way, the thermo-neutral reaction of the wet combustion occurring in all living cells is made possible by an internal "cooling process".

Concerning NAD+ (**106**) and FAD (**107**), two questions may be phrased: (Q1) What is the role of the amide functionality and why the *meta*-substituted NAD+ structure was selected during molecular evolution? (Q2) Why a complex, three-ring structure is necessary for proper function and catalytic efficacy of the FAD molecular system? A systemic approach is required to answer these. Making use of the recently established methodology[15-19], hydrogenation reactions were used to determine aromaticity, amidicity and olefinicity values.

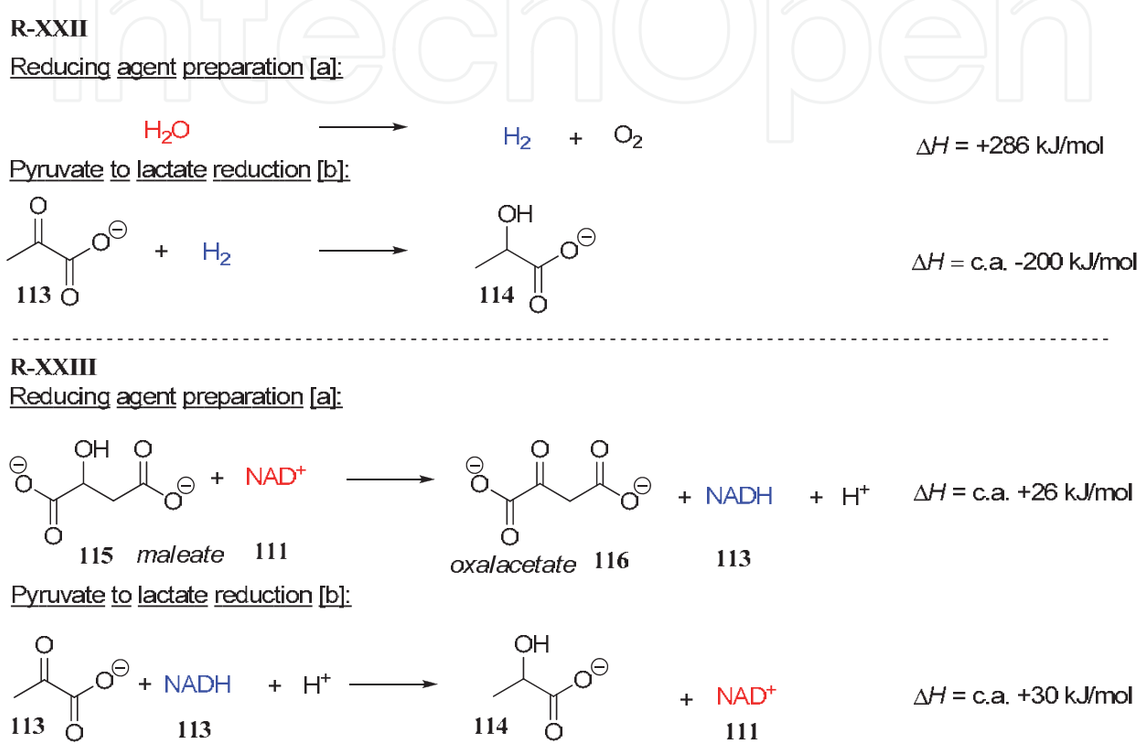

Fig. 28. A schematic depiction of the order of magnitude difference in energetic efficiency between synthetic and natural processes. The preparation of the reducing agents [I/a and II/a] and redox processes [I/b and II/b] in the case of a certain, biologically significant reaction are used as examples.

3.2.1 NAD Coenzyme and its models

From the Systems Chemistry point of view, many organic molecules are comprised of aromatic, amidic and olefinic portions, linked together by the global electronic structure of the system. These organic functional groups may easily be described by the concept of 'conjugativicity'; a term analogous to aromaticity,[15] amidicity,[16,17] carbonylicity[18] and olefinicity.[19] Accordingly, the structure of NAD+ and related models I–III (**106**, **112**, **114**, **116**) are composed of an aromatic (pyridine) and most of them an amidic part; each described using aromaticity and amidicity parameters, respectively. The structure of NADH and its related models I–III (**107**, **113**, **115**, **117**) are composed of one amidic and two olefinic parts, described by one amidicity and two olefinicity parameters, respectively.

Figure 29 provides a comparison of resonance enthalpy (RH) change in the naturally occurring nicotinic amide (NAD+, **106**) as well as its model congeners [models I (**112**), II (**114**

and III (**116**)]. **Table 2** shows the naturally occurring *meta* isomer having the greatest RH 'benefit' (+42.5 kJ mol^{-1}), manifested as an exothermic –42.5 kJ mol^{-1} reaction enthalpy. Our novel Systems Chemistry analysis shows that the principle RH component, originally stored as aromaticity (145.8 kJ mol^{-1}) in the pyridine ring of NAD^+ (**106**), is partly transferred post-reduction (**106** → **108**), to the two olefinicities *a* and *b*.

		Systems Chemistry						
		aromaticity		**amidicity**		**olefinicity**		
		%	**kJ/mol**	**%**	**kJ/mol**	**%**	**kJ/mol**	**kJ/mol**
Natural	**106**	95.1	**145.8**	35.2	**28.1**	0.0	**0.0**	
form	**108**	0.0	**0.0**	109.0	**86.7**	34.6+54.4	**129.5**	
			+145.8		**–58.7**		**–129.5**	**–42.5**
	112	91.6	**140.8**	36.4	**29.0**	0.0	**0.0**	
Model I	**113**	0.0	**0.0**	103.7	**86.7**	36.1+32.1	**97.6.5**	
			+140.8		**–53.5**		**–97.6**	**–10.6**
	114	101.0	**154.8**	66.1	**52.6**	0.0	**0.0**	
Model II	**115**	0.0	**0.0**	98.2	**78.1**	38.1+38.1	**109.0**	
			+154.8		**–25.5**		**109.0**	**+20.2**
	116	94.9	**145.5**	0.0	**0.0**	0.0	**0.0**	
Model III	**117**	0.0	**0.0**	0.0	**0.0**	32.6+32.6	**93.4**	
			+145.5		**0.0**		**–93.4**	**+52.1**

Table 2. Summary of different "icity" values (aromaticity, amidicity and olefinicity) and related resonance energies in kJ/mol calculated for **106**,**108**, **112–117**. For details see **Figure 29**.

This resulted in 16.8 kJ mol^{-1} less than complete energy recovery. However, the change in amidicity of the amide functionality provides 58.7 kJ mol^{-1} to RH, covering not only the 'missing' 16.8 kJ mol^{-1}, but also makes the overall process 42.5 kJ mol^{-1} advantageous from an RH point of view. In comparison, both the *ortho* (model I, **112** → **113**) and *para* (model II, **114** → **115**) isomers of NAD^+ are not able to provide overall RH 'recovery' (**Table 2**, **Figure 29**) during the reduction ; the principle reason that the natural form **106** uses the *meta* isomer of NAD^+ as a part of this redox system. Not only is the *meta* position the most suitable, it holds the most biologically available functional group, supporting the notion of 'molecular selection' being operative during the evolution of redox biochemistry of all life.

Our study also indicated that the entire amide functionality is crucial from the Systems Chemistry point of view, as the structurally simpler model III (**117**, **Table 2**, **Figure 29**) cannot recover the loss of RH from the loss of aromaticity during the reduction (**116** → **117**), due to the lack of an electron withdrawing group (EWG) in the *meta* position. The biologically more prevalent COOH functionality, mostly existing as COO^- at biological pH 6–8 (COO^- is an electron donating group, or EDG), would be far less effective than the $CONH_2$ EWG. Due to the highly effective energy recovery in both the forward and reverse reactions, is the principle reason that the NAD^+/NADH redox pair (**106**/**108**) works as a near-thermoneutral bio-reagent in biochemeical reactions.

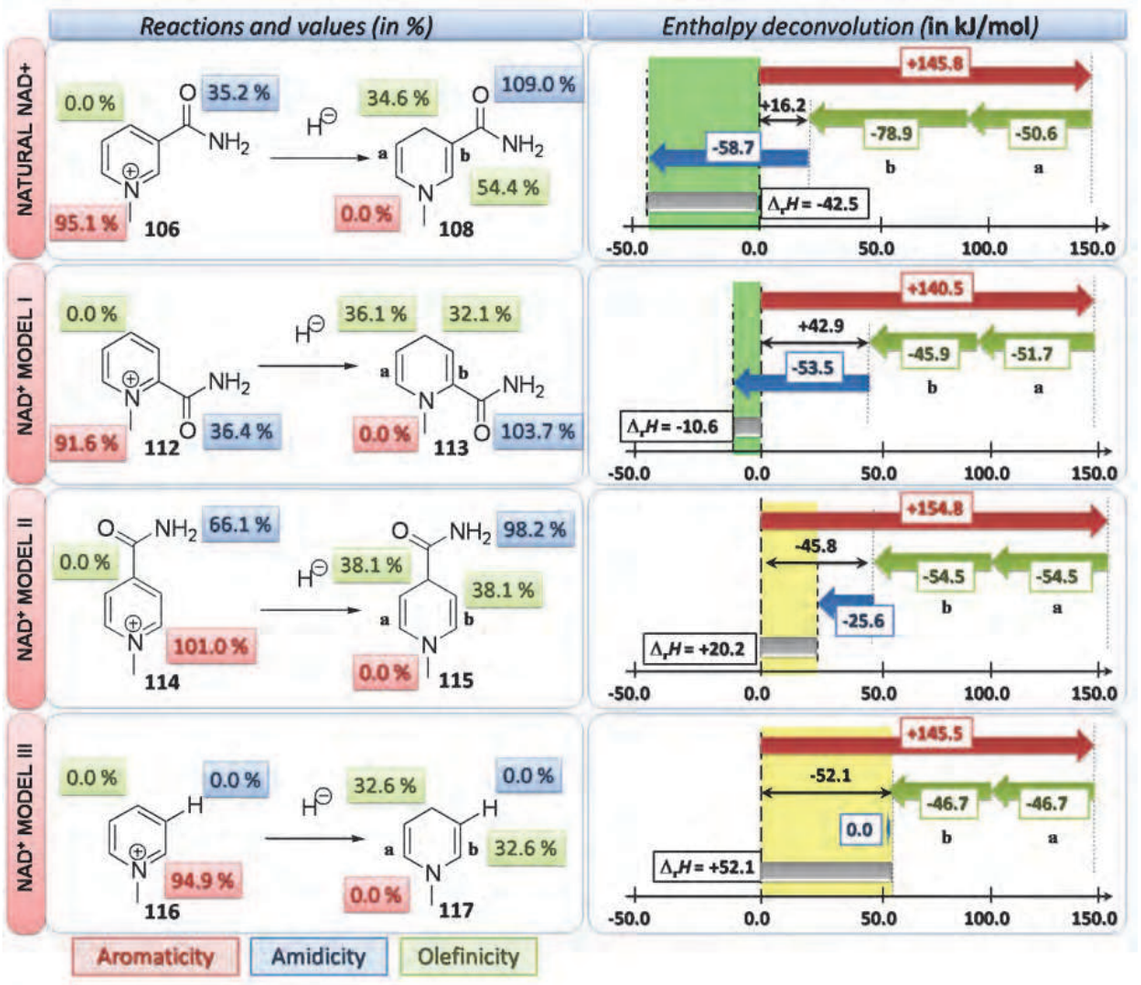

Fig. 29. **LEFT**: Redox reactions of the natural form of NAD^+ and related pyrimidium ion congener model systems (**106**, **112**, **114**, **116**) and their respective reduced products (**108**, **113**, **115**, **117**), including percentages of conjugative aromaticity (red), amidicity (blue) and olefinicity (green) values. **RIGHT**: Changes in resonance enthalpy (RH) values related to conjugativity, indicated by arrows using the same colour scheme as used at left, including both the sign and magnitude of change.

3.2.2 Systems chemistry analysis of FAD

Analogously, the three ring FAD (**107**) and $FADH_2$ (**109**) can be dissected to an aromatic portion composed of two rings (A and B) in addition to two-amide bond forming ring C, accounted for by a combined aromaticity value and two amidicity parameters, respectively. In this study some modified models of FAD–$FADH_2$ system are also considered as **118–119**; **120–121** and **122–123**. It may be demonstrated that all components of the FAD system (**112**) (tricyclic form with ring A, B and C, involving two amide bonds; *a* and *b*; see **Figure 30** and **Table 3**) are essential. Thus such natural arrangement of functional groups is requisite for proper function. From the Systems Chemistry point of view, FAD (**107**) may be considered as being similar to NAD^+ (**106**). The oxidized form (**108**) is comprised of two fused-rings in

the aromatic portion (ring A and B), characterized by a single 131.2 % aromaticity value (RH = 201.2 kJ mol^{-1}). The aromatic component is connected to a 3rd ring, itself substituted by two amide bonds having 111.6 % and 71.0 % amidicity values (RH = 88.7 kJ mol^{-1} and 56.4 kJ mol^{-1}), respectively (first line of **Figure 30** and **Table 3**). The aromaticity in the double-ring of the reduced form (**109**) is lowered to 100.9 % (RH = 154.7 kJ mol^{-1}), while amidicity rises in both amide bonds to 140.1 % and 125.4 %, respectively (RH = 111.9 kJ mol^{-1} and 99.7 kJ mol^{-1}). Loss of aromaticity upon reduction (**107** + H_2 → **109**), is rationalized by an observed antiaromatisation of ring B (6 electron pairs in rings A and B), manifested as a bent, non-planar, 3D fused-ring structure (**109**). However, amidicity values increase significantly, resulting in an overall RH change of +20.1 kJ mol^{-1}, representing a relatively large exothermic change (–20.1 kJ mol^{-1}) in the systemic RH.

The aromatic ring A of the FAD system serves to buffer the antiaromatisation of ring B, appearing as a non-planar 3D structure of **107** and **118**. This is exemplified on reduction of FAD model **I** (**118** → **119**; second line **Figure 30** and **Table 3**), wherein ring A is removed, resulting in a corresponding Δaromaticity = –72.9 % in contrast to the –30.3 % change in the natural form.

		Systems Chemistry						
		aromaticity		amidicity (a)		amidicty (b)		
		%	kJ/mol	%	kJ/mol	%	kJ/mol	kJ/mol
Natural	**107**	131.2	**201.1**	111.6	**89.1**	71.0	**56.7**	
form	**109**	100.9	**154.7**	140.1	**111.8**	125.4	**100.1**	
			+46.5		**–23.3**		**–43.3**	**–20.1**
	118	41.2	**63.2**	111.4	**88.9**	72.4	**57.8**	
Model I	**119**	–31.7	**–48.6**	144.8	**115.6**	126.4	**100.9**	
			+111.9		**–26.6**		**–42.9**	**+42.4**
	120	126.2	**193.5**	122.2	**97.6**	59.2	**47.3**	
Model II	**121**	111.5	**170.9**	111.2	**88.8**	49.7	**39.7**	
			+22.5		**+8.8**		**+7.6**	**+38.8**
	122	124.7	**191.2**	51.5	**41.2**	0.0	**0.0**	
Model III	**123**	103.2	**158.2**	80.0	**63.9**	0.0	**0.0**	
Natural			**+32.9**		**–22.7**		**0.0**	**+10.3**

Table 3. Summary of different "icity" values (aromaticity, amidicity and olefinicity) and related resonance energies in kJ/mol calculated for **107**,**109**, **118–123**. For details see **Figure 30**.

This is due to the large degree of antiaromaticity in the heterocycle component of **119** (aromaticity = –31.7 %), which is not offset by a corresponding, stabilizing increase in amidicity; Δamidicity for **118** → **119** is similar to that of the **107** → **109** and the overall RH for the reduction of model **I** is no longer favorable (+42.4 kJ mol^{-1}).

The *b* amide component also serves a crucial systemic role, helping stabilize the system upon reduction through a 54.4% amidicity increase in the natural form (**107** → **109**; 71.0 % → 125.4 %). Its removal (FAD model **II (120**); third line in **Figure 30** and **Table 3**) 'softens' the destabilizing reduction of aromaticity (**120** → **121**; 124.7 % → 103.2 % = -21.5%) relative to the natural process (**107** → **109 =** -30.3%). However, the absence of this secondary –CONH– functionality excludes its thermodynamically advantageous amidicity increase, resulting in an overall unfavorable process (**120** → **121** = +10.3 kJ mol^{-1}).

The role of the chemical linkage between ring II and amide B was also examined using the truncated FAD model **III** (**122** → **123**; fourth row in **Figure 30**). Removal of the bond destroys ring C and raises the overall RH, making reduction +58.9 kJ mol^{-1} less favorable relative to the natural system, due to the absence of amidicity increase in amide II. In the natural compound (**107**), ring C buffers the appearing antiaromaticity, manifested in its own increased aromaticity and amidicity values (**109**). Truncation of this very important bond eliminates the systemic linkage between ring B and amide *b*. In the reduction of FAD, only the ring B and amide *a* components take chemical part in the reaction, together receiving two electrons and two protons. One may therefore conclude that the role of all other

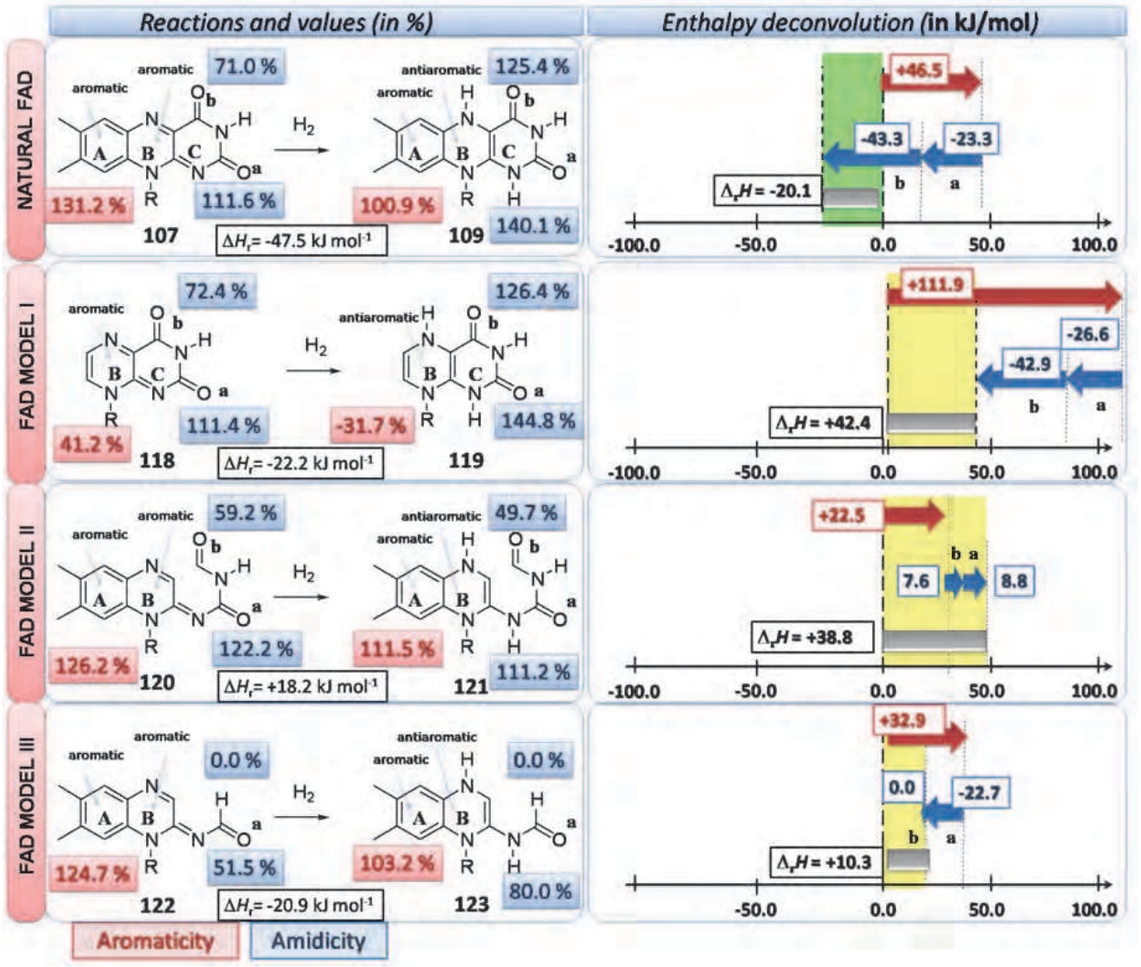

Fig. 30. **LEFT**: Redox reactions of the natural form of FAD (**107**) and their different models (**I**, **118**; **II**, **120** and **III**, **122**) leading to reduced products (**109**, **119**, **121**, **123**) and their percentages of their respective conjugative [aromaticity (red), amidicity (blue)] values. **RIGTH**: Changes of resonance enthalpy (RH) values related to conjugativity [indicated by arrows with the same color as was used left, referring to both the sign and the amount of these]. FAD (**107**) and its models **118**, **120**, **122** as well as $FADH_2$ (**109**) together with its congeners (**119**, **121**, **123**) is composed of an aromatic ring (aromaticity, ring A and B) and two amide functionalities (amidicity, amide *a* and *b*).

functional components is systemic, compensating for (reducing) the antiaromatization of ring B. This leads to the thought that, were Nature truly so efficient, it would remove the antiaromatization and the need for other components; unless antiaromatization itself were essential, playing a secondary role in the process. Considering only the reductive part of FAD (model **III**, **122**, last line in **Figure 30** and **Table 3**), removes the need to compensate the disadvantageous antiaromaticity. The reductive power of the resultant small molecule (**122** → **123**) is extremely large, meaning that by means of specialized enzymes, it has the ability to reduce each reducable compound in the cell. However the associated large exothermic reaction enthalpy would call for an intensive cooling process to bring the temperature under control; antiaromaticity providing the 'counterbalance' to the process and a means by which energy may be stored.

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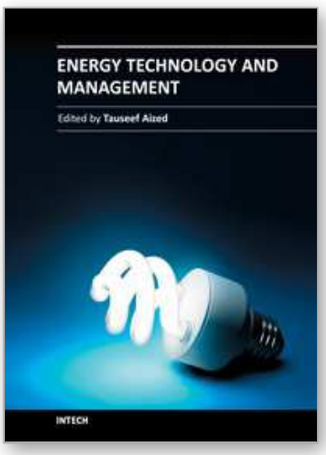

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