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A conceptual DFT study of hydrazino peptides: Assessment of the nucleophilicity of the nitrogen atoms by means of the dual descriptor $\Delta f(r)$

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Abstract

Hydrazinopeptides are pseudopeptide molecules containing a N–N bond. To understand the compared reactivity as a nucleophile of the two nitrogen atoms included in this moiety with respect to the surrounding rest of the molecule, a conceptual DFT study is carried on with the analysis of the dual descriptor $\Delta f(r)$ in a series of molecules, at the B3LYP/6-31G(d,p) level. The dual descriptor is a tool based on the Principle of Maximal Hardness within the framework of conceptual DFT which characterises the nucleophilic and electrophilic areas within a molecule.

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Keywords: Hydrazine; Amide; Carbamate; Conceptual DFT; Nucleophilicity; Dual descriptor

1. Introduction

Hydrazinopeptides are viewed as promising pseudopeptides in order to build self-organizing foldamers, mimicking the secondary structure of biomolecules. The introduction of a supplementary nitrogen inside the peptidic backbone is supposed to allow new intramolecular interactions involving this particular supplementary nitrogen atom, or the hydrogen atom directly bound to it [1,2].

From a peptidic synthesis point of view, the moieties used to build these polypeptidic structures pose new problems of reactivity due to the presence of two consecutive nitrogen atoms. One issue is the question of the compared nucleophilicities of the two nitrogen atoms in hydrazinopeptides [3,4]. In order to assess the nucleophilicity of the molecules used in the steps of pseudopeptidic synthesis, the idea of the present study is to undertake calculations on model compounds illustrating the N–N bond that these

molecules share in common, with a diversity of substituents on the nitrogen atoms according to the substituents or functional groups that are used in the synthesis.

The list of eight model compounds that constitute our set of molecules is shown in Fig. 1. It departs from the simplest molecule containing a N–N bond (hydrazine $\text{H}_2\text{N}-\text{NH}_2$) and then adds more or less complex substituents to one of the two nitrogen atoms in order to compare the reactivity of the two nitrogen atoms when the substituent changes. Such substituents in the syntheses carried on in the laboratory include methyl, acetyl, methoxycarbonyl, or the protective group Boc (or tertibutyloxycarbonyl), which are common protecting groups in peptidic synthesis. From hereto now, N1 will refer to the nitrogen atom without substituent and N2 will refer to the nitrogen atom bearing the substituents.

2. Theoretical background

Conceptual Density Functional Theory [5–8] (DFT) is a very elegant way to describe chemical processes.

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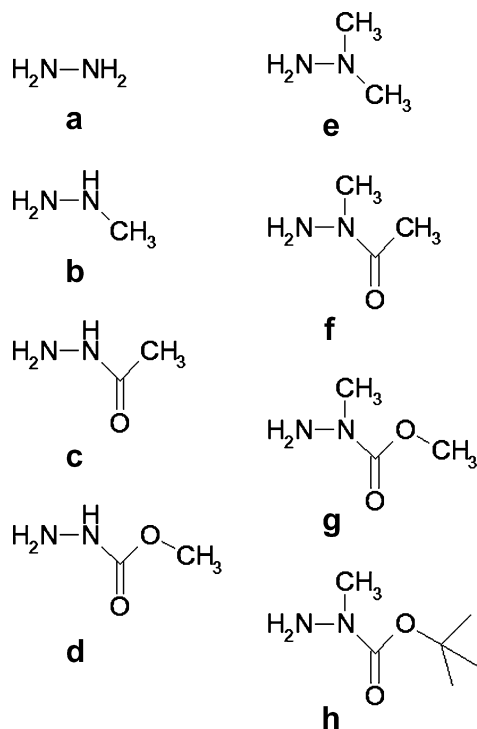


Fig. 1. Eight model compounds including the hydrazino functional group. N1 will henceforth refer to the left nitrogen atom, and N2 to the nitrogen atom that bears substituents.

In DFT, one assesses the chemical reactivity of reactants through the response of the electronic energy to a change of either the number of electron (N) or the external potential [$v(r)$]. On the one hand, the chemical potential [9] identified as the opposite of the electronegativity, is defined as the first derivative of the electronic energy with respect to the number of electron (N) at constant external potential. The absolute hardness [10], defined as the derivative of the chemical potential at constant external potential, characterises the resistance to charge transfer of an electronic system. Chemical potential and absolute hardness are both global indexes which describe chemical reactivity. On the other hand, the electronic density is the derivative of the energy with respect to the external potential at constant number of electron (N). The Fukui function [11], yet another important local descriptor, is defined either as the variation of the chemical potential with respect to the external potential, or as the derivative of the electronic density over the number of electrons. Both electronic density and Fukui function are local descriptors for chemical selectivity.

In this paper the main index is the so-called dual descriptor [12,13], sometimes also called the second order Fukui function [14]. This descriptor can be defined as the second derivative of the electronic density with respect to the number of electron (N) at fixed nuclear geometry.

$$\Delta f(r) = \left(\frac{\partial^2 \rho(r)}{\partial N^2} \right)_{v(r)} \quad (1)$$

The finite difference approximation applied to Eq. (1), leads to an expression that links the dual descriptor with the well known Fukui functions:

$$\Delta f(r) \approx \rho_{N+1}(r) + \rho_{N-1}(r) - 2\rho_N(r) = f^+(r) - f^-(r) \quad (2)$$

where $f^+(r)$ and $f^-(r)$ are the electrophilic and nucleophilic Fukui function, respectively. Since the electrophilic/nucleophilic Fukui functions measure how the electronic density changes when an electron is added/removed from the electronic system, it becomes clear that the sign of the dual descriptor characterises the electrophilic/nucleophilic behaviour of a molecular site within a molecule. Indeed, a positive/negative value of $\Delta f(r)$ indicates a point r in which the electrophilic/nucleophilic Fukui function is larger than the nucleophilic/electrophilic one. Basically, the dual descriptor will exhibit positive value at places which are better at accepting electron than they are at donating electrons. Conversely, zones with negative values of the dual descriptor characterise site that are better at donating electrons than they are at accepting electrons.

$\Delta f(r) > 0$ Electrophilic regions

$\Delta f(r) < 0$ Nucleophilic regions

Of same importance, the very definition of $\Delta f(r)$ is also related to the global concept of chemical hardness. The use of a Maxwell relation allows one to rewrite the dual descriptor in term of derivative of the hardness with respect to the external potential:

$$\Delta f(r) = \left(\frac{\Delta \eta}{\Delta v(r)} \right)_N \quad (3)$$

In the latter equation $\Delta v(r)$ is the variation of the external potential at point r . The integral form of Eq. (3) helps to understand the meaning of the dual descriptor by using the Principle of Maximum Hardness.

$$\Delta \eta = \int \Delta f(r) \Delta v(r) dr \quad (4)$$

Basically, a molecule that undergoes an electrophilic attack experiences a lowering of its external potential. Therefore, the chemical hardness of the molecule will increase if the electrophile approach positions with negative values of the dual descriptor. Conversely, the chemical hardness of the molecule will increase again if a nucleophile interacts mainly with positions that display positive values of the dual descriptor, since nucleophiles are supposed to increase the external potential of the targeted molecule. These results are consistent with what is expected from the Principle of Maximum Hardness, which state that the molecules tend to rearrange themselves to be as hard as possible.

Thus both theoretical definitions provide the same understanding of the sign of the dual descriptor and allow its use to the rationalization of chemical processes. Since the dual descriptor has been very versatile for describing the region and/or stereo selectivity of chemical reaction

[15], it seems interesting to use it to assess the nucleophilicity of both the nitrogen atoms of the hydrazinopeptides.

3. Computational details

Structures of eight molecules were optimized at the B3LYP/6-31G(d,p) [16,17] level of theory and checked for imaginary frequencies, with the Gaussian 03 [18] software using default conditions. The pictures of the optimized geometries are available on Fig. 2. In order to calculate Fukui functions and then the $\Delta f(r)$ descriptor, single point energies were performed for the radical anion ($N + 1$ electrons) and radical cation ($N - 1$ electrons) at the optimized geometry of each neutral (N electrons) molecule. The Mulliken [19] partitioning has been used to calculate charges and condensed Fukui functions. Although the condensation of charges or Fukui functions presents some issues [20] in partitioning the molecular space, it

can provide quantitative results in order to compare regions within a molecule.

4. Results and discussion

The dual descriptor is described in two ways. First, an isodensity surface, showing nucleophilic (in blue) and electrophilic (in red) regions of the molecule, can display the compared nucleophilicity of the two nitrogen atoms with the size of the blue lobe on each atom (Fig. 3). In this case, as the dual descriptor is defined in every point in space, it is written $\Delta f(r)$. Secondly, a condensed value based on the Mulliken partitioning, allowing to compare figures. This last condensed value can also be compared with other conceptual descriptors such as: the Mulliken charge or the f_k^- nucleophilic Fukui function. In this case, as the dual descriptor is a condensed value defined for every atom k , it is written Δf_k . All figures are gathered in Table 1. Even

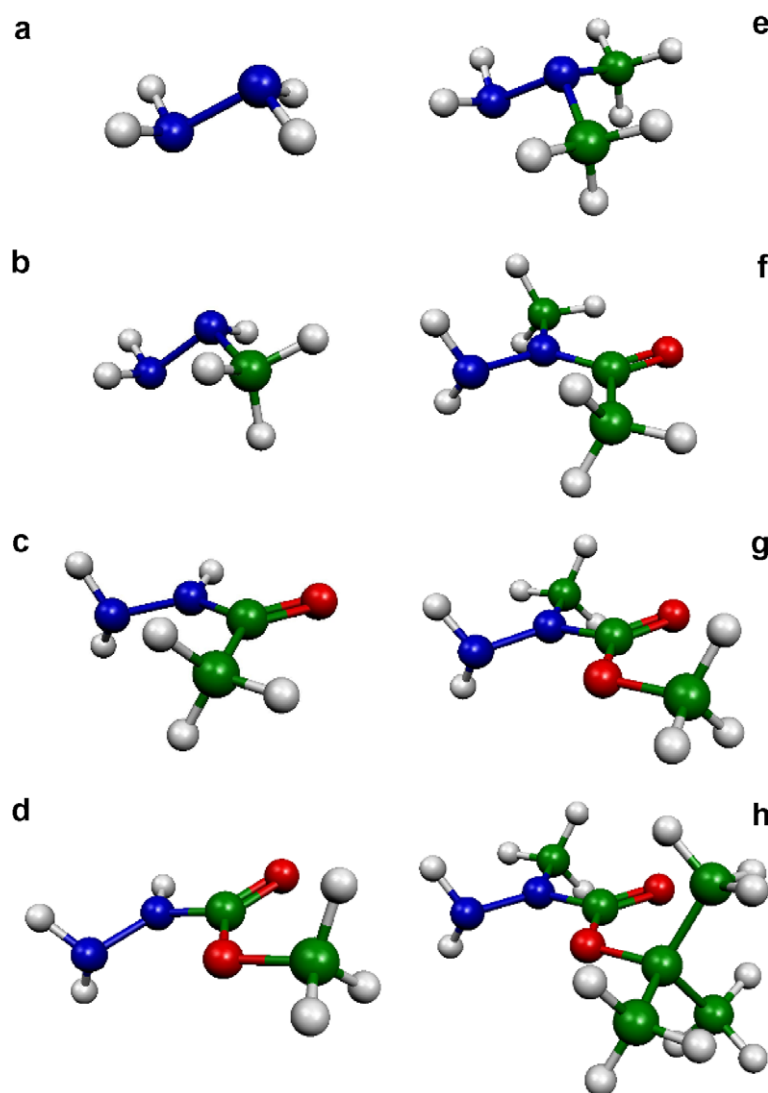


Fig. 2. Eight model compounds optimized geometries.

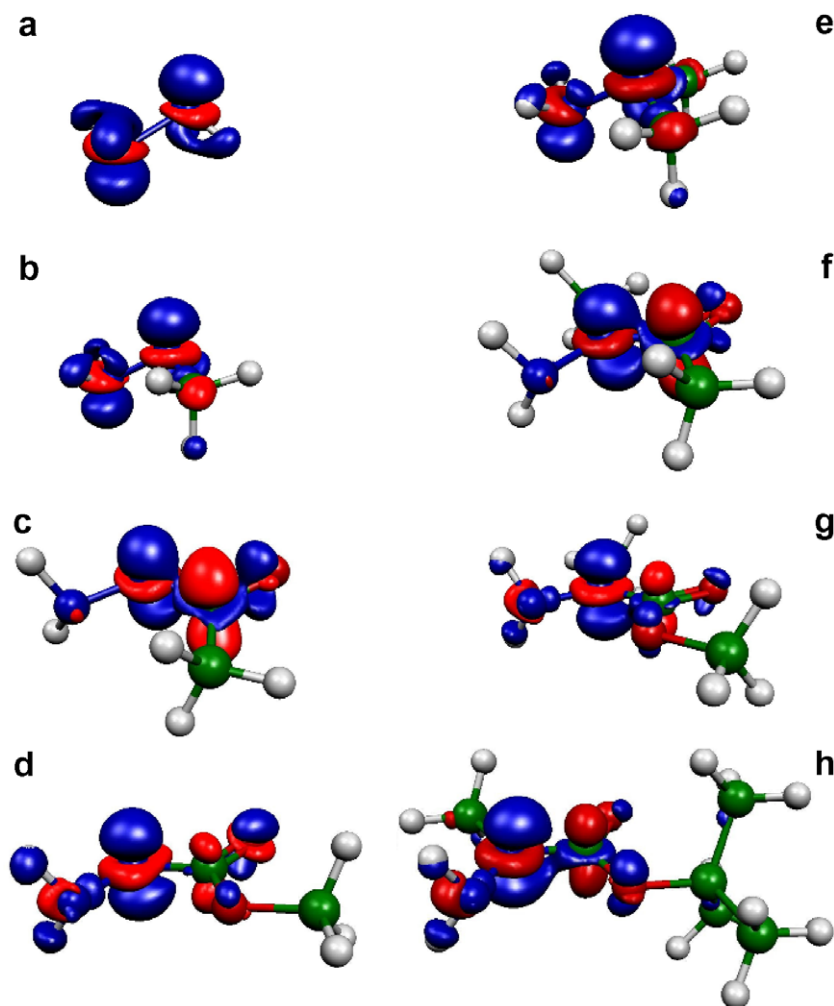


Fig. 3. Δf isovalue surfaces showing nucleophilic (blue) and electrophilic (red) regions. The N1 nitrogen atom is on the left side of the molecule, and the N2 nitrogen atom to the right of N1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tough condensed indexes are necessary for compared reactivity studies between molecules, it should be kept in mind that the condensation process might be dependant of the population analysis method chosen. In that respect, isodensity maps are more accurate.

From the isodensity surfaces and Δf_k condensed figures, it appears that N1 Δf_k values are systematically lower than N2 on every molecule except B and E. It is thus remarkable that for every molecule that contains a π system (namely a C=O double bond) in the molecule, the Δf_k descriptor (and this is confirmed by the condensed values of the electrophilic Fukui function f_k^-) shows that the N1 atom is considerably less nucleophile than the N2 nitrogen atom, even though this N2 atom may have its lone pair involved in an amide bond. If we look at charges, the situation is the opposite. The N1 nitrogen atom possesses the highest (negative) charge on almost every molecule. It appears thus that the N1 nitrogen atom would be more nucleophile in a hard interaction (as witnessed by the charge indicator) while the nucleophilicity of the N1 nitrogen atom would be seriously

diminished in a soft interaction (as witnessed by the f_k^- and Δf_k indexes).

Thus, the exceptions are molecules B and E, the only molecules that do not possess a π system. For B and E, the nucleophilicity of the N1 nitrogen atom is of the same order of magnitude than the nucleophilicity of the N2 nitrogen atom.

If we compare the Δf_k and f_k^- descriptors, the nucleophilicities of N1 and N2 are consistent. There is nevertheless a slight discrepancy for the N1 atom of molecules D, G and H. For these three molecules, the Fukui function depicts a similar situation to molecules C and F, whereas for the Δf descriptor, the N1 nucleophilicity (for molecules D, G and H) is slightly enhanced, and is comparable to the nucleophilicity of the N2 atom. It is worth noting that molecules C and F are hydrazinoamides (with respect to the carbonyl C=O double bond), whereas molecules D, G and H belong to the category of hydrazinocarbamates: the C=O carbonyl double bond is surrounded by the N2 nitrogen atom on the one hand, and an oxygen atom on the other hand.

Table 1
Condensed atomic charges (q), condensed nucleophilic Fukui functions (f^-), condensed dual descriptors (Δf) of N1 and N2 atoms on every studied molecule

	A		B		C		D		E		F		G		H	
	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2
q	-0.504	-0.504	-0.484	-0.409	-0.451	-0.417	-0.428	-0.473	-0.462	-0.337	-0.448	-0.348	-0.427	-0.405	-0.425	-0.415
f^-	0.243	0.243	0.198	0.209	0.036	0.225	0.044	0.227	0.165	0.179	0.036	0.179	0.036	0.188	0.026	0.162
Δf	-0.400	-0.400	-0.352	-0.283	-0.043	-0.203	-0.225	-0.288	-0.315	-0.192	-0.037	-0.198	-0.179	-0.211	-0.145	-0.187

Let us compare molecules C and F (let us call them the amides, though they actually belong to the category of hydrazinoamides) with molecules D, G and H (let us call them the carbamates). First of all, the Mulliken charge q on N2 is relatively (negatively) high (with respect to the charge on N1) for the carbamates, as compared to the amides. This is in agreement with the fact that the carbamate N2 lone pair is probably less delocalized than the amide N2 lone pair, knowing that amides N—C internal rotation is energetically more difficult than carbamates N—C internal rotation. As a matter of fact, the barrier of rotation around the N—C bond has been proven both experimentally and computationally to be lower for carbamates than for amides [21]. It is thus logical to describe the nitrogen atom in an amide structure (as compared to carbamates) as a (relatively) electron poor atom: the resonance form revealing the double bond character of the N—C bond showing a cationic nitrogen atom. For carbamates, this is less the case. According to the Δf dual descriptor, there is also a difference of behaviour between the carbamates and the amides. The lower nucleophilicity of N1 is more pronounced for the amides than for the carbamates, as if the commitment of the N2 lone pair in the N—C bond resonance (more pronounced for the amides than for the carbamates) would lower the nucleophilicity of N1 even further for the amides. This is also shown by the f^+ Fukui function (not shown in Table 1, but can be obtained by adding f_k^- and Δf_k). The tendency to accept one electron (as revealed by the f_k^+ Fukui function) is more important on the nitrogen atom of amides (molecules C and F), due to amidic double bond commitment than on the nitrogen atoms of the carbamates. There is thus a correlation between the tendency for the molecules to present a low N—C double bond character and the nucleophilicity as expressed by the condensed values of Δf_k . It can be concluded that this very behaviour is revealed by the dual descriptor Δf_k , but not by the f_k^- Fukui function, which lacks the influence of f_k^+ in its description of reactivity. If the charge transfer from N2 to the carbon is weak such as in carbamates, the reactivities of the nitrogen atoms (N1 and N2) are of the same order. This is exactly what happens in A and B (no charge transfer at all). If a charge transfer is possible (as is the case for the amides), then it seems that this charge transfer is partly compensated by the donation from N1 to N2 in amides. The comparison between the electronic density on N2 in carbamate and amide confirms this assumption, since they are of the same order of magnitude. This compensation leads to a deactivation of N1 while N2 holds the same reactivity.

5. Conclusions

From an organic chemist's point of view, the nucleophilicity of these compounds is pivotal in order to synthesize hydrazino compounds. In most situations [22] the reactivity of N1 is superior to the reactivity of N2, so this would correspond within the framework of our study to a

nucleophilic attack represented by a hard–hard interaction. Nevertheless, in some cases, the N2 atom does actually react as a better nucleophile than N1 [23], even though the N2 lone pair is supposed to be delocalized within the amide bond, thus logically lowering its nucleophilicity. This would be in agreement with a soft–soft interaction as described by the dual descriptor and the Fukui function. Finally, according to Δf , the reduced nucleophilicity of N1 is observed in hydrazinoamides (like molecules C and F) but less so in hydrazinocarbamates (like molecules D, G and H). Thus the dual descriptor allows to rationally categorize different experimental reactivities as hard or soft interactions. This is a useful achievement of a conceptual DFT descriptor.

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