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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 $\Delta f(r)$

Christophe Morell [a], Alexandre Hocquet [b,*], André Grand [a], Brigitte Jamart-Grégoire [b]

[a] *CEA/DRFMC/LCIB/ (FRE2600), 38054 Grenoble, France*
[b] *LCPM, UMR CNRS INPL 7568, B.P. 451, 54001 Nancy, France*

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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.

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 $H_2N—NH_2$) 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 tertiobutyloxycarbonyl), 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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[*] Corresponding author.
E-mail address: alexandre.hocquet@ensic.inpl-nancy.fr (A. Hocquet).

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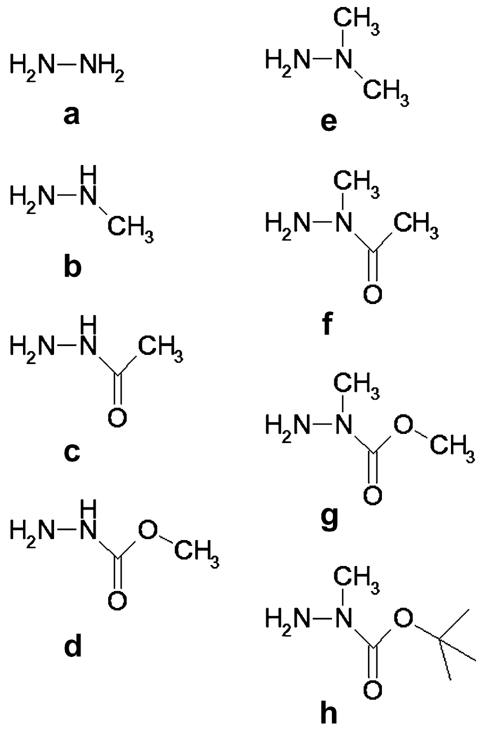

Fig. 1. Eight model compounds including the hydrazino functional group. N1 will henceforth refer to the left nitrogen atom, and N2 to the nitrogen atom that bears substituents.

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.

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

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

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

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:

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

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.

$$\Delta \eta = \int \Delta f(r) \Delta v(r) \mathrm{d}r \tag{4}$$

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