J Mol Model (2010) 16:825–830
DOI 10.1007/s00894-009-0579-x

ORIGINAL PAPER

Aminequinone-hydroxylquinoneimine tautomeric equilibrium revisited: molecular modeling study of the tautomeric equilibrium and substituent effects in 4-(4-R-phenylamino)naphthalene-1,2-diones

Thaís P. Fragoso · José Walkimar de Mesquita Carneiro · Maria D. Vargas

Received: 5 May 2009 / Accepted: 12 August 2009 / Published online: 13 September 2009

Abstract Semi-empirical (AM1 and PM3) and DFT (B3LYP/6-31G(d)) calculations were employed to study the tautomeric equilibrium between the aminequinone **A** and hydroxylquinoneimine **B** forms of 4-(4-R-phenylamino)naphthalene-1,2-diones. Substituent effects on the tautomeric equilibrium as well as on geometric and electronic parameters were also determined. In the gas phase the hydroxylquinoneimine **B** form is the most stable, whereas in water the aminequinone **A** form becomes more stable. The substituents do not modify the relative energies of the two tautomers. These results are in accordance with experimental data reported in the literature.

Keywords Enamine-quinone tautomerism · 4-(4-R-phenylamino)naphthalene-1,2-diones · Solvent effect · Tautomeric equilibrium

Introduction

The quinone moiety is a very usual and frequent chemical building block, found in synthetic as well as in natural products [1, 2] and is present in several drugs, such as anthracyclines, mitomycins and mitoxantrones, which are used clinically in the therapy of solid cancers [3]. The ability of quinones to interfere in the electron transport chain of different microorganisms opens an attractive avenue to exploration for new biological applications. The biological activity of naphthoquinones is generally associated to their ability to accept one or two electrons [4–6]. Therefore their electron-accepting potential may be modeled by carbonyl position changes (1,2- x 1,4- naphthoquinones), different substituents or functions that can be attached to the quinone moiety or even to the phenyl ring directly bonded to the quinone moiety. Thus electron-attracting or electron-donor substituents may diversely change the redox properties of these molecules [7, 8].

In the present study we analyze the conformational behavior and substituent effects in 4-anilino-1,2-naphthoquinones in order to establish the effect of electron-donor and electron-acceptor substituents on relevant structural and electronic properties of this class of compounds.

4-Anilino-1,2-naphthoquinones compounds have been known to exhibit tautomerism involving the aminequinone **A** [4-(R-phenylamino)naphthalene-1,2-dione] and hydroxylquinoneimine **B** [2-hydroxy-4-(R-phenylimino)naphthalen-1(4H)-one] forms (Fig. 1) [9] and conflicting reports have appeared in the literature. Based on electronic spectral data Harmon *et al.* [10] found that in aqueous solution (pH 4–13) the compounds exist predominantly in the aminequinone form **A**, but in strongly acidic solution (pH 0–0.8) the hydroxylquinoneimine form **B** becomes more stable. In the solid state, infrared spectra has suggested predominance of tautomer **A** [11]. Measurements of ^{13}C NMR chemical shifts [12] indicated that in DMSO-d_6 (R = H, 3-OH, 4-OH) **A** is the predominant tautomer, whereas in pyridine-d_5 (R = 3-OH and 4-NO_2) tautomer **B** predominates and in D_2O solution of NaOD the anion of **B** predominates; furthermore the electronic spectrum in aqueous strong acid solution in-

Electronic supplementary material The online version of this article (doi:10.1007/s00894-009-0579-x) contains supplementary material, which is available to authorized users.

T. P. Fragoso · J. W. de Mesquita Carneiro (✉) · M. D. Vargas
Departamento de Química Inorgânica, Instituto de Química,
Universidade Federal Fluminense,
Outeiro de São João Batista, s/n,
24020-141 Niterói, RJ, Brazil
e-mail: walk@vm.uff.br

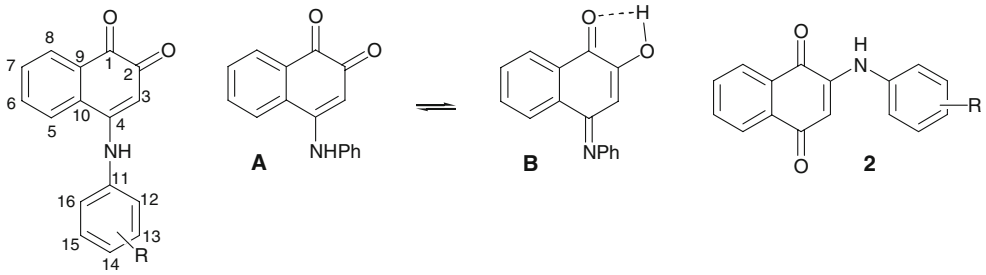


Fig. 1 4-[(R-phenyl)amine]-1,2-naphthoquinone (tautomers **A** and **B**) and 2-[(R-phenyl) amine]-1,4-naphthoquinone (**2**)

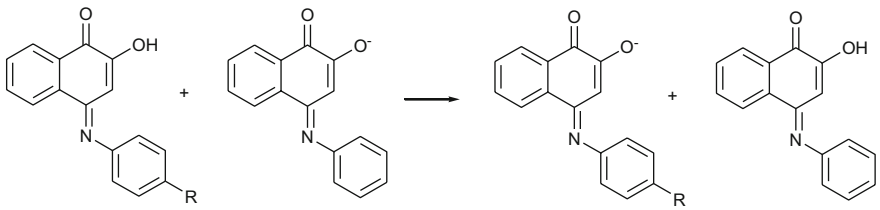
dicated tautomer **A** as the main component [12]. Similarly to a number of 2-[(R-phenylamino)]-1,4-naphthoquinone analogous compounds (Figs. 1, 2) [13] some of the [4-(R-phenylamino)naphthalene-1,2-dione] derivatives (R = H, 4-Et, 4-Me and 2,3-Me) also exhibit dimorphism in the solid state evidenced by IR spectroscopy, which has been associated to a change in the molecular configuration centered around the N-H group [14].

Contrary to what is found in the case of the 2-[(R-phenylamino)]-1,4-naphthoquinones [15], where the hydroxylquinoneimine tautomer is considerably less stable than the aminequinone form, in the case of the 4-[(R-phenyl)amine]-1,2-naphthoquinone derivatives, due to an intramolecular hydrogen bond (Fig. 2), the hydroxylquinoneimine tautomer may be stable enough to interfere in the redox and other properties of these compounds. We therefore dedicated special attention to the question of the relative stability of the different tautomers.

Computational details

As a first approach we used the semi-empirical AM1 [16] and PM3 [17] procedures available in the MOPAC software to fully optimize the geometry of all compounds studied. Any of the two tautomers for each derivative may exist in two main conformations, as shown in Fig. 2, $\mathbf{A_1}$, $\mathbf{A_2}$, $\mathbf{B_1}$ and $\mathbf{B_2}$, structures 1 and 2 differing by rotation around the C-N bond.

For all derivatives the two conformations for each tautomer were calculated. In order to determine the effect of a polar solvent on the tautomeric equilibrium the COSMO facility [18] was employed to calculate the relative energies of the several species in the presence of the solvent water, defined by specifying a dielectric constant of 78.5. From the optimized geometries the following geometric and electronic parameters were analyzed: the degree of coplanarity between the naphthoquinone and the phenyl rings, defined by the dihedral angle C(3)-C(4)-C(11)-C(12), charge density and energy of the frontier orbitals (HOMO and LUMO). In addition we defined an isodesmic equation (Eq. 1), to quantify the effect of each substituent in the stabilization of the anion derived from the hydroxylquinoneimine form after deprotonation. This is relevant because of the possibility of these species to complex metal ions. Indeed, complexation of a number of naphthoquinones or naphthoquinone derived compounds has been shown to result in increased cytotoxicity [19], antimalarial [20, 21], anticancer [22], and antibacterial activity [23], among others.



(1)

Calculations were carried out for derivatives R = H, NH_2, OH, OCH_3, Ph, CH_3, t-C_4H_9, $COCH_3$, Cl, F, CN, and NO_2. This set includes both electron-donor and electron-attractor substituents. The ability of each substituent to donate or to attract electrons may also be quantified by the heat of reaction calculated with Eq. 1.

To verify the reliability of the semi-empirical results, DFT calculations using the B3LYP [24] functional with the 6-31G(d) basis set [25] were employed to optimize the geometry and to calculate properties of four derivatives (R = H, NH_2, NO_2, and OCH_3). Additionally, one of us has been interested in the chemistry of the ferrocenyl group [8] due to its capacity to enhance the biological activity when attached to a number of biologically active molecules [26, 27]. Therefore, using the DFT approach we also calculated the effect of the ferrocenyl group on the geometric and electronic properties of the naphthoquinones. Finally, these properties were correlated to the Hammet σ_p constant of each derivative.

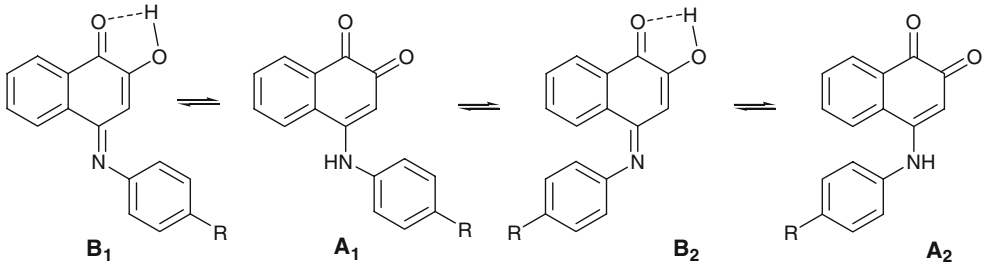


Fig. 2 Possible tautomers for 4-[(R-phenyl)amine]-1,2-naphthoquinones

Results and discussion

The main goal of our investigation was to determine the relative stability of each tautomer. Calculations with the semi-empirical AM1 and PM3 methods give divergent ordering of relative stabilities. While AM1 predicts the hydroxylquinoneimine form **B1** to be the most stable by 0.4 to 1.0 kcal mol^{-1}, PM3 predicts the aminequinone form **A1** as the most stable by 0.9 to 3.3 kcal mol^{-1}. The alternative **A2** and **B2** conformers (see Fig. 2) are always less stable than the corresponding **A1** and **B1** conformers, probably due to steric interactions (see supplementary material for Tables with absolute and relative energies). The relative stability order is the same for all substituents. Indeed the different substituents have only negligible influence on the relative stability of the two tautomers (although for other properties, as will be discussed below, the substituent effects are more pronounced). To illustrate the effect of the substituents on the relative stabilities we plotted the AM1 heat of formation for the two tautomers (**A1** and **B1**). As shown in Fig. 3, the two values correlate perfectly (r^2=0.99), indicating that the substituents have essentially the same effect on the energy of the two forms.

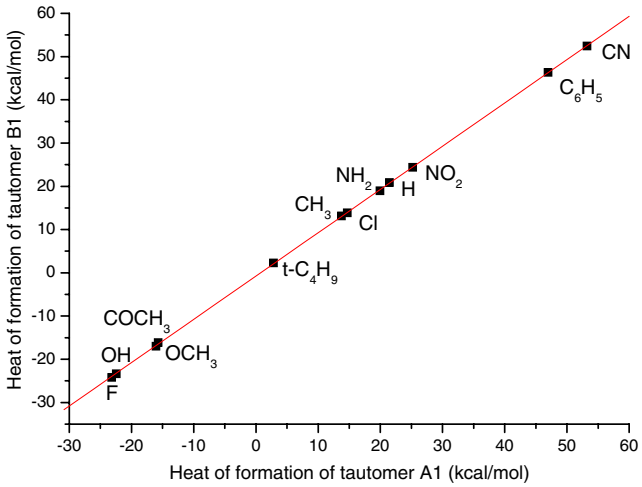


Fig. 3 Effect of substituents on the (AM1) heat of formation of the two tautomers **A1** and **B1** (r^2=0.99)

To verify which of the AM1 or PM3 relative stability order is most reasonable we compared the relative stability for four members of the set (R = H, NH_2, OCH_3 NO_2) against B3LYP/6-31G(d) results. For these derivatives B3LYP/6-31G(d) predicts the hydroxylquinoneimine form **B1** more stable by 5.4 to 6.6 kcal mol^{-1}. Although the energy difference is significantly larger than that calculated with any of the semi-empirical procedures, it is closer to the AM1 than to the PM3 results. For the ferrocenyl derivative, which was calculated only at the DFT level, the hydroxylquinoneimine form **B1** is more stable by 5.7 kcal mol^{-1}. We assumed therefore that the AM1 results are more satisfactory than the corresponding PM3 ones.

To determine the effect of a polar solvent on the relative stabilities of the two tautomers, the geometries of all species were fully reoptimized using the COSMO methodology available in MOPAC [18], using water as the solvent (dielectric constant of 78.5). Results show that the solvent is able to fully reverse the relative stability order. The polar solvent preferentially stabilizes the aminequinone form **A1**, so that it becomes more stable than the hydroxylquinoneimine form **B1**, by both methods. Calculations of solvent effects at the B3LYP level also preferentially stabilize the aminequinone form **A1**. However, as the gas-phase energy difference between the two tautomers with B3LYP is considerably larger than with the AM1 or PM3 methods, the aminequinone form becomes the most stable in the polar solvent, although by a smaller value (1.6-2.3 kcal mol^{-1}). The preferential stabilization of the aminequinone tautomer in the polar solvent is due to a higher dipole moment for this form. Dipole moments for the aminequinone form **A1** are at least two times larger than the corresponding values for the hydroxylquinoneimine form **B1** in all cases. As is well known, species with higher dipole moment are preferentially stabilized in polar solvents. These results are in accord with the experimental results of Harmon *et al.* [10] and Yano *et al.* [12].

The effect of the substituent on the geometrical, electronic and physical properties of the tautomers has also been assessed. Although the nature of the substituent R has no influence on the

relative stabilities of the tautomers, as discussed above, geometrical and electronic properties undergo subtle but systematic changes as a function of the substituent.

The first property to be analyzed is the heat of reaction for the isodesmic equation shown in Eq. 1. With this equation the effect of each substituent on the relative stability of the anion formed upon deprotonation of the enamine tautomer can be quantified. Substituents that stabilize the negative charge on the anion, thereby behaving as electron acceptors, should lead to an exothermic reaction. On the contrary, electron donor substituents should destabilize the negative charge and lead to an endothermic reaction.

The calculated order of increasing reaction enthalpy is the following: NO_2 < CN < $COCH_3$ < Cl < F < Ph < Fc < OH < H < CH_3 < OCH_3 < t-C_4H_9 < NH_2 (Fc derivative was calculated with B3LYP/6-31G(d) and all the other derivatives were calculated with AM1). This is essentially the expected order on the basis of the known donor/acceptor properties of these substituents, except for the OH group which appears as a stronger acceptor than hydrogen. To confirm that the above heat of reaction is a good parameter to quantify the donor/acceptor ability of the substituents, the calculated values were correlated with the σ_p Hammett constant. As shown in Fig. 4, there is indeed a good correlation between these two parameters (r^2=0.87) except for the NO_2 group. For this group, the calculated stabilization of the negative charge is larger than would be predicted on the basis of the σ_p Hammett constant. *p*-Nitro derivatives were also found as outliers in correlation of the σ_p Hammett constant with p*K*a and natural charges [28].

A relevant geometrical aspect to be considered is the coplanarity of the two aromatic moieties. Upon deprotonation of the hydroxylquinoneimine form **B1**, the negative charge which builds up in the naphthoquinone ring may be more or less stabilized or destabilized by the substituent, depending on the degree of charge delocalization through the enamine nitrogen. Highest degree of delocalization can be expected in the case where the two rings are most closely aligned, although steric interactions between *ortho* hydrogens would hinder full coplanarity. Therefore these two forces, electron delocalization and steric interactions operate in opposite direction.

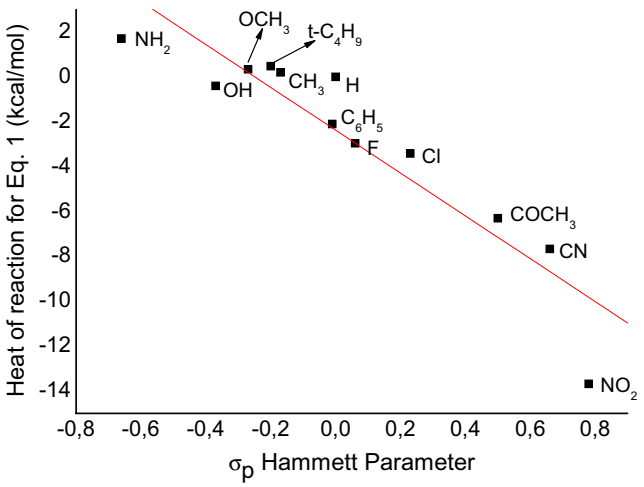


Fig. 4 Heat of reaction for Eq. 1 versus σ_p Hammett constant values of the substituents (r^2=0.87)

As no dihedral angle definition along bonds exists to describe the planarity of the two rings, the dihedral angle formed by the C(3)-C(4) and C(11)-C(12) bonds was used for this purpose. For the neutral **A1** tautomer this dihedral angle varies from 44° to 48°. Electron donor substituents lead to the largest angles and electron acceptor substituents to the smallest ones. For the **B1** tautomer, however, electron donor substituents produce the smallest dihedral angles that vary from 41° to 51°. For the anionic deprotonated species this angle varies from 35° to 44°, therefore more coplanar than in the neutral cases. For the anionic species no regular behavior was observed as a function of the substituent.

It is also important to analyze the charge distribution, mainly for the anionic species. In the case of the neutral species the substituents have only subtle influence on charge densities, although a clear tendency emerges: as expected, charge density on the carbonyl oxygen atoms, O(1) and O(2), increases with electron donor substituents and decreases with electron attractor ones. This behavior is observed for both tautomers. For other relevant atoms, for example, C(3) and N(1), changes in charge densities are still smaller, but again some trends are clear. For example, electron donor substituents increase charges on C(3) for the **A1** tautomer whereas for the **B1** tautomer charge on C(3) decreases. The opposite is observed for electron acceptor substituents. Electron attractor substituents increase charges on N(1) while electron donor substituents decrease charge on N(1) in both tautomers.

For the anionic species essentially the same behavior is observed, although charge reallocation is more evident. Thus charge densities on O(1) and on O(2) increase with electron donor substituents and decrease with electron attractor substituents. Similarly, electron donor substituents increase charge density on C(3) and decrease charge density on N(1) while electron acceptor substituents decrease charge density on C(3) and increase charge density on N(1).

One of the main reaction pathways for these systems is, for example, electrophilic addition to a base [29]. Therefore it is important to know how the substituents modify the relative energy of the frontier orbitals. Most commonly electron donating substituents are able to increase the energy of both the HOMO and the LUMO. On the contrary, electron withdrawing substituents reduce the energy of the HOMO and LUMO orbitals, therefore increasing electrophilicity. This is exactly the behavior found in the present

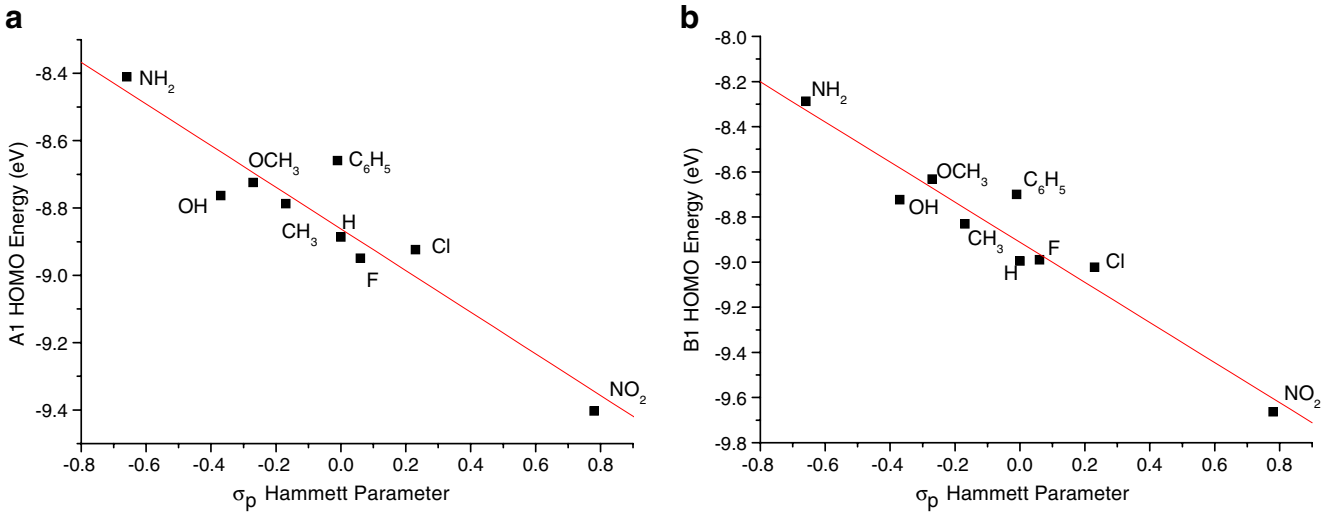


Fig. 5 HOMO energy versus the σ_p Hammett constant for the a) **A1** (r^2=0.87) and b) **B1** (r^2=0.92) tautomers

situation. However, changes in energy are more significant for the HOMO than for the LUMO. Additionally, we found a nice correlation between the energy of the HOMO and the σ_p Hammett constant for the substituents (Fig. 5). For the anionic species the LUMO is centered mainly on the quinone ring while the HOMO is found mainly on carbon atom C(3) (Fig. 6).

Charge densities and the HOMO amplitude for the anionic form, as pictured above, would suggest, for example, that addition of an electrophilic group should happen to the carbon atom C(3). However, reaction of 4-(phenylamino)naphthalene-1,2-dione with dimethylsulfate in the presence of sodium hydroxide results in the formation of 2-methoxy-4-(phenylimino)naphthalen-1(4H)-one [12], instead of the alternative 3-methyl-4-(phenylamino)naphthalene-1,2-dione. Qualitative analysis indicates that addition to the oxygen atom seems indeed more reasonable. We therefore calculated the transition structures for the two possibilities, addition of the Me^+ group from Me_2SO_4 to the carbon atom C(3) and to the oxygen atom O(2). Relative energies calculated at the B3LYP/6-31+G(d) level indicate that the transition state for addition at the oxygen atom is 7.1 kcal mol^{-1} more stable than the corresponding transition state for addition at the carbon, in full agreement with the experimental observation.

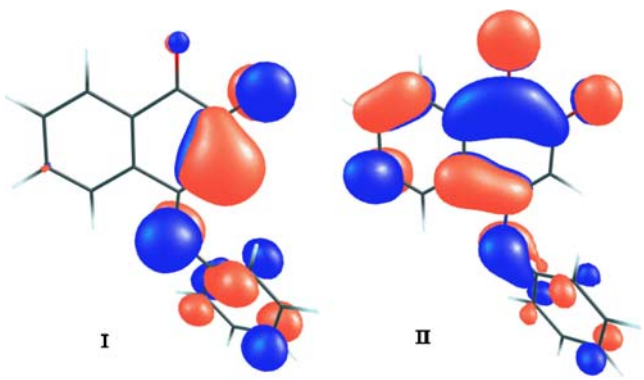


Fig. 6 HOMO (**I**) and LUMO (**II**) of the anionic form

Conclusions

In the present work semi-empirical and DFT calculations were employed to study the tautomeric equilibrium between the hydroxylquinoneimine and aminequinone forms of 4-(4-R-phenylamino)naphthalene-1,2-diones. In the gas-phase the hydroxylquinoneimine form is the most stable (by 0.5-1.0 kcal mol^{-1} with the AM1 method and 5.4–6.6 kcal mol^{-1} with B3LYP/6-31G(d)). Polar solvent preferentially stabilizes the aminequinone form, which then becomes more stable. Electron donor and electron acceptor substituents have only marginal influence on the relative stabilities of the two tautomers. However, they are able to systematically modify some geometric and electronic parameters. In addition, electron acceptor substituents stabilize the anion produced by deprotonation while electron donor substituents destabilize that anion. HOMO and LUMO energies are similarly modified. These results are in accordance with the most recent experimental data reported in the literature [12].

Acknowledgments The authors thank the Brazilian agencies 'Conselho Nacional de Desenvolvimento Científico e Tecnológico' (CNPq), 'Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro' (FAPERJ) and Pronex-FAPERJ for financial support. J. W D. Carneiro and M. D. Vargas are recipients of CNPq research fellowships. T. P. Fragoso was benefited with a PIBIC-CNPq fellowship which made possible her participation in the work.

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