Egyptian Journal of Chemistry

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Theoretical Construction of Thermodynamic Relations for a Solvent-controlled Phase Transition to Improve the Bioavailability of Drugs: A Case Study of Indomethacin

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Abstract

The thermodynamic aspects of the polymorphic phase transition from α-indomethacin to γ-indomethacin are the fundamental key to find the most bioavailable phase of indomethacin. In the present work, varying the solvent permittivity changes the polymorphic transitions. Hence, the thermodynamic properties such as enthalpy, Gibbs free energy, and entropy of both indomethacin polymorphs are determined in terms of the solvent permittivity at T0=298.15 K and P0=1 atm., which are crucially related to the stability, spontaneity, and reversibility of the polymorphic transformation.

Keywords: Bioavailability, Indomethacin, DFT methods, Polymorphic phase transition, Thermodynamic functions.

1. Introduction

A drug can crystallize into different polymorphs, which are characterized by their unique spatial arrangement with distinct physicochemical properties, in particular, different solubilities and bioavailabilities [1]. Furthermore, one crystalline arrangement can be transformed into another by the so-called polymorphic phase transition [2]. Understanding on how to induce or suppress polymorphic phase transitions plays a valuable role in the pharmaceutical industry concerning to the bioavailability and patentability of the medicine development process [1,3–5]. Indomethacin ($C_{19}H_{16}ClNO_4$), whose molecular structure is shown in Figure 1, is a relatively common drug that is mostly prescribed for its analgesic, anti-inflammatory, and antipyretic characteristics; however, it comes in at least seven distinct crystalline forms. The α- and γ-indomethacin polymorphs, shown in Figures 2 and 3, are the most stable and allow crystallographic description, while the rest of the indomethacin polymorphs are metastable [6,7].

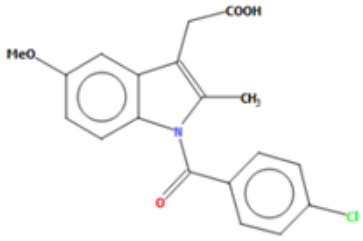

Fig. 1: Indomethacin molecule

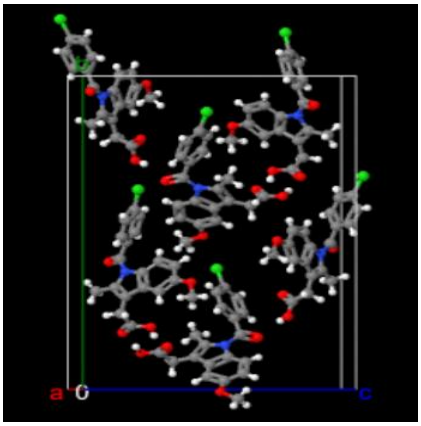

Fig. 2: α-indomethacin

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Receive Date: 07 November 2021, **Revise Date:** 27 November 2021, **Accept Date:** 07 December 2021, **First Publish Date:** 07 December 2021
DOI: 10.21608/EJCHEM.2021.104860.4841

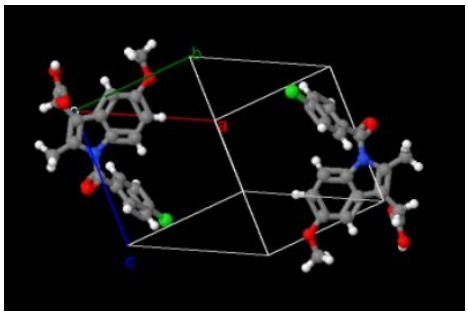

Fig. 3: γ-indomethacin

Here, the thermodynamic properties of indomethacin are investigated in order to find a phase transition driven by the permittivity of the medium [2]. The permittivity εm in a binary system composed of two solvents, 1 and 2, the expression of the permittivity are found as ε1 and ε2, respectively, as expressed in equation (1) [8]:

$$\ln \varepsilon m = a1 \ln \varepsilon 1 + a2 \ln \varepsilon 2 + a1a2 [K0+K1(a1-a2)+K2(a1-a2)2], \quad (1)$$

in which a1 and a2 are the volumetric fractions of solvents 1 and 2. While, Ki represent experimental constants, with i=0,1 and 2 [8,9]. A binary mixture's permittivity value changes continuously as the binary mixture changes. Because of all this, as well as the fact that permittivity is a thermodynamic parameter that is independent of system size [10,11], a polymorphic permittivity-dependent transition can be induced by gradually changing the proportion of two solvents with very different values of permittivity, such as: glycerine and water [2,8].

The importance of this study is in the fact that crystals belonging to the same spatial group have similar physical properties [12,13]. According to the Cambridge Crystallographic Data Centre (CCDC), the α- and γ-indomethacin polymorphs belong to the space groups P21 and P-1 respectively, which in turn are among the five most common space groups of organic compounds. The five most popular space groups are as follows: P21/c (27.8%), P-1 (23.5%), P21 (13.8%), P1 (8.5%) and P212121 (7.8%). Therefore, there is a great importance for investigate the molecular and electronic aspects of this phase transition.

Because indomethacin is a common anaesthetic, antipyretic, and nonsteroidal anti-inflammatory that has been extensively studied, we investigated the α- and γ- indomethacin polymorphic phase transition in this study. Then, density function theory (DFT) is used to simulate the polymorphic phase transition between α- and γ-indomethacin, which is induced by a range of distinct permittivity values for solvents at a fixed temperature of 298.15 K [6,7]. This range can be precisely controlled by considering the different proportions of solvents in a binary mixture as expressed in equation (1) [8,14]. Hence, changes in the drug's composition delivery vehicle changes its permittivity, as well as the permittivity and pH values can be related [15,16]. Consequently, several polymorphs of indomethacin can be experimentally synthesised by varying the pH of the solvent [6], allowing for proper polymorphic transition analysis.

Phase transitions go through various space groups by changing pressure or temperature [43-47]. For example, a theoretical study was carried out by first principle calculations using the plane wave pseudopotential method to investigate the crystal structures, relative stabilities and elastic properties of seven known polymorphs of titanium dioxide (TiO_2) [46]. In which, a phase transition was carried out on a curve plotted in Energy versus Volume, where each point refers to a space group. In other study, the infrared and Raman spectra of the quartz, rutile and amorphous forms of GeO_2 were evaluated under pressure and temperature in order to study how crystalline - or amorphous - transformations of this compound in the solid state [47]. In a similar way, those transitions can be evaluated by changing the solvent permittivity [48-50]. Despite a large experimental corpus, there is a dearth understanding of the thermodynamics relations for a solvent-controlled phase transition to increase medication bioavailability.

Thus, the goal of this work is to propose a solvent-controlled phase transition strategy to increase - indomethacin bioavailability using DFT simulations linked to the stability, spontaneity, reversibility, and bioavailability of the - and -polymorphs and their transformation.

2. Materials and Methods

The Gaussian09 program was used to determine standard thermodynamic quantities at 1 atm, such as the enthalpy (H), Gibbs free energy (G) and entropy (S) for the α- and γ-indomethacin phases, which are functions of permittivity of different solvents at a fixed temperature of 298.15 K. The computation was performed using DFT with the B3LYP functional at the 6-321G basis set via the polarizable continuum model (PCM) [19–22], using the integral equation formalism variant (IEFPCM) in the default self-consistent reaction field (SCRF) computation. To keep the number of indomethacin molecules constant, the

initial creation of the α -structure within the solvent requires the nucleation of six indomethacin molecules per unit cell, whereas the nucleation of the γ -structure inside the solvent requires three-unit cells [23]. Remember there are two molecules of indomethacin per unit cell in the γ- structure. Both structures are described in the table 1 [24,25].

The enthalpy, Gibbs free energy and solvation heat can be generalized as follows [17,18]:

$$P=Pi+c(\varepsilon-\varepsilon i)-1 \quad (2)$$

where Pi, εi and c are the experimental constants. The behavior of the thermodynamic function P near a phase transition is characterized by the critical exponent -1. Hence, P can be expanded around the value ε=0, and for very large ε, it is given by:

$$P=Pi+c[-(1/\varepsilon i)-(\varepsilon/\varepsilon i2)-(\varepsilon 2/\varepsilon i3)+O(\varepsilon 3)] \quad (3a)$$

$$P=Pi+c[(1/\varepsilon)+(\varepsilon i/\varepsilon 2)+(\varepsilon i2/\varepsilon 3)+O(\varepsilon 4)] \quad (3b)$$

Equations (1) and (3) were derived from ab initio and first-order computations of a thermodynamic function involving an electric field D medium, in which a term due to the electric energy stored in the dielectric medium of the solvent is incorporated into the thermodynamic structure. The Gibbs free energy is shown by the following:

$$G = U - TS + PV = \mu N + D2/8\pi\varepsilon \quad (4)$$

Other thermodynamic functions thus come similarly [11].

Denoting extensive parameters by E_1, E_2, ...,En and intensive parameters by I1, I2, ..., In, a phase transition can be defined by a discontinuity in the derivative of thermodynamic functions (denoted by P) in terms of an intensive parameter Ii [26]. In this way, a n-order phase transition dependent on Ei is characterized by a discontinuity in the transition point at the (n-1)-th derivative of the function P(Ei (Ii),Ii), in which Ei is an extensive thermodynamic parameter that depends on the intensive parameters Ii: pressure [27,28], temperature, voltage [29], laser frequency [30], electric field [29], pressure [31,32], permittivity [11] and so forth. The differential form of the thermodynamic function P(Ei (Ii),Ii) can be expressed as dP = I1 dE1+ I2 dE2+ ...+In dEn[33] . For the present case, the Gibbs free energy is G=μN+D2/(8πε), and its differential is given straightforwardly by dG=μdN+DdD/4πε. Therefore, quantities such as the spontaneity, stability and reversibility of a phase transition can be interpreted by means of G(Ei (Ii), Ii), H(Ei (Ii), Ii) and S(Ei (Ii), Ii), respectively [15,34]. As a particular case, a first-order transition is a discontinuity in the function P(Ei (Ii), Ii) [23]. Therefore, the α to γ structural transitions can be described as a first-order phase transition in the Gibbs free energy as a function of the permittivity, as it will be shown.

3. Results and Discussion

Parameters such as the temperature, solvent permittivity, pressure in the organic crystal and pH of the medium can significantly change the stability, solubility and bioavailability of drugs [15,35]. To improve drug bioavailability knowledge, the solvent permittivity was chosen as the order parameter for thermodynamic analysis. The main standard thermodynamic functions, namely, H(D; ε, P0, T0, N), G(D; ε, P0, T0, N) and S(D; ε, P0, T0, N), were computed for six molecules of indomethacin (N=6) in terms of the solvent permittivity ε at T0=298.15 K and P0=1 atm.

The enthalpy and the Gibbs free energy are plotted in figure 4 for both indomethacin polymorphs, in such a way that the quantities H(D; ε, P0, T0, N), G(D; ε, P0, T0, N) and S(D; ε, P0, T0, N), where S= (H-G)/T, are all expressed in terms of the permittivity ε. As seen in the figure 4, enthalpy and Gibbs free energy can be approximated by sigmoid functions [36,37]. Consequently, the theoretical predictions for some transformation properties, such as spontaneity, stability and reversibility, are provided from Gibbs free energy, enthalpy, and entropy, respectively [15,34].

Table 1: Structure of the unit cell of indomethacin polymorphs (size of its edges (in Å) and angles).

1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid ($C_{14}H_9ClO_3$)							
Polymorph	Space Group	unit cell edge			unit cell angle		
		a	b	c	*α*	*β*	*γ*
α-indomethacin	$P2_1$ (4)	5.4616(16)	25.310(9)	18.152(7)	90°	94.38(3)°	90°
γ-indomethacin	P1 (2)	9.236(5)	9.620(5)	10.887(5)	69.897(5)°	87.328(5)°	69.501(5)°

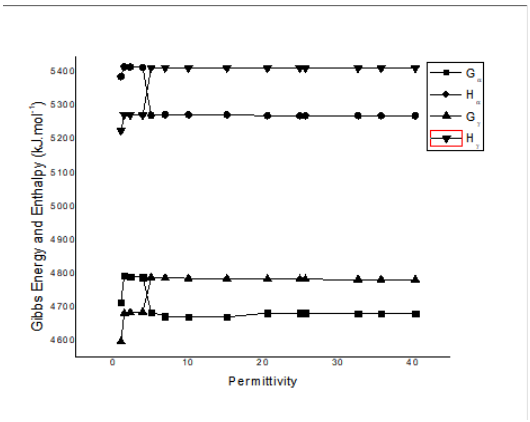

Fig. 4: Enthalpy and Gibbs free energy.

We found a plot that is approximated by a sigmoid function, which has been expanded with its head term similar to a step function. The plot of figure 4 can be smoothly adjusted by a sigmoid function:

$$\Sigma(x) = \Sigma 0 + a/(1+\exp(-\lambda(\varepsilon-\varepsilon 0))) = (a/2)\tanh(\lambda(\varepsilon-\varepsilon 0)) + \Sigma 0 \quad (5)$$

which can be split in a function Θ(x) that is similar to a step function (with linear pieces), exponential terms Ξ(x) and terms of higher orders less than 2% error. Summarily, Σ(x)≈ Θ(x)+2aΞ(x)/3, in which

$$\Theta(\varepsilon)=a\left[\frac{\lambda(\epsilon-\epsilon_0)}{5}+\frac{1}{2}\right]+\begin{cases}\sum, if -\infty<\epsilon<\epsilon_0-\frac{1}{\lambda}\\ \sum, if \epsilon_0-\frac{1}{\lambda}<x<\epsilon_0+\frac{1}{\lambda}\\ a+\sum, if \epsilon_0+\frac{1}{\lambda}<\epsilon<\infty\end{cases} \quad (6)$$

$$\Xi(x)=\begin{cases}exp\left(\lambda(\epsilon-\epsilon_0)\right), if -\infty<\epsilon<\epsilon_0-\frac{1}{\lambda}\\ 0, if \epsilon_0-\frac{1}{\lambda}<x<\epsilon_0+\frac{1}{\lambda}\\ -exp\left(-\lambda(\epsilon-\epsilon_0)\right), if \epsilon_0+\frac{1}{\lambda}<\epsilon<\infty\end{cases}$$

The first point in the plot of Figure. 4 can be considered a spurious point, because is in vacuum condition. Besides this, for a thermodynamics function P(ε),

$$\Sigma 0=(P2+P1)/2 \text{ and } a= P2-P1 \quad (7)$$

in which P1 ={P(ε); ε <<-ε0} and P1 ={P(ε); ε >> ε0}. Based in the Figure. 4, Gα and Gγ have their parameters computed: P1=4790.98, P2=4678.86, ε0= 4.46, λ=1.78 and P1=4682.56, P2=4783.54, ε0= 4.46, λ=1.78, respectively. The function Σ(x) is very important for topological studies also.

The sign of enthalpy variation (ΔH=Hγ-Hα) between α- and γ-indomethacin characterizes an endothermic (positive) or exothermic (negative) polymorphic transformation. As an exceptional case, there is no heat exchange if Hα=Hγ.

The polar solvents employed in the energy computation SCRF=PCM are depicted, and the respective permittivity value of each solvent is shown in parentheses: 1-bromooctane (5.02), aniline (6.89), pentanal (10.0), 1-pentanol (15.13), 1-propanol (20.52), ethanol (24.85), 1-benzonitrile (25.59), methanol (32.61), acetonitrile (35.69), 1,2-ethanediol (40.25), and water (78.36).

The spontaneity of the phase transformation can be determined as a function of the Gibbs free energy variation, as described by figureure 4 [38]. A polymorphic transformation is spontaneous if ΔG=Gγ-Gα < 0 [9], which also gives the direction of transition from α → γ, i.e., establishing that the transformation from α- to γ-indomethacin is spontaneous for values below permittivity 5.024, the direction of transition is from α- to γ-indomethacin. The transformation reaches equilibrium if ΔG is close to zero, and according to figureure 4, this equilibrium state is reached if the relative permittivity is close to 5.024 [38]. In addition, for values of permittivity greater than 5.024, the transformation is reversed, meaning that the transition for the more bioavailable polymorph is favorable. These results are corroborated by the references 10 and 39.

3.1. Influence of the Entropy

The last thermodynamic function analyzed is the entropy, which provides information about the reversibility of the polymorphic transformation and measures the degree of disorder of the corresponding compound, whose values for both indomethacin forms are computed based on the enthalpy H(D;ε,P0,T0,N) and Gibbs free energy G(D;ε,P0,T0,N) by means of the standard expression S(D;ε,P0,T0,N) = (H−G)/T, as outlined in figureure 5. From the second thermodynamic law, the transformation is reversible only if ΔS=0; otherwise, the process is irreversible. Moreover, the entropy of the whole system always increases [33,39]. Hence, the decrease in the entropy of indomethacin results in an increase in the entropy of the solvent counterpart. The change in the sign of ΔS emerges by means of a discontinuity and occurs at ε ≈ 5,024.

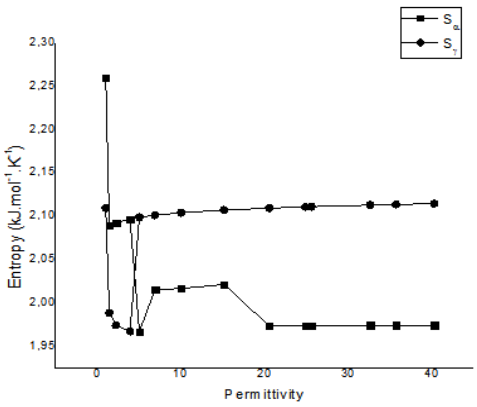

Fig. 5: Entropy versus relative permittivity at the B3LYP/6-321G/PCM level.

This discontinuity in the entropy characterizes a phase transition driven by the permittivity of the solvent [8]. As seen from equation (8), there is also a discontinuity in the first derivative of the entropy.

$$\frac{\Delta S}{\Delta \varepsilon} \approx \frac{\partial S}{\partial \varepsilon} = -\left[\frac{\partial}{\partial \varepsilon}\left(\frac{\partial G}{\partial T}\right)_{\varepsilon}\right]_{T} = -\left[\frac{\partial}{\partial T}\left(\frac{\partial G}{\partial \varepsilon}\right)_{T}\right]_{\varepsilon} \quad (8)$$

Permittivity is the order parameter that dominates the polymorphic transformations, although pressure should be considered as well. In this case, crystallization occurs at high pressure, and new polymorphs may arise with a higher degree of symmetry and hence less disorder [40]. From another point of view, the same process occurs if the temperature is decreased [41]. Note that γ-indomethacin is in the space group P-1, thus having a higher degree of symmetry than the α-structure and the smallest disorder as result [40]. Therefore, γ-indomethacin is produced from α-indomethacin if the pressure increases through dry milling [9,10]. Note that the reversibility aspect of the transformation comes from the difference in the entropy ΔS=Sγ-Sα. The α-indomethacin entropy is greater than γ -indomethacin entropy for permittivity below 5.024, and his entropy is lower if its permittivity is greater than 5.024. This says α -indomethacin has a more crystallized form for permittivity greater than 5.024.

3.2. Effect of the solvent permittivity on the solvation Gibbs free energy

The cycle of the solvation process can be evaluated from figure 6.

As seen from figure 6, the spontaneity of a transformation depends on the difference between the Gibbs free energies of the polymorphs. The solvation Gibbs free energies ΔG^{γ}_{Solv} and ΔG^{α}_{Solv} are directly related to the difference between the Gibbs free energy of transformation into different solvents and in the vacuum, as established by the following equation [38]:

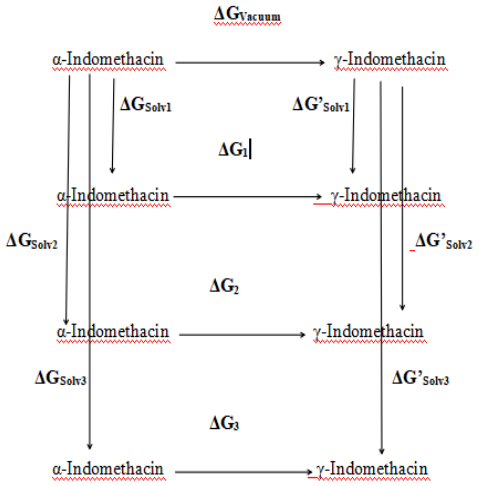

Fig. 6: Thermodynamic cycle of solvation Gibbs free energies.

$$\Delta G = \Delta G_{vac} + \left(\Delta G^{\gamma}_{Solv} - \Delta G^{\alpha}_{Solv}\right) \quad (9)$$

Next, indomethacin treated in different solvents shows diverse values of ΔG because of the medium permittivity, which provides a particular equilibrium constant K for each solvent, as schematized in the following equation [38]:

$$\ln K = -\frac{\Delta G(\varepsilon)}{RT} \Rightarrow K = \frac{[\gamma]}{[\alpha]} = \exp\left(-\frac{\Delta G(\varepsilon)}{RT}\right) \quad (10)$$

where [α] and [γ] denote the molarity of α- and γ-indomethacin, respectively. Then, the sign of ΔG determines which polymorph is the most abundant and its proportion. The molarity of γ-indomethacin is greater than that of α-indomethacin if $\Delta G < 0$, which happens for permittivity values below 5.024. For other side, α-indomethacin can be more abundant than γ-indomethacin in solvents with permittivity values greater than 5.024. Hence, for those permittivity values, α-indomethacin is more bioavailable than γ-indomethacin, i.e., the molar ratio $[\alpha]/[\gamma]$ is higher. The solvation energies can also be assigned as a function of permittivity.

4. Conclusions

The present study focuses on the thermodynamic behaviour of polymorphic phase transitions between the α and γ phases of indomethacin induced by different polar solvents and in terms of their permittivity. The conclusion of this work is that in solvents with permittivity between 1.0 and 5.0, γ-

indomethacin is the more stable form, and in solvents with values of permittivity above 5.0 α-indomethacin is more stable.

Our theoretical findings are in good agreement with experiments, because in the air, while permittivity is approximately 1.0, the stable form of indomethacin is gamma and alpha indomethacin is precipice in a solution of ethanol and water, which permittivity is between 24.85 and 78.36 [42].

As a result, the enthalpy, Gibbs free energy, entropy, and solvation Gibbs free energy were calculated in a nucleation process at 298.15 K for varied permittivity values of the solvents. The primary findings, which give insights into the processes of medication bioavailability, are summarised as follows:

- The enthalpy shows exothermic transformations from α- to γ-indomethacin for value of the permittivity less than 5.024, and from γ- to α-indomethacin for permittivity greater than 5.024.
- The Gibbs free energy analysis guarantees the spontaneous transformation from α- to γ-indomethacin and, consequently, a higher concentration of γ-indomethacin for permittivity values less than 5.024. Otherwise, for values of permittivity greater than 5.024, the transformation occurs from γ- to α-indomethacin;

Due to the discontinuity in S and $(\partial S/\partial \varepsilon)|\varepsilon- \neq (\partial S/\partial \varepsilon)|\varepsilon+$, wherein the subscript signs - and + indicate the left and right limits of ε, respectively, there is a first-order and a second-order phase transition at $\varepsilon = 5.024$. For $\varepsilon < 5.024$, the γ-indomethacin phase is more ordered; otherwise, α-indomethacin is more ordered for $\varepsilon > 5.024$.

To the best of our knowledge, this is the first application of theoretical calculations aimed at developing a novel mathematical relationship taking solvent permittivity into account in order to maximise the bioavailability of drug polymorphs. Currently, one of the most serious issues in modern pharmacology is medication solubility and bioavailability. It is critical to remember that inducing or suppressing polymorphic phase transitions plays a vital function in the pharmaceutical business in terms of bioavailability and patentability of the drug development process. Medication polymorphism must be regulated to avoid inefficient therapy and/or incorrect dose. We believe that such research might be useful in investigating the logical design of medication bioavailability.

5. Conflicts of interest

The authors have no conflicts of interest regarding publication of this paper **Formatting of funding sources**

6. Acknowledgments

K. P. S. de Brito thanks CNPq for financial support through the project no. 150882/2017-3.T. C. Ramalho thanks CAPES, CNPq and FAPEMIG. T.R. Cardoso acknowledges support from FAPESP through project no. 2016/03921-8. E.F.F. da Cunha thanks CAPES, CNPq and FAPEMIG. The authors are particularly grateful to D.H.S. Leal, J.M. Silla and R. Bufalo for their valuable discussion and advice.

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