Morphology Prediction and Dissolution Behavior of α-Succinic Acid in Ethanol Solution Using Molecular Dynamic Simulation

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***Abstract*— Succinic acid is a potential co-former to produce co-crystal, thus an understanding of the dissolution behavior of succinic acid crystal is crucial for designing the co-crystal. In this works, α-succinic acid was chosen as a model compound for this study regardless its attractive crystal chemistry and its diverse surface properties. The aims of this study are to analyze the morphology of succinic acid crystal (form A) and to simulate the dissolution behavior of succinic acid crystal (form A) in the ethanol solution using molecular dynamic simulation. Molecular dynamics simulations have been performed by using Material Studio 4.4 by ACCELERYS. The most suitable morphology of the crystal was found in the combination of ESP charges with CVFF potential function and the morphology shape is elongated hexagonal needle-like shape which gives good agreement with the experimental crystal shape. In this research work, the MD simulation of dissolution of α-succinic acid has been successfully carried out. The less morphological important facet and high attachment energy which located at the tip of the crystal tends to dissolve faster compare to the most morphological important crystalline facet.**

Keywords*— *α-succinic acid, dissolution, molecular dynamic simulation, morphology

I. INTRODUCTION

The pharmaceutical industry has discovered, develops and markets drug as they find drug medicine is an important part of the medical field. For a continual advancement in pharmacology, a research and development for a better drug performance is being developed and continuously perform. Crystallization is important in the pharmaceutical industry as it offer the opportunity to purify, improve and tailor physicochemical properties of pharmaceutical [2].Crystallization is the main choice for separation and purification process in numerous areas such as the fine chemical, food, agrochemical and pharmaceutical industries. In pharmaceutical co-crystal, usually succinic acid crystal (pure crystal) act as co-former to produce a co-crystal in which will help or increase the dissolution rate of APIs. The development of co-crystal can be one possibility to improve bioavailability without altering the API per se [3].

In recent years, modeling strategies supported by simulation became a great tool in crystallization processes. Recent growing advances in the molecular modeling approach offers benefits to simulate the intervention on drug delivery system is better than pricey and time-wasting direct experimentation. Molecular dynamic simulation allow for microscopic probes of the physical concerned in each standard and space-based measure of nucleation and crystal growth in mixture or colloidal system [7].

In pharmaceutical industry, the desirable crystal shape is crystalline shape. For filtering and downstream processing consideration, morphology prediction and screening is very essential. Bravais, Friedal, Donny and Hanker model (BGDH) is one of the models that have been use in earlier crystallization revolution to identify the morphologically dominant faces (hkl). In the study of Roberts [8], it has been illustrated in the prediction of morphology of β-succinic acid using BHDH approach. The result shows that BHDH approach does not adequately deal with H-bonding direction interaction since this model ignore the interaction present within the crystal. Selection of program used is then being study, and from the previous study on para-amino benzoic acid with two identical H-bonded cycles also applied on MS software [4]. Overall result from the research concludes that molecular dynamic simulation gives a better understanding for the dissolution of organic crystal process. Thus for this work, the morphology prediction of α-succinic acid is applied on MS due to the present of strong H-bonding interaction in succinic acid.

In Hartman and Perdok series of research, they have developed an approach on the intermolecular and intramolecular interaction between the molecules in the crystal [11]. They manage to introduce the slice energy (E_{sl}) and attachment energy (E_{att}). The total of both energies deliver the total lattice energy (E_{latt})

$$E_{latt} = E_{sl} + E_{att} \qquad \text{Eq (1)}$$

For lattice energy calculation, the growth rate of α-succinic acid is very slow [6], hence the equation of lattice energy of various organic acid can be determined by the summation of intermolecular interaction method.

$$E_{latt} = -\Delta H_{sub} - 2RT \qquad \text{Eq (2)}$$

Where Elatt is the lattice energy, ΔHsub is the enthalpy of sublimation, R is the gas constant, and T is the temperature.

Succinic acid is a dicarboxylic acid which is organic compound that consist of two carboxyl functional group (-COOH) with the with chemical formula $(CH_2)_2(CO_2H)_2$. Succinic acid crystals have found in two different polymorph with different packing arrangement and hydrogen bonding patterns which are α and β succinic acid. α-Succinic acid has a triclinic structure which found to be stable above the temperature of 137ºC and have needle-like shape as it grown from the gas phase [6] . The melting point and heat of fusion of this crystal are 190.78 ºC and 36.44 kJ/mol respectively [9]. This paper will study the morphology prediction

and dissolution behavior of α-succinic acid in ethanol solution and hope this work can provide an understanding and some support material for further studies.

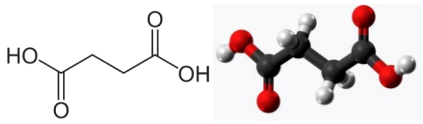


Figure 1: The structural formulas succinic acids

II. METHODOLOGY

A. Detail of Crystal Structures

The model of crystal structures of α-succinic acid were retrieved from the Cambridge Structural Data (CSD) (ref code: SUCACBO7). The asymmetric unit of the α-succinic acid comprises two molecules and the unit cell contains ten molecules. The unit cell dimensions are a = 6.867, b = 7 .198, c = 5.272, α = 109.1° β = 97.18° γ = 101.84° with the space group $P2_1/a$, Z = 4. The arrangements of molecule in one unit cell are present in Figure 2 with the hydrogen bond patterns.

B. Computational Details

The prediction of morphology and dissolution of α-succinic acid crystal was carried out by using Material Studio 4.4 from ACCERLYS. This computational program was used to determine atomic charges, lattice energy, morphology and the dissolution behavior.

C. Atomic Charges

Atomic charges were determined by using MAPOC and an initio DMol3 calculation by using Material Studio 4.4. There are three charges that can be obtained from DMol3 calculation which are Mulliken, Hirsfield and Electrostatic Potential Fitting (ESP), whilst the MOPAC calculations are Austin Model 1 (AM1), Parameter Model 3 (PM3) and Modified Neglect of Differential Overlap (MNDO). The first action was taken to obtain the structure file of succinic acid crystal is Crystallographic Information file (CIF file) of the crystal structure was access from Cambridge Structure Database (CSD) 2014. The setup for DMol3 calculation used for this study is geometry optimization as a task with medium quality. Functional are the combination of GGA and BLYP gradient corrected functional correlation. Select use symmetry and set population analysis as the job control while the others were set as default. By assigning DMol3 calculation, the electronic properties of atom can be estimated accurately. For MOPAC calculation, the unit cell of the crystal was built to apply the symmetry and the structure was then exported as a .car file (Cartesian coordinates). Next, the Cartesian coordinates were converted into fractional coordinates and execute using a single self-consistent-field method the surface diffusion of solvent molecules at the interface (keyword 1SCF) assembles by Anuar works.

D. Lattice Energy Determination and Morphology Prediction

In Material Studio software, the potential functions assign were Compass, Compass26, Compass27, Dreiding, Universal, CVFF, PCFF and PCFF30. The potential function of Compass is a high quality force field in which able to predict different solid-state properties for instance unit cell structure and lattice energy. Dreiding force field is based on an ordinary force constants and geometry parameter. This method applies over elementary hybridization consideration instead of individual force constant and geometric parameters which rely on the specific combination of atom involved in the bond, angles, or torsion term [1].While, CVFF is known as universal valence potential function which able to handle a wide range of organic system. In addition, this potential function is ideal for small organic crystals and gas phase structures such as amides and carboxylic acids. The obtained atomic charges earlier were assigned to the crystal molecules. By using the potential function, the crystal lattice then was being subjected to geometry optimization which mean the conformation of the molecules were kept fixed while allowing the packing forces to change. Then energy minimization was assign. The energy reduction process allows the entire structure to move and vary the packing style as well as the structural confirmation. The charges assign for geometry optimization and energy minimization was use current and force field assigned [7].

For the calculation of lattice energy, the same potential function was applied. The non-bonded interaction including electrostatic and the van der Waals contributions was calculated using Ewald summation method [12]. Then resultant structure will be used for morphology assembling. The selected morphology was verified with the legitimate structure to secure the validity of the modelling approaches adopted and will used for the molecular dynamic simulation to archive this work objective [6].

E. Dynamic Simulation

The dynamic simulation was performed completely using Materia Studio 4.4 software. First, ethanol structure is import from the document structure into the software. The asymmetric ethanol unit is then being optimized by geometric optimization calculation by using CVFF force field and use current charges with coarse quality. The three-dimensional periodic solvent box with 5000 random distributed ethanol molecules was constructed by the Amorphous Cell tool at 298 K with no of configuration of 1 compass force field which has being confirmed as the most accurate prediction of structure. The obtained three-dimensional periodic ethanol solvent is paste on the new 3D atomistic document. The molecule at the center of the solvent box was removed to fit the crystal lattice. Before paste the crystal, the lattice of the solvent box was set as an original style in order to make sure the crystal is in one unit cell[1].

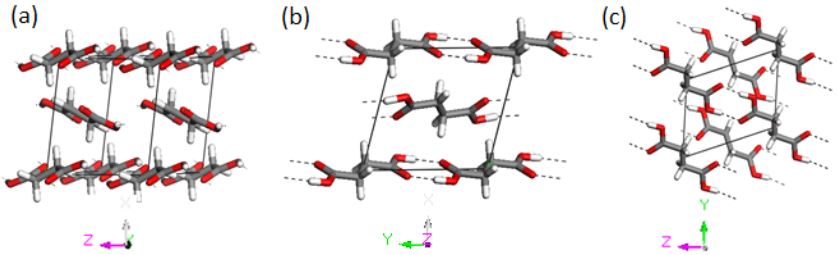


Figure 2: Molecular diagram of α-succinic acid crystal lattice, in the order (a) view of crystal lattice showing the hydrogen bond network from the y-direction; (b) view from the z-direction; and (c) view from the x-direction.

Next, geometry optimizations were assigned with the consistent lattice parameter by using coarse quality with 0.001 kcal/mol energy. Then, the respective MD simulations were run with NPT ensemble were carried out at 298 K, which were controlled by the Berendsen barostat. The period assign is 100 ps with time step 1 fs [5].

III. RESULTS AND DISCUSSION

A. Atomic Charges determination and Lattice Energy Calculation

DMol3 calculation performed with ESP functional was chosen as the most accurate ab initio screening method for α-succinic acid. In calculating the lattice energy, the types of charges used are Mulliken, Hirshfield and Electrostatic potential (ESP). Table 1 shows the calculated lattice energy corresponds to the potential function and force field by using use current charges. The values of lattice energy are seemed to be very dependent on the charges assign and potential function used. Different type of charges and potential functions exhibit different values for morphology lattice energy.

Table 1: Lattice Energies (kcal/mol) of α-succinic acid Computed Using Different Potential Function and force field for use current charge type

Potential Function	*Forcefield*	E_{latt} *(kcal/mol)*
Compass	Muliken	-83.916
	Hirsfield	-38.485
	ESP	-103.136
Compass 26	Muliken	-83.916
	Hirsfield	-38.485
	ESP	-103.136
Dreiding	Muliken	-156.092
	Hirsfield	-57.104
	ESP	-156.092
Universal	Muliken	-52.831
	Hirsfield	-31.542
	ESP	-58.502
CVFF	Muliken	-56.643
	Hirsfield	-37.000
	ESP	-61.220
PCFF	Muliken	-54.537
	Hirsfield	-40.732
	ESP	-58.891

The selection of the predicted morphology obtain cannot be compared with the experimental result since there are no reported ΔH_{sub} for α-succinic acid. α-succinic acid are stable above 137°C only, most of the value reported are below than that which favored to β-succinic acid. Therefore, the validation is be made by comparing the shape of the morphology with the experiment crystal shape declare by Yu Qiushuo in 2012 [6]. The most preferable morphology selected is the lattice energy calculated by CVFF potential function with ESP force field assign and -61.22kcal/mol amount of lattice energy.

B. Morphological Prediction of α-succinic acid

Figure 3(a) and (c) shows the morphology obtained from the molecular modelling by using MS software. The morphology of α-succinic acid obtained was then compared with the experimental morphology form paper Yu Qiushuo in 2012 as shown in Figure 3(b).The morphology from molecular modelling using MS software shows a good agreement when compared to the experimental morphology. Yu Qiushuo declares that α-succinic acid crystal has a needle –like morphology as shown in the Figure 3(b). The morphology obtain from the MS software have a shape more too elongated hexagonal needle-like shape. This is very significant to notice since the predicted morphology was packed in vacuum condition, while the experimental morphology was grown in water.

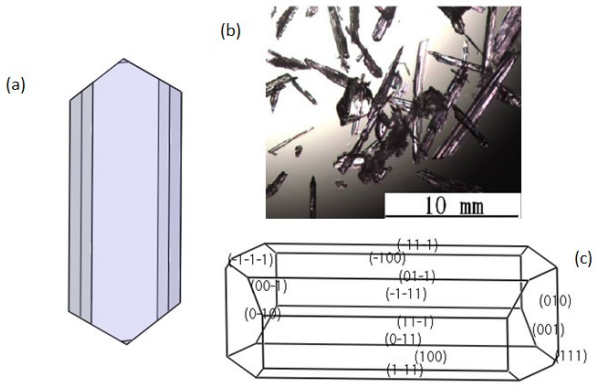


Figure 3: (a) Simulated crystal morphology obtained from Material Studio.(b) α-succinic acid crystal grown in water and (c) Simulated crystal morphology obtained from Material Studio with habit facet.

Table 2: Face Multiplicity and d-Spacing from MS software analysis Showing the Respective Attachment and Slice Energy Calculated

face	multiplicity	$d_{spacing}$	attachment energy (kcal/mol)	slice energy (kcal/mol)	% total facet area
{1 0 0}	2	6.39	-14.74	-46.48	37.59
{0 1-1}	2	5.58	-18.53	-42.69	19.50
{1 1-1}	2	4.20	- 17.97	-43.26	14.73
{0 0 1}	2	5.92	-37.81	-23.41	10.37
{0 1 0}	2	6.57	-40.98	-20.24	10.32

Figure 3(c) clearly shows the most morphologically important (hkl) facets of α-succinic acid were dominated by the five facets {100}, {01-1}, {11-1}, {001} and {010} predicted by the attachment energy model. Among these facets, the total facet area of the {100} facet was the largest as it occupies 37.6% of total facet areas which is nearly half of the morphology and also has the slowest growth slice energy, indicating most morphologically important facet [7]. {11-1} facet happens to be the second slowest growth slice. {010} facet was exhibits the smallest growth slice energy as it has the slowest attachment energy which is -40.98 kcal/mol. Crystal facets with larger absolute attachment energies are the fastest growing surfaces and hence the less important the corresponding form within the morphology. Therefore, facets of α-succinic acid crystal interest the most to be subjected to the dynamics simulation were {11-1}, {010} and {001}.

Figure 4.4 shows the molecular packing and orientation of α-succinic acid crystal facets. {01-1},{001} and {010} facets were exposed on the surface as the carboxylic acid groups and hydrogen bond interaction can be observed from the surface chemistry of these facets Figure 4.4 (c),(g) and (i). The electronegative oxygens in the carboxylic acid produce H-bonds, making the compound polar. The polarity of a facet was governed by atoms that were exposed normal to a facet, thus possibly indicating that these facets were categorized as polar surfaces atoms. The highest electrostatic energy among the facets were {010} and {001} facets, which are -37 kcal/mol and -34 kcal/mol (MS software). High electrostatic energy is believed to have high polarity.

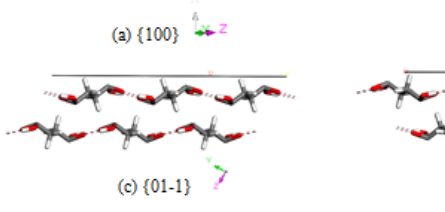


Figure 4: Molecular packing structure of α- succinic acid demonstrating the surface chemistry of crystal facet: (a) {100}, (b){-100} , (c){01-1}, (d){0-11}, (e){11-1}, (f) {-1-11}, (g) {001}, (h){00-1}, (i) {010}, and (j) {0-10} determined using the method available in the MS default package; the force field used was CVFF. Colors: Red, white and grey balls indicate oxygen, hydrogen and carbon atoms, respectively.

On the terminating {010},{01-1} and {001} facets and their symmetry surface, it can be seen that there are oxygen atoms expose on the surface which are known to have high polarity.

Other observation, there were some differences on the structural arrangement of the symmetric facet. Furthermore, some of the symmetric facet has less number of molecules on the same cleaved surface. For example as shown in Figure 4.4 (a) and (b), {100} facet consist of 6 molecule on surface, but the symmetric facet consist of 7 molecules. This phenomenon might occur due to the nature of α-succinic acid polarity.

C. Dissolution Behavior of α-Succinic Acid in Ethanol Solution

Molecular dynamic (MD) simulation was adopted to simulate α-succinic acid dissolution behavior in ethanol. All the simulation were in manner and the result demonstrated the crystal molecules was being separated from the crystal surface and entering the solvent phase. The angled facets of {010} is predicted to dissolve first as these facets located at corners, followed by facets {001} and facet {100} will be dissolved last as it has a largest facet area and long range in order.

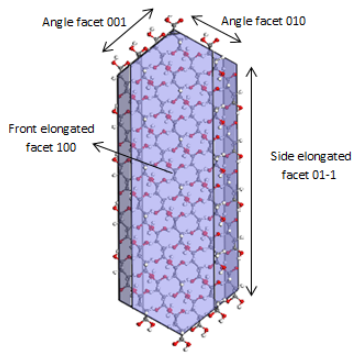


Figure 5: Demonstrations of α-succinic acid facets

The simulation on the dissolution of α-succinic acid crystal in ethanol solvent system was simulated for 100 ps at time step 1 fs (100 frames). Figure 6 showed the snapshot configuration of the dissolution behavior of the α-succinic acid crystal in ethanol solvent system at time 0 ps, 25 ps, 50 ps and 100ps respectively. At time 25 ps, α-succinic acid starts leaving the crystal and entering the solvent phase. The movement of the crystal was very gently and takes quiet sometimes to step out from the crystal. The dissolution behaviors of the molecules were seen to move around within the ethanol slab in a random manner and sometimes repositioned itself close to the surfaces of the crystal [5].

As expected, the angled facets of {010} was dissolved first as the crystal facets has larger absolute attachment energies. From Figure 6 (d), it can be observed obviously that the molecule crystal leaving the crystal to accumulate itself with the ethanolic solvent. This Figure also clearly shows that the dissolution only occurs for molecules located on the surface layer of crystal meanwhile the crystallinity (long range- order) of the crystal is sustain.

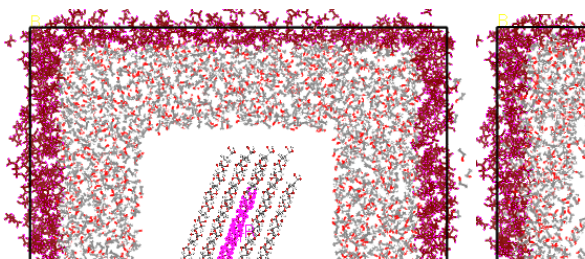
D. Mean Square displacement (MSD) analysis

Mean square displacement analysis was used to measure the distance traveled by particles following random travel is proportional to the time expire. The relationship between these is written as below:

$$< r2 > = 2nDt \qquad \text{Eq (3)}$$

Where < r2 > is mean square distance, n is 3 since all MD simulation are performed in three dimensions (3D), D is diffusion rate or also known as diffusion coefficient and t is time.

(a)



(d)

Figure 6: Snapshots configuration of simulation boxes, dark red and pink in color are constrain molecule, (a) image at 0 ps (b) image at 25 ps (c) image at 50 ps (d) image at 100 ps

Besides, understanding the solvent effects of crystal morphology can be archive by measuring the surface diffusion of solvent molecules at the interface by executing mean square displacement (MSD). The diffusion coefficient (D) is defined as the derivative of the MSD with respect to time, calculated by the following equation

$$D = \frac{1}{6}\lim_{t\to\infty}\frac{d}{dt}\sum_{i=1}^{N}\langle|r_i(t) - r_i(0)|^2\rangle \qquad \text{Eq (4)}$$

Therefore, by plotting MSD versus time, the diffusion coefficient of solvent on different facets of crystal is determined based on the slop of the graph.

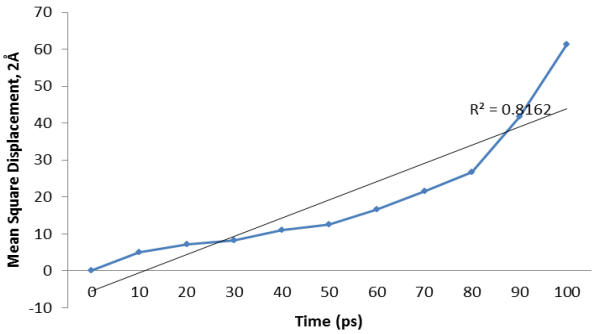


Figure 7: Distance evolution of one single α-succinic acid molecule (set 1) in simulation processes

MSD curve of set 1 are presented in Figure 7. Only on single molecule of α-succinic acid was consider for preparing the MSD curve. The selected molecule was taking into consideration because it was the most vigorously molecule pointing out from the crystal. The movement of the molecule is proportional to the slopes of MSD curves and therefore the MSD would behave similarly for others molecule in the system. At the beginning of the simulation, the molecule travel slowly with time, start at 80 ps of simulation the molecule move faster. According to this finding, the diffusion coefficient obtained is 0.8162 and displacement of the molecule was increasing ultimately with time.

E. Radial distribution function (RDF) analysis

The principle of the interaction between ethanol solvent and with α-succinic acid crystal surface can be accessed by employing radial circular function RDF, g(r). The radial distribution function is a useful tool to describe the structure interaction particularly of liquids by specific interactions such as hydrogen bonding. Figure 8 present RDF curve of crystal set as rigid-set 1 molecule calculated from the MD simulation. At short separation the RDF curves were zero at which shown the sufficient width of the atom. This is due to the strong repulsive forces and the atoms could not approach any more closely. The first and second large peak occurs at r = 0.97Å giving the RDF value about 22461. This means that the two molecules have been found at this separation. The radial distribution function then falls and rise back at the highest peak at about r = 1.11 having the RDF value of 30563. Then, the RDF is drastically drop at zero at distance r = 1.19 until r = 1.29, which means no finding of two molecule. The RDF value then was

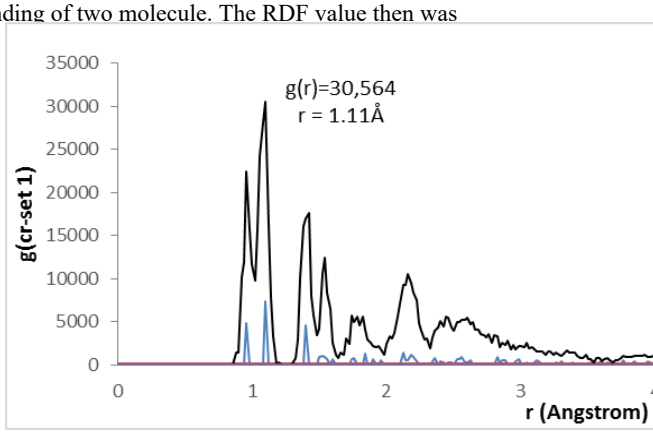


Figure 8: Radial Distribution Function curve of the rigid or constrain crystal-set 1 molecule

increasing back and at long distance start at r =3, RDF approaches decreasing until there is no long range order. From the finding in Reza and co-work in 2017, high temperature will give wide peak which acknowledge thermal motion whilst lower temperature the will form high gradient and peaks will be sharper. Therefore, the creation of peaks in RDF curve was very dependent on the reaction temperature.

IV. Conclusion

The results of lattice energy and morphology prediction as well as molecular dynamic (MD) simulation of succinic acid Form A polymorph dissolving into ethanolic solvent have presented here. The prediction of lattice energy has successfully carried out with ESP force filed and CVFF charges, but the comparison with the experimental lattice energy cannot be made since no reported data for $\Delta H_{sub.}$ The predicted morphology then was compare with the experimental shape in which showing good agreement. In this research work, the MD simulation of dissolution of α-succinic acid has been successfully carried out. The dissolution was preferred to occur at the corner edges of the crystal as mention in the Goa and coauthor research [5]. Facet {010} molecule located at the corner edges was found leaving the crystal surface first and entering the ethanol solvent phase. These conclude that, the less morphological important facet and high attachment energy which located at the tip of the crystal tends to dissolve faster compare to the most morphological important crystalline facet. The results are also supported by mean square displacement and radial distribution function analysis. These result and simulation helps in enhancing the dissolution rate of α-succinic acid crystal in future works.

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