

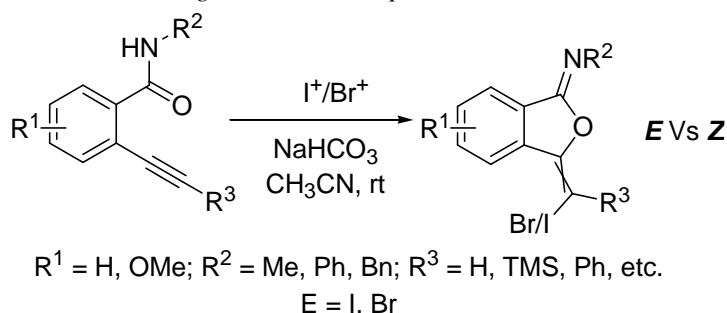
Product Geometry Analysis of Cyclic Imidates using Molecular Mechanics

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ABSTRACT

Under mildly basic conditions the *o*-(1-alkynyl)benzamides undergo electrophilic cyclization yielding cyclic imidates. The products formed were found to possess exclusive *E*-geometry across the exocyclic C=C double bond which was confirmed by single crystal X-ray crystallographic data and NMR spectroscopic data. The observed stereoselectivity of the reaction was investigated, and the thermodynamic stability of the cyclic imidates having exocyclic C=C bond was calculated using molecular mechanics (MM2) methods. Various parameters like stretch, bend, torsion, Van der Waals forces and dipole were evaluated to calculate the total energy. The MM2 results obtained were in close agreement with the experimental findings, thereby, confirming that the cyclic imidates having *E*-geometry across the C=C bond are thermodynamically more stable than their *Z*-geometric counterparts.



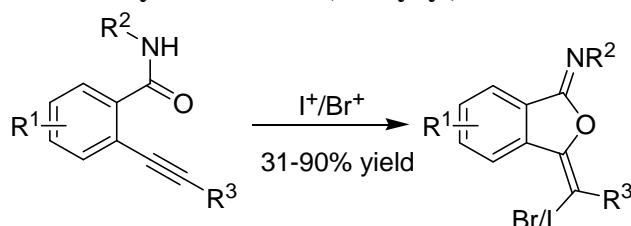
KEYWORDS: Calculations, Cyclic Imidate, MM2, Molecular Mechanics

INTRODUCTION

Heterocyclic frameworks having diverse substitution patterns are found in several naturally occurring as well as medicinally important compounds, and have displayed great importance in diverse areas, including medicinal chemistry, materials science, *etc.*¹ Amongst the vast variety of heterocyclic compounds known, cyclic imidates have gained attention of the chemists owing to their useful biological activities.²⁻⁷ Several research groups have developed various interesting approaches for the synthesis of cyclic imidates which includes metal mediated cyclizations,⁸⁻¹⁰ base mediated cyclizations¹¹⁻¹³ *etc.*¹⁴

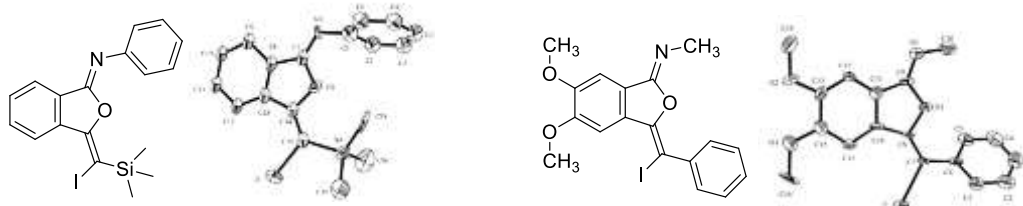
We and others have reported that under the mild reaction conditions 2-(1-alkynyl)-benzamides undergoes regio- and stereoselective cyclization affording corresponding cyclic imidates in high yields and the cyclization occurred regioselectively *via* the *O*-atom of the amide group (**Figure 1**).¹¹

Figure 1. Regio- and Stereoselective cyclization of 2-(1-alkynyl)-Benzamides to form Cyclic Imidates



The alkynyl amides were found to cyclize *via* 5-*exo-dig* cyclization in the presence of suitable electrophile and the resulting cyclic imidates formed were found to possess the exclusive *E*-geometry across the exocyclic C=C bond (confirmed using single-crystal X-ray crystallographic data and NMR spectroscopic data, **Figure 2**).

Figure 2. ORTEP diagrams of cyclic imidates formed confirming the formation of *E*-geometric isomer.¹¹



A similar finding (*O*-cyclization of 2-(1-alkynyl)-benzamides) was reported by Schlemmer *et. al.*¹³ Moreover, all cyclic imidates formed during this methodology were found to exhibit *E*-geometry across the exocyclic C=C bonds. Since the methodology could have resulted in the formation of both *E* and *Z*-isomers, so we became interested to find the factors responsible for the selective formation of the *E*-product. To justify the formation of the actual products during the experimentation, we did the additional computational experiments on the cyclic imidates formed.

Over the years the developments in computational chemistry have helped researchers in exploring new avenues and crossing the traditional boundaries that separated chemistry from other research areas of biology, physics, *etc.* In Molecular modelling computer simulations are used for describing the behaviour of molecules and it presents a reasonable alternative in situations where the actual laboratory exploration may not be practical. Molecular mechanics is a classical physics approach that is routinely used by chemists.^{15,16} It comprises of a set of potential energy functions for modelling the behaviour of matter. Molecular modelling methods have been valuable aids to the synthetic chemists.¹⁷ Various parameters and potential energy functions used for the evaluation of molecular mechanics are collectively known as a “force-field” and are governed by the fundamental principles of molecular mechanics.^{18–20} Popular force fields include MM2, MM3, and MMFF.^{21,22} The MM2 force field was developed by N. L. Allinger²³ and it was found to be suitable for various organic compounds. In molecular mechanics, a force field (bond angles, lengths, electrostatic properties, torsional parameters, Van der Waals interactions, *etc.*) is used for analyzing the steric energy of the molecule and amending the conformation to minimize the steric energy. MM2 calculations are very fast and can be used for calculation of molecular dynamics for even bulky molecules such as enzymes. The parameters of MM2 were postulated by N. L. Allinger²³ and others.^{18,24,25} In molecular mechanics, atoms and bonds are considered as per the spheres and spring model where the ability to stretch, bend, and the twist is defined using the Hooke’s Law. The non-bonded interactions include the electrostatic attraction, steric repulsion, van der Waals attraction,²⁶ *etc.* The significant energy contribution is from the torsional energy and from the 1,4-VDW interactions. The summation of various interactions such as Stretch Energy (E_{str}), Bending Energy (E_{bend}), Dipole-Dipole Energy (E_{el}), Van der Waals Energy (E_{vdw}), Stretch-Bend Energy ($E_{str-bend}$), Torsion Energy (E_{tors}), describes the total energy (E_{total}) of the molecule:

$$E_{total} = E_{str} + E_{bend} + E_{str-bend} + E_{vdw} + E_{tors} + E_{el}$$

Figure 3. Major interactions in a molecule

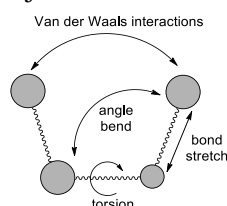
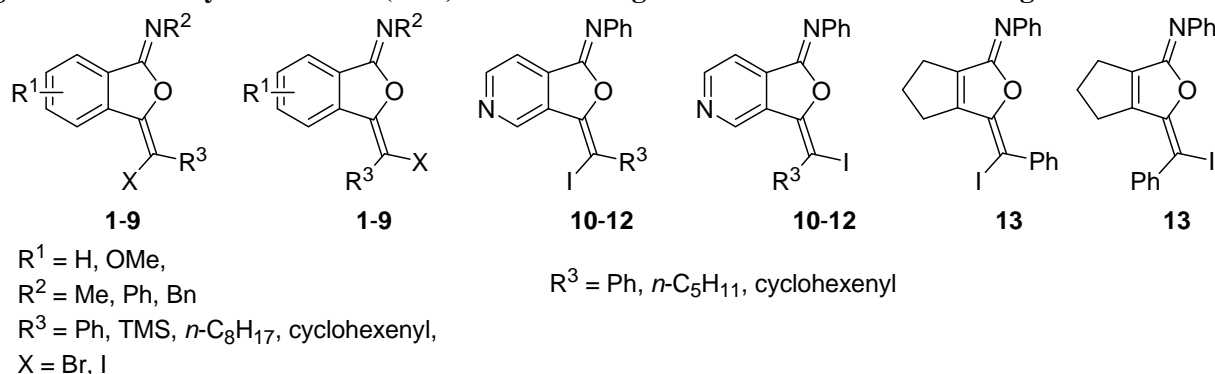
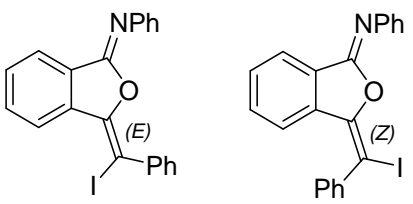


Figure 4. Various cyclic imidates (1-13) screened using the MM2 molecular modelling


RESULTS AND DISCUSSION

Application of the Molecular mechanics for the calculation of the thermodynamic stability of various geometric cyclic imidates that could be formed during the electrophilic cyclization of *o*-(1-Alkynyl)benzamides provides with the interesting insights. Using the experimental procedure for the calculation of MM2 results for the cyclic imidate **1** (both *E* & *Z*-geometric isomers), the results and the parameters obtained were summarized as given below (**Table 1**). It was observed that the MM2 results were in close agreement with the experimental outcomes. MM2 results confirmed that the product having the *E*-geometry across the exocyclic C=C product to be more stable than the product having the *Z*-geometry having an energy difference {**1(Z)**-**1(E)**} of 1.4077 kcal/mol (calculated, **Table 1**).

Table 1: Output tab displaying energy calculations of various parameters from an MM2 job for imidate 1.


Energy Term	1(E) -isomer	1(Z) -isomer
Stretch	2.3617	2.1053
Bend	21.1967	20.0511
Stretch-Bend	0.2384	0.1250
Torsion	-16.9884	-12.7264
Non-1,4 VDW	5.3041	2.6720
1,4 VDW	22.5889	22.9525
Dipole/Dipole	0.4099	1.3394
Total energy	35.1113 kcal/mol	36.5190 kcal/mol

Intrigued by these results, we performed the MM2 calculations for both the geometrical isomers (*E* & *Z*) of all the cyclic imidates (**1-13**) and the results are summarized in **Table 2**. The MM2 results obtained for all the cyclic imidates showed that in all the cases, the total energy values for the *E*-geometric product were less as compared to the *Z*-geometric product, which is in agreement with the experimental results. Therefore, during the electrophilic cyclization of 2-(1-alkynyl)benzamides the *E*-geometric product was the chemically favoured and thermodynamically stable product. The results of the comparison of various MM2 calculation parameters

for both the geometric products were summarized in **Table 2**. After obtaining the MM2 calculation results, the energy difference between the thermodynamic stability of cyclic imidates (**1-13**) and their corresponding isomeric counterparts was found to be greatest in case of imidate **11** (9.9538 kcal/mol) while it was found to be least in case of imidate **6** (0.0003 kcal/mol). The details of the energy difference of the corresponding geometrical isomers of various cyclic imidates were summarized in **Table 2**. A comparison of the total energy of both (*E* and *Z*) geometric isomers is shown in **Figure 5**, and the calculated energy difference between corresponding geometrical isomers (*E-Z*) is displayed in **Figure 6**.

Table 2: Comparison of the MM2 energy parameters of *E*- & *Z* cyclic imidates (1-13)

Cyclic imidate	Stretch energy		Bend energy		Torsion		Non-1,4 VDW		1,4 VDW		Dipole/Dipole		Total energy		Energy difference (kcal/mol) (<i>Z</i> - <i>E</i>)
	<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>	<i>E</i>	<i>Z</i>	
1	2.3617	2.1053	21.1967	20.0511	-16.9884	-12.7263	5.3041	2.6720	22.5889	22.9525	0.4099	1.3394	35.1113	36.5190	1.4077
2	2.2793	2.0998	1.1360	20.0920	-18.1119	-12.8479	5.0533	2.8018	23.0548	23.5098	0.5785	1.8802	34.2327	37.6771	3.4444
3	2.2635	1.7233	18.1455	19.9756	-14.0794	-7.0548	5.8469	3.2220	16.4471	16.2720	-0.8260	2.6942	28.0261	36.8613	8.8352
4	2.5255	2.0104	18.1607	20.0385	-20.3998	-13.4418	4.5750	2.0846	22.6106	22.5281	-0.7274	2.9618	26.9603	36.1932	9.2329
5	1.4867	1.6694	19.0825	20.3755	-15.4636	-15.1509	-3.2829	-0.4805	20.7267	20.6602	0.9071	-0.0928	23.6497	27.2394	3.5897
6	1.1908	1.1901	20.3437	20.3357	-15.8424	-15.8305	-2.0641	-2.0652	14.1684	14.1660	2.0822	2.0824	19.8509	19.8512	0.0003
7	2.9289	2.2214	23.6185	20.8137	-15.4076	-6.9241	6.1008	2.0226	21.5653	21.7513	-0.0592	0.7631	39.0216	40.7910	1.7694
8	2.0330	2.2415	20.2973	26.9058	-14.5679	-17.6490	-4.6619	-1.1011	19.5676	18.6052	1.4173	3.6445	24.0170	32.6400	8.623
9	1.5974	1.8407	16.9616	23.0831	-14.9627	-17.9503	-3.4649	0.0019	20.0960	19.1094	0.3474	2.5382	20.5614	28.6844	8.123
10	2.3730	2.1475	22.5495	21.4567	-11.8081	-7.4838	5.0765	2.5523	22.9717	23.3673	0.9222	1.8557	42.3556	44.0537	1.6981
11	1.4556	2.0559	19.9808	28.4685	-9.7094	-10.5460	-1.3111	-0.3999	19.2465	20.2425	1.4620	1.4181	31.3342	41.2880	9.9538
12	2.8699	2.2633	24.7224	22.2194	-9.8715	-1.6923	5.6004	1.9049	21.9160	22.1670	0.4251	1.1981	45.9653	48.2357	2.2704
13	2.8925	2.8741	29.8902	31.0545	-11.2512	-9.4784	3.3194	1.6203	18.4813	19.2414	-0.6517	0.2396	42.9079	45.6424	2.7345

Figure 5: Comparison of Total energy of *E* & *Z* isomers

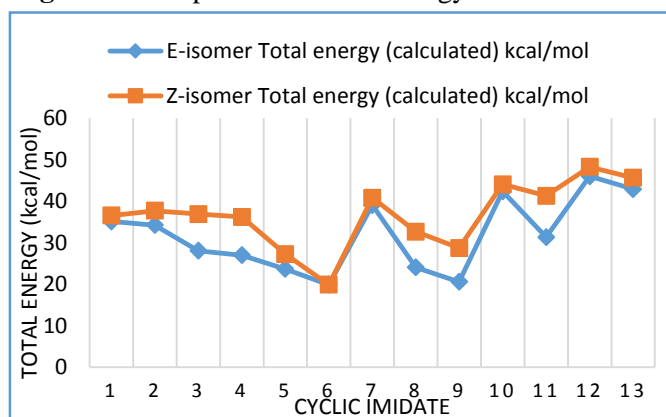
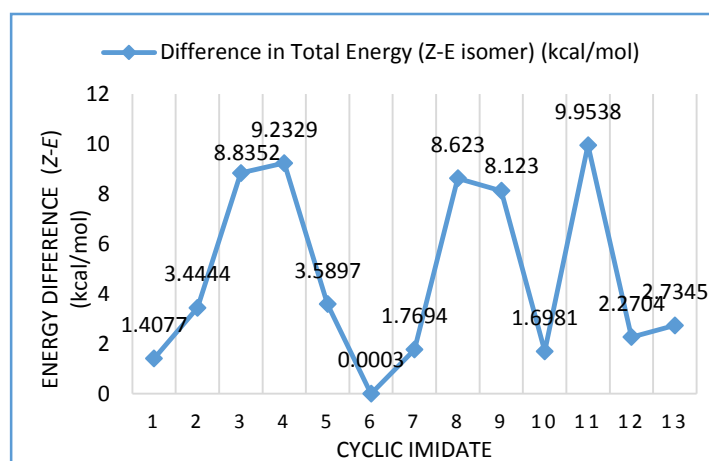


Figure 6: Energy difference between *E* & *Z* isomers



EXPERIMENTAL SECTION

General procedure for calculation of total energy using molecular modelling experiments:

The desired compound structure was drawn in ChemDraw, and the structure was transferred to chem3D Pro 12.0. The desired molecular model could be drawn directly in chem3D Pro 12.0. A ball-and-stick molecular model appeared. Various models like wireframe, sticks, cylindrical bonds or space-filling models used also be used depending upon the size and structure of the molecule. The structure was cleaned up using the *Structure* tab. To obtain minimized energy values, the settings were kept to default; selected the *Calculations* toolbar, *Minimize Energy* job function was selected through the *MM2* tab. A small window displaying the minimum energy bar showed the four parameters namely *Job Type*; *Dynamics*; *Properties and General*. Under the *Job Type* bar, set the job type to *Minimize Energy* from the drop-down menu.

The columns displaying *Setup new Atom Types before Calculation*; *Setup new Atom Charges before Calculation* would be marked by default while the columns displaying *Display Every Iteration* and *Copy Measurements to Output Box* should be marked to get the complete information on the output tab. Set the value of *Minimum RMS Gradient* to 0.001. The *Run* button at the bottom of the *Minimize Energy* window is pressed. As the command is performed, an output tab appears at the bottom of the page where all the parameters (including stretch, bend, stretch-bend, torsion, Non-1,4 VDW, 1,4 VDW and Dipole/Dipole) along with the total steric energy (in kcal/mol) values were displayed. The results including the various parameters were recorded in their respective columns in the energy table (**Table 2**). For MM2 calculations of the other Z-geometric (not formed in experimental part) isomer structure was drawn in ChemDraw, copied and pasted through *Edit* tab (*Paste Special*) command from the submenu followed by the selection of *Preserve Coordinates*. After this, all other steps were repeated as defined in the procedure for the calculation of the total energy.

CONCLUSIONS

We believe that the MM2 molecular modelling calculations provide interesting results for the thermodynamic stability of the geometrical forms of cyclic imidates (**1-13**). The molecular modelling results were found to be in close agreement with the observed experimental results. This information may be useful for synthetic and medicinal chemists working on similar heterocyclic compounds, and may also help in developing new synthetic methodologies for similar compounds.

LIST OF ABBREVIATIONS

MM = Molecular Modelling

VDW = Van der Waals Forces

MMFF = Merck Molecular Force Field

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