



---

## EXPERIMENTAL AND THEORETICAL RESULTS OF AZA-MICHAEL ADDITION TO AMINES USING METHYL PROPIOLATE

Prabhudev S. Mathapati<sup>1</sup>, Dr. Mrunal Krishanrao Shirsat<sup>2</sup>

<sup>1</sup>Research Scholar, Sunrise University, Alwar, Rajasthan

<sup>2</sup>Research Supervisor, Sunrise University, Alwar, Rajasthan

### ABSTRACT

The double bond of maleic anhydride is electron-deficient, making it a potent electron-accepting monomer. Both C=O substituents have a strong electron-withdrawing action, which is where the electron shortage comes from. In addition to the double bond, C=O groups are notoriously reactive. Maleic anhydride (4) was dissolved in methylene chloride at a low temperature (-78°C or -15°C) and then 1 equivalent of amine (68a-h) was added. The mixture was agitated at the same temperature for 0.5 hours before the solvent was evaporated (at the same low temperature). The 1H-13C correlated 2D NMR spectra were used to unequivocally establish the structures of the maleamic acids generated from the reaction of 1-methylpiperazine and pyrrolidine with maleic anhydride. It was already noted that unlike the acyclic, unsaturated carbonyl compounds, maleic anhydride does not undergo amine addition across the C=C functionality even when subjected to thermodynamic control. The resultant chiral-nitrogen-containing organic compounds have fascinating biological properties and are important building blocks for chemical synthesis.

**KEYWORDS** Aza-Michael, chemical synthesis, Theoretical, asymmetric synthesis

### INTRODUCTION

Due to the existence of multiple reactive functionalities in this molecule, the chemistry of maleic anhydride continues to draw the interest of chemists working in the area of organic synthesis and material sciences. Several different chemicals have been reported to react with maleic anhydride under the right circumstances. As a result of the double bond's lack of an electron, maleic anhydride is a very efficient electron-accepting monomer. It is the two C=O substituents' powerful electron-withdrawing impact that causes the electron shortage. C=O groups are notoriously reactive, and they share this trait with the reactive double bond. Maleic anhydride reactions may be roughly divided into the two categories below based on the nature of the chemical reactions that take place.

## Reactions of the electron-deficient double bond functionality –

Conjugation with carbonyl groups on either side of maleic anhydride activates the unsaturated linkage (C=C) in the molecule. Hence, maleic anhydride participates in reactions such as nucleophilic addition in addition to those characteristic of olefins. Maleic anhydride participates in a wide variety of reactions, such as the Diels-Alder, certain photo-reactions, the ene reaction, and so on, due to the electrophilic nature at the double bond created by conjugation. Below are some examples of addition reactions that occur over a double bond:

### LITERATURE REVIEW

**Aqsa Khalid (2022)** In situ synthesis of 2,4-dichlorobenzoyl isothiocyanate from 2,4-dichlorobenzoyl chloride and potassium thiocyanate in dry acetone afforded (4) in fair yield and high purity by reaction with acetyl aniline. Single crystal X-ray diffraction, FT-IR, <sup>1</sup>H-NMR, and <sup>13</sup>C-NMR analyses, and spectroscopic methods all corroborated the molecule. The dihedral angle of the plane rings was set at 33.32 degrees (6). These molecules formed infinite double chains along [101] thanks to the intermolecular C-H/O and N-H/S hydrogen bonds that enclosed R<sub>2</sub> 2 (8) ring motifs and were formed by the intramolecular N-H/O hydrogen bonds that formed S(6) ring motifs inside the molecules. The inter-centroid distance between C-H/p and p/p interactions in was 3.694 (1) Å, which aided in the consolidation of a three-dimensional architecture. According to the results of the Hirshfeld surface (HS) investigation, the most significant contributions to the crystal packing were from H/C/C/H (20.9%), H/H (20.5%), H/Cl/Cl/H (19.4%), H/O/O/H (13.8%), and H/S/S/S/H (8.2%). Hence, the primary forces in crystal packing were C-H-p (ring), p-p, van der Waals, and hydrogen bonds. The reactivity profile of the molecule was determined by its electronic structure and the DFT (density functional theory) parameters that were calculated for it (4). DNA docking experiments suggested that (4) is a powerful groove binder, and in silico binding of (4) with RNA suggested that a stable protein-ligand complex was formed through hydrogen bonding.

**GottimukkalaRambabu (2022)** The synthesis of -aminocarbonyl compounds now benefits from a green catalyst that is both effective and recyclable. Aryl amines, aliphatic/aromatic aldehydes, and beta-ketoesters were reacted in the presence of Montmorillonite K10 clay to produce -aminocarbonyl compounds (1a-1r) in a novel and environmentally friendly method. All compounds (1a-1r) were molecularly docked with the *S. aureus* and *E. coli* proteins PDB ID: 1JJJ and 1KZN, respectively. Good to strong interactions were detected between the active sites and all compounds. Antibacterial and antioxidant properties of -aminocarbonyl compounds were also evaluated to learn more about their biological roles. In other words, the findings showed that -aminocarbonyl compounds have the potential to be turned into novel medications with strong antibacterial and antioxidant effects.

**Lopera-Valle (2019)** There is a well-documented ring opening amidation reaction between amines and succinic anhydride (SAh) at temperatures close to room temperature, yielding succinamic acid (succinic acid-amine). In this study, we suggest grafting SAh onto a poly(lactic acid) (PLA) backbone to create an amine-responsive polymer, with the PLA serving to stabilize the functional SAh chemically and mechanically throughout the amidation process. The grafting process and film production both take place in a toluene solution containing anywhere from 10 weight percent to 75 weight percent maleic anhydride (MAh) (relative to PLA and initiator). Gel

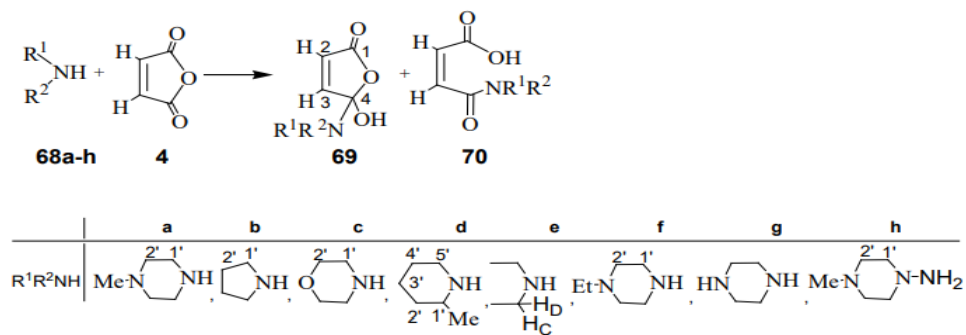
permeation chromatography and differential scanning calorimetry are used to determine the molecular weight and thermal characteristics of the various grafted polymers, while infrared spectroscopy is used to investigate the chemical alteration of these substances. Thermogravimetric analysis provides an approximation of the grafting reaction yield. A grafting degree of between 5% and 42% is shown to be optimal for engineering an amine-responsive material. Using X-ray photoelectron spectroscopy, infrared spectroscopy, and differential scanning calorimetry, we analyze the graft-polymers' reactivity to amines. After being exposed to the fumes from a 400 ppm methylamine solution, the chemical and thermal characteristics of the graft-polymers change. Control samples of clean PLA do not experience similar changes in characteristics when exposed to methylamine vapor, in contrast to the test samples. Moreover, deionized water without amines does not cause any structural alterations to the PLA-g-SAH. As a result of this study, new avenues for creating real-time amine sensors have been opened.

**Rossino, G. (2018)** In order to successfully find drugs with a specific target in mind, compound libraries are necessary. This study combines microwave-assisted organic synthesis (MAOS) with polymer-assisted solution phase synthesis (PASPS) and solid-phase extraction in place of typical purification processes throughout the reaction workup to create a small, targeted chemical library based on a -aminoketone scaffold (SPE). Dioxane, dimethylformamide (DMF), polyethylene glycol 400 (PEG 400), temperature, irradiation period, stoichiometric ratio of reagents, and catalysts (HCl, acetic acid, cerium ammonium nitrate (CAN)) were all studied for their potential to affect conversion and yield. Overall, the improved procedure provided the expected results with sufficient yields and purities. To aid in the discovery of new potential hit molecules, the developed library is a component of our ongoing study of sigma 1 receptor modulators.

**Kebukawa, Y.; Chan (2017)** The origin of life on early Earth may have been significantly aided by the external introduction of organic compounds. There is some agreement that carbonaceous chondrites include organic chemicals and complex macromolecular components, such as insoluble organic matter (IOM), although the sources of the organic matter are still up for discussion. We provide evidence that in the presence of liquid water, formaldehyde, glycolaldehyde, and ammonia may be converted into water-soluble amino acid precursors and other macromolecular organic solids with structures comparable to the chondritic IOM. Acid hydrolysis in a hydrothermal experiment yields amino acids with up to five carbon atoms, including -, -, and -amino acids, with abundances that are comparable to those found in carbonaceous chondrites. Hence, the vast range of meteoritic organic matter, from amino acid precursors to macromolecular IOM in chondrite parent bodies, may be produced through a single-step water processing from simple ubiquitous molecules.

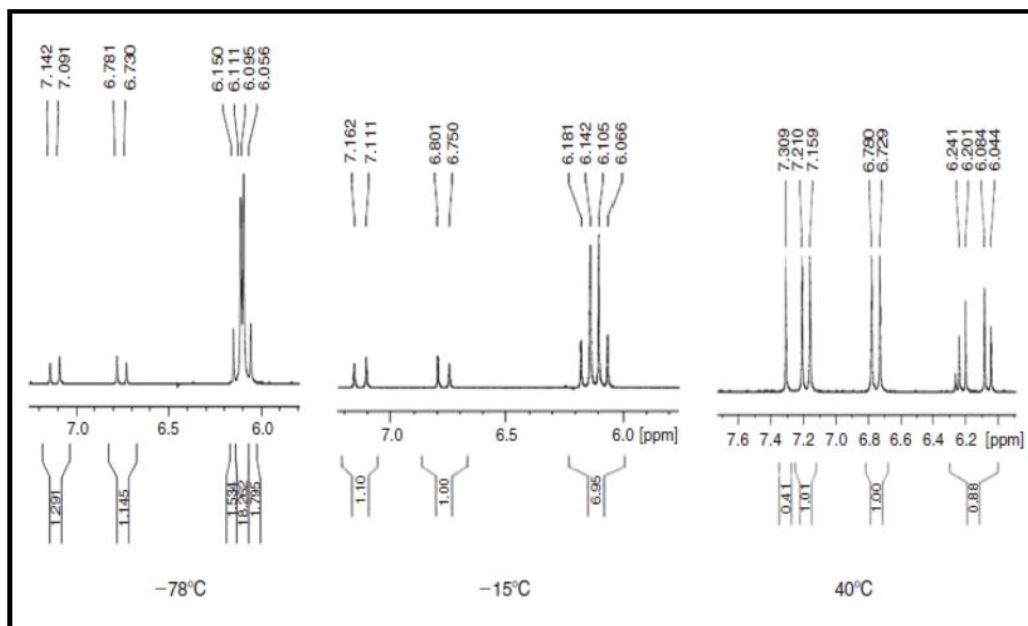
## EXPERIMENTAL RESULTS

Under kinetic control, i.e. at low temperatures (-78oC or -15oC), amines (68a-h) react with maleic anhydride (4) in methylene chloride to create the appropriate C=O products and/or maleimic acids, but at higher temperatures (40oC), the reaction is more thermodynamically controlled.



**Scheme 1. Reaction of amines with maleic anhydride.**

Typically, 1 equivalent of amine (68a-h) was added to a cooled solution (-78°C or -15°C) of maleic anhydride (4) in methylene chloride, and the combination was agitated at the same temperature for 0.5h before the solvent was evaporated (at the same low temperature). After adding the amine to the maleic anhydride in methylene chloride solution, the mixture was refluxed for 1h before being distilled to remove the solvent in the event of the reaction at higher temperature. The acquired viscous mass' <sup>1</sup>H NMR spectra were analyzed with CDCl<sub>3</sub>. The existence of two doublets in the <sup>1</sup>H NMR spectra at 6 ppm with a 3J<sub>HH</sub> of 12 Hz due to an AB spin system composed by two cis-vinyl protons verified the formation of the product 69, which results from the addition of amine across the C=O group of maleic anhydrides. Formation of maleimic acid derivative 70 was suggested, however, by the existence of two doublets somewhat farther downfield with a 3J<sub>HH</sub> of 11-15 Hz. The results of the reaction of 1-methylpiperazine and maleic anhydride at various temperatures are shown in Figure1 as a portion of their <sup>1</sup>H NMR spectra.



**Figure 1. Part of the <sup>1</sup>H NMR spectra of the products formed from the reaction of 1-methylpiperazine with maleic anhydride at different temperatures**

With the use of the <sup>1</sup>H NMR doublet intensities of the vinylic proton in products 69 and 70, we were able to determine their respective percentages, which are shown in Table 1.

**Table 1. Relative percentages of the products 69 and 70 in the reactions of amines with maleic anhydride (solvent: methylene chloride).**

Entry no.	Amine	Temp(°C)	Relative Percentage (%)	
			C=O Addition product 69	Maleimic acid derivative 70
1	68a	-78	90	10
2		-15	77	23
3		40	30	70
4	68b	-78	72	28
5		-15	11	89
6		40	-	100
7	68c	-15	95	5
8		40	7	93
9	68d	-15	A	A
10		40	A	A
11	68e	-15	100	-
12		40	91	9
13	68f	-15	A	A
14		40	A	A
15	68g	-15	Polymer formed	
16		40	Polymer formed	
17	68h	-15	A	A
18		40	A	A

Note that in this case, the product formed from adding a secondary amine across the C=O functionality of maleic anhydride isomerizes to the N-substituted maleimic acid under thermodynamic control, i.e. at higher temperature and no Michael addition occurs, in contrast to the acyclic, unsaturated carbonyl compounds. Preferred synthesis of these compounds seems to stem from stabilization of the maleimic acid derivative due to delocalization of the nitrogen lone pair of the amidic moiety.

## CHARACTERIZATION OF THE PRODUCTS

White crystalline solids were produced by the reactions of amines 68a, 68b, and 68c with maleic anhydride at elevated temperatures, and these solids were analyzed through high-resolution mass spectrometry (HRMS) and other spectroscopic methods. Other times, the products were discovered to be mixes of the C=O addition product and the matching maleimic acid, which could not be separated by column chromatography. Nonetheless, the signals could be independently attributed to these products in <sup>1</sup>H NMR spectra. Tabular 2 provides product physical and spectral data.

**Table 2 Physical data of the products obtained from the reaction of amines with maleic anhydride.**

Product No.	Physical State	Yield (%)	Melting Point (oC)	Soluble In	HRMS m/z
69a+70a	Viscous Mass	93	-	Water, Methanol, Chloroform	-
70a	White Crystalline  Solid	92	168-170	Water, Methanol	198.21; + [M] requires 198.22
69b+70b	Viscous Mass	80	-	Water, Methanol, Chloroform	-
70b	White Crystalline  Solid	78	162-164	Water, Methanol	170.18;  [M+H] requires 170.19
69c+70c	Viscous Mass	80	-	Water, Methanol, Chloroform	-
70c	White Crystalline  Solid	82	134-136	Water, Methanol	186.18 ; + [M] requires 186.18
69d + 70d	Viscous Mass	78	-	Water, Methanol, Chloroform	-
69e + 70e	Viscous Mass	80	-	Water, Methanol, Chloroform	-
69f + 70f	Viscous Mass	79	-	Water, Methanol, Chloroform	-
69g + 70g	Viscous Mass	80	-	Water, Methanol, Chloroform	-
69h + 70h	Viscous Mass	68	-	Water, Methanol, Chloroform	-

## Heteronuclear Single-Quantum Correlation (HSQC) NMR

Maliemic acids were synthesized by reacting 1-methylpiperazine and pyrrolidine with maleic anhydride, and their structures were unequivocally determined by recording their  $^1\text{H}$ - $^{13}\text{C}$  correlated 2D NMR spectra, as shown in Figures 2 and 3, respectively.

The peaks at 130.9 and 133.2 ppm in the  $^{13}\text{C}$  NMR spectra correlate with the vinylic proton signals at 6.7 and 6.9 ppm in 72a, respectively, proving that the carbon atoms are  $\text{sp}^2$  hybridized. Similar to how the  $\text{sp}^2$  hybridized nature of C2 and C3 is confirmed by the correlation of two proton signals at 7.85 and 7.26 ppm with the  $^{13}\text{C}$  NMR signals at 130.9 and 134.5 ppm in the instance of 70b.

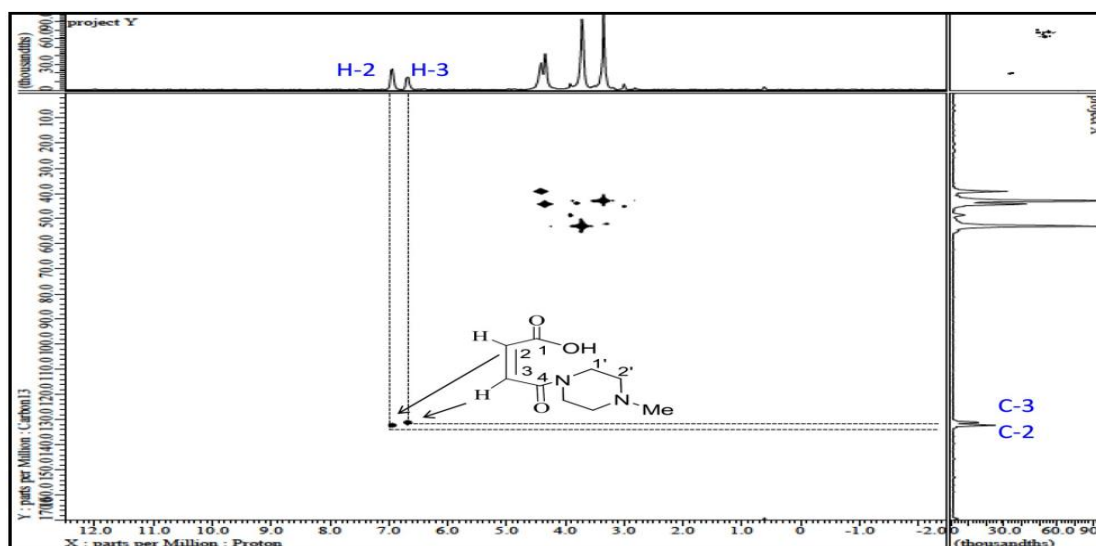


Figure 2  $^1\text{H}$ - $^{13}\text{C}$  correlated 2D NMR (HSQC) spectrum of 70a.

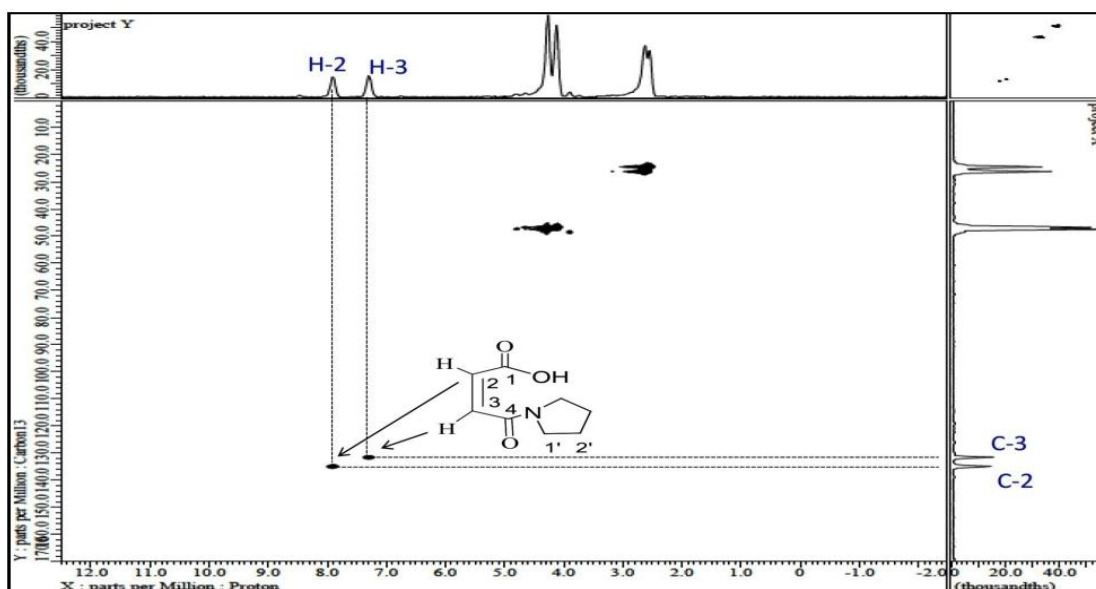


Figure 3  $^1\text{H}$ - $^{13}\text{C}$  correlated 2D NMR (HSQC) spectrum of 70b.

## THEORETICAL RESULTS

Maleic anhydride is unique among carbonyl compounds in that, unlike acyclic, -unsaturated carbonyl compounds, amine does not contribute across the C=C functionality even when subject to thermodynamic regulation. To do this, we followed a previously described approach and estimated local condensed Fukui functions for a variety of maleic anhydride locations.

For maleic anhydride (4), acrolein, and all amines (68a-h), Table 3 lists their total energies, ionization potentials, electron affinities, global hardnesses, and global softness's.

**Table 3** Total energies, Ionization potential, Electron affinity, Global hardness and Global softness of 69a-h, 4 and acrolein.

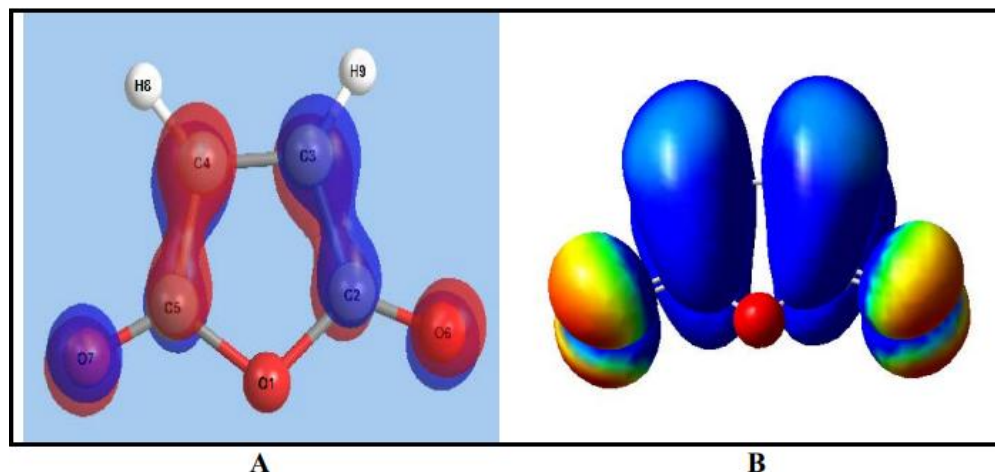
	Total Energy Neutral species [a] (a.u.) X	Total Energy Cation [a] (a.u.) Y	Total Energy Anion [a] (a.u.) Z	Ionization Potential (I) (a.u.) Y-X	Electron Affinity (A) (a.u.) Z-X	Global Hardness ( $\eta$ ) (a.u.) $\eta = I-A/2$	Global Softness (s) (a.u.) $0.5/\eta$
68a	-307.1544131	-306.8894934	-307.1356203	0.2649197	0.0187928	0.1230635	4.0629448
68b	-213.5163962	-213.1992697	-213.4958146	0.3171265	0.0205816	0.1482725	3.3721706
68c	-287.7461884	-287.4399808	-287.7261297	0.3062076	0.0200587	0.1430745	3.4946841
68d	-291.1184845	-290.8171814	-291.0984239	0.3013031	0.0200606	0.1406213	3.5556504
68e	-213.7104254	-213.4014631	-213.6909487	0.3089623	0.0194767	0.1447428	3.45440326
68f	-346.4505703	-346.1600931	-346.4327801	0.2904772	0.0177902	0.1363435	3.6672082
68g	-267.8635686	-267.5649654	-267.8449706	0.2986032	0.018598	0.1400026	3.5713623
68h	-363.4721399	-363.1853079	-363.4554618	0.2868320	0.0166781	0.1350770	3.7015924
4	-379.3472384	-378.9459073	-378.4013482	0.4013312	0.94589020	-0.2722795	-1.8363470
Acrolein	-191.9091906	-191.5426656	-191.9206136	0.3665250	-0.0114230	0.1889740	3.6458666



The sum of the single-point energies computed at the B3LYP/6-311++G\*\* level and the zero-point correction energies computed at the B3LYP/6-31+G\* level was used to get the total energies.

## FMO ANALYSIS

Examining the maleic anhydride molecule's FMO reveals that its LUMO (lowest unoccupied molecular orbital) is made up of a combination of the  $\pi^*_{\text{C=O}}$  and  $\pi^*_{\text{C=C}}$  orbitals. That's why the nucleophile that attacks may choose between attacking the carbonyl carbon or the C atom of the C=C functionality. Nevertheless, the relative condensed Fukui functions for the nucleophilic attack (f+r) at these two locations and the experimental circumstances will decide this choice. The amine group is characterized by its moderate hardness and its ability to attack either of the two sites. Hence, the carbonyl carbon atom is attacked, leading to the C=O addition product, under kinetic control, i.e., at low temperature. The electrostatic potential map, which exhibits the greatest electron shortage (the greatest density of blue color), coincides with the observation that amines preferentially target carbonyl carbon atoms. Figure 4 displays LUMO and the electrostatic potential map of the maleic anhydride molecule.



**Figure 4. LUMO (A) and electrostatic potential map (B) of maleic anhydride molecule.**

## CONCLUSION

The asymmetric synthesis of  $\alpha$ -amino carbonyl compounds and related derivatives is facilitated by one of the most appealing and easy procedures: the aza-Michael addition. In addition to being valuable building blocks in chemical synthesis, the resultant chiral-nitrogen-containing organic compounds have intriguing biological activity. Using a wide range of chiral auxiliaries and a number of different approaches, it has been feasible to create asymmetry in these processes. Depending on whether reactant chiral induction is integrated, a variety of techniques are used to obtain the requisite high stereo-control. A few examples are included to help explain these methods, although this is by no means an exhaustive study of the asymmetric aza-Michael reactions.

## REFERENCE

1. Aqsa Khalid (2022),” Structure and surface analyses of a newly synthesized acyl thiourea derivative along with its in silico and in vitro investigations for RNR, DNA binding, urease inhibition and radical scavenging activities†,” 17194 | RSC Adv., 2022, 12, 17194–17207 © 2022 The Author(s). Published by the Royal Society of Chemistry
2. Kebukawa, Y.; Chan, Q. H.; Tachibana, S.; Kobayashi, K.; Zolensky, M. E. One-Pot Synthesis of Amino Acid Precursors with Insoluble Organic Matter in Planetesimals with Aqueous Activity. *Sci. Adv.* 2017, 3, e1602093 DOI: 10.1126/sciadv.1602093
3. Rossino, G.; Raimondi, M.V.; Rui, M.; Di Giacomo, M.; Rossi, D.; Collina, S. PEG 400/Cerium Ammonium Nitrate Combined with Microwave-Assisted Synthesis for Rapid Access to Beta-Amino Ketones. An Easy-to-Use Protocol for Discovering New Hit Compounds. *Molecules* 2018, 23, 775. <https://doi.org/10.3390/molecules23040775>
4. Ali, M. A., Tandon, N., Nag, A., and Takada, K. (2019). Molecular orientation of biopolyamides after cryogenic nanohybridization with montmorillonites. *Arab. J. Sci. Eng.* 44, 153–158. doi: 10.1007/s13369-018-3290-3
5. Lopera-Valle, A.; Elias, A. Amine Responsive Poly(lactic acid) (PLA) and Succinic Anhydride (SAh) Graft-Polymer: Synthesis and Characterization. *Polymers* 2019, 11, 1466. <https://doi.org/10.3390/polym11091466>
6. Gurjar, Asha&Sinha, Pragya & Bansal, Raj. (2014). Tandem Michael addition of amines to maleic anhydride and 1,3-prototropic shift: Experimental and theoretical results. *Tetrahedron.* 70. 5052–5056. 10.1016/j.tet.2014.06.003
7. Ramu R, Shirahatti PS, Deepika TH, Bajpe SN, Sreepathi N, Patil SM, Nagendra Prasad MN. Investigating *Musa paradisiaca* (Var. Nanjangud rasa bale) pseudostem in preventing hyperglycemia along with improvement of diabetic complications. *J App Biol Biotech.* 2022;10(4):56-65. DOI: 10.7324/JABB.2022.100408
8. Heravi, M.M., Behbahani, F.K., Daraie, M. *et al.* Fe(ClO<sub>4</sub>)<sub>3</sub>· 6H<sub>2</sub>O: a mild and efficient catalyst for one-pot three component synthesis of β-acetamido carbonyl compounds under solvent-free conditions. *Mol Divers* 13, 375–378 (2009). <https://doi.org/10.1007/s11030-009-9118-z>
9. Davide Rigo (2022) ,” Isopropenyl Esters (iPEs) in Green Organic Synthesis,” Volume28, Issue40 July 15, 2022 e202200431
10. Liu, M.; Yu, Z.; Li, J.; Xiao, Y. Versatile Fluorine-Containing Building Blocks: β-CF<sub>3</sub>-1,3-enynes. *Molecules* 2022, 27, 9020. <https://doi.org/10.3390/molecules27249020>
11. Avny, Y., Saghian, N., and Zilkha, A. (1972). Thermally stable polymers derived from itaconic acid. *Isr. J. Chem.* 10, 949–957. doi: 10.1002/ijch.197200098

12. Ayadi, F., Mamzed, S., Portella, C., and Dole, P. (2013). Synthesis of bis(pyrrolidone-4-carboxylic acid)-based polyamides derived from renewable itaconic acid—application as a compatibilizer in biopolymer blends. *Polym. J.* 45, 766–774. doi: 10.1038/pj.2012.206
13. Baruah, R., Kumar, A., Ujjwal, R. R., Kedia, S., Ranjan, A., Ojha, U. (2016). Recyclable thermosets based on dynamic amidation and aza-michael addition chemistry. *Macromolecules* 49, 7814–7824. doi: 10.1021/acs.macromol.6b01807
14. Cao, H., Zheng, Y., Zhou, J., Wang, W., and Pandit, A. (2011). A novel hyperbranched polyester made from aconitic acid (B3) and di(ethylene glycol) (A2). *Polym. Int.* 60, 630–634. doi: 10.1002/pi.2993
15. Chanda, S., and Ramakrishnan, S. (2015). Poly(alkylene itaconate)s – an interesting class of polyesters with periodically located exo-chain double bonds susceptible to Michael addition. *Polym. Chem.* 6, 2108–2114. doi: 10.1039/C4PY01613