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Full Paper

Experimental and Theoretical Investigation of the Reaction of Secondary Amines with Maleic Anhydride

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The reaction of secondary amines, namely 1-methylpiperazine, pyrrolidine, morpholine, 2-methylpiperidine, and diethylamine, with maleic anhydride has been investigated experimentally and theoretically at the DFT level. Under kinetic control, i.e. at −78°C or −15°C, amines add across the C=O functionality exclusively and the initially formed addition products isomerize to the corresponding N-substituted maleimic acid derivatives. In contrast to the acyclic α,β-unsaturated carbonyl compounds, amine does not add across the C=C functionality in maleic anhydride even under thermodynamic control. This behaviour of maleic anhydride can be rationalized on the basis of the local condensed Fukui functions, which reveal that the carbonyl carbon atoms in maleic anhydride are much harder than in an acyclic α,β-unsaturated carbonyl compound, such as acrolein. This prompts the amines to attack the carbonyl group in maleic anhydride exclusively.

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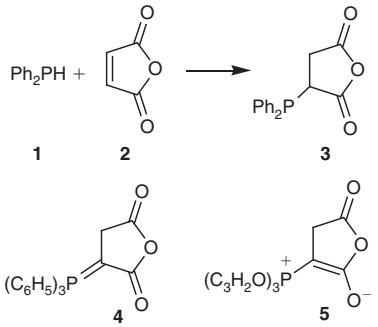
Introduction

The chemistry of maleic anhydride continues to attract the attention of chemists working in the fields of organic synthesis and material sciences owing to the presence of several reactive functionalities in this molecule.[1,2] A C=C functionality, activated by its conjugation with the carbonyl groups on both sides, makes it a potent dienophile.[3,4] This may be expected to undergo nucleophilic addition across the C=O functionality. In fact, maleic anhydride has been reported to react with primary amines to yield maleimic acids, which change to N-substituted maleimides on heating in the presence of a dehydrating agent.[5–8] However, only one report could be found about the reaction of maleic anhydride with a secondary amine, namely 1-methylpiperazine, to give N-(1-methylpiperazin-4-yl)maleimic acid, which does not cyclize in the absence of an NH atom. However, no spectral data of this compound were given in the paper.[9] The integration of an α,β-unsaturated carbonyl functionality in a maleic anhydride molecule is expected to make it a good Michael acceptor. Diphenylphosphine reacts with maleic anhydride and its α-methyl derivative to afford the corresponding Michael adducts (Scheme 1).[10] However, triphenylphosphine[11,12] and triethyl phosphite,[13] which have no hydrogen atoms on the donor P atom, react with maleic anhydride to form ylide-type products **4** and **5**, respectively, involving nucleophilic attack at the α-alkenyl carbon atom followed by the transfer of the proton to the adjacent carbon atom (Scheme 1).

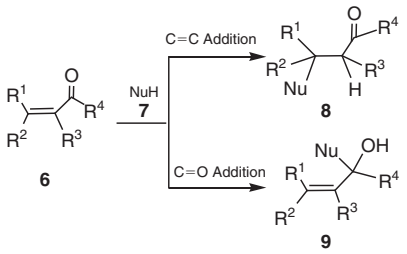
Michael addition of nucleophiles to activated alkenes and alkynes provides one of the most commonly used methods for making C-C and C-X (X = N, O, P, S) bonds in organic synthesis.[14–23] However, in the reaction with α,β-unsaturated carbonyl compounds, such as maleic anhydride, the possibility



Scheme 1.

exists for the addition across the C=C bond or the C=O functionality, and these types of additions have been named as conjugate (1,4-) versus direct (1,2-) addition, respectively, in the literature. However, in the present article, we have used the terminology of additions across the C=C and C=O functionalities (Scheme 2) in order to avoid confusion, such as 1,2- versus 1,4-addition of halogens to the conjugated dienes.

Schultz and co-workers[24] were the first to systematically study the factors affecting addition of the stabilised enolates derived from α-substituted methyl propiolates across the C=C and C=O functionalities in 2-cyclohexen-1-one. They found that addition across the C=O group is kinetically preferred and occurs predominantly or exclusively at low temperature, i.e. at −78°C, whereas addition to the C=C moiety is, in general, thermodynamically selective and the initially formed C=O addition product on raising the temperature to 25°C changes into the C=C addition product. However, the reaction of the enolate ion derived from the



Scheme 2.

acetonide of lactic acid with 2-cyclohexen-1-one at −78°C or 25°C over a prolonged reaction time yielded only the C=O addition product ruling out the reversibility of the reaction at the latter reaction conditions. From these results, they concluded that by simple structural modification and careful choice of reaction temperature, it was possible to direct the reaction of enolates to cyclohexenone either to the C=O or the C=C addition. In a similar study, Reich et al.[25] investigated the role of the solvent in the reaction of sulphur-substituted carbanionic lithium reagents with 2-cyclohexen-1-one and concluded that under contact ion pairs (CIP) conditions (in the presence of tetrahydrofuran or diethyl ether), the C=O addition product is favoured exclusively, whereas under solvent-separated ion pair (SIP) conditions (in the presence of hexamethylphosphoramide), C=C addition occurs predominantly.

In contrast to the intensive kinetic studies of the reactions of enolates with α,β-unsaturated carbonyl compounds, only one report[26] could be found about these aspects of the reaction for primary amines with α,β-unsaturated aldehydes and ketones although the aza-Michael reaction has been extensively used for obtaining important synthons, such as β-amino carbonyl compounds and heterocyclic scaffolds.[27–31] Whiting and co-workers[26] investigated the addition of primary amines to α,β-unsaturated aldehydes and ketones (C=O versus C=C addition) by using a combination of in situ IR, ^{1}H NMR and DFT calculations, and concluded that formation of the α,β-unsaturated imines (through addition to the C=O group) is kinetically controlled for all enols and most enones with the exception of methyl vinyl ketone, which resulted in addition across the C=C functionality exclusively. Furthermore, DFT calculations indicated that the selectivities are governed by conformational and stereo-electronic effects.

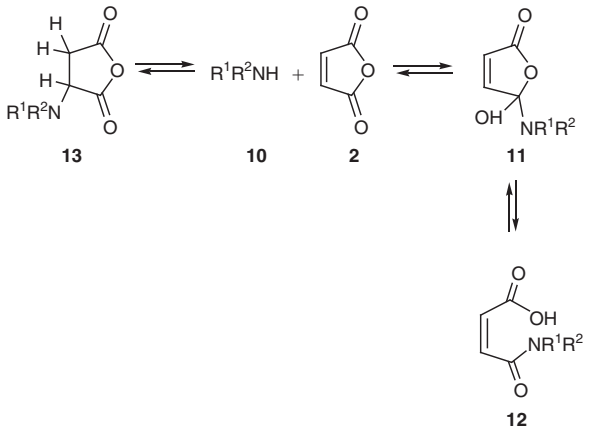
Gázquez and Mendez[32] extended the concept of hard-soft acid-base (HSAB) theory[33–35] to explain the global and local reactivity of organic molecules towards nucleophilic and electrophilic reagents. Thus, the chemical reactivity at a particular molecular site could be rationalized by using a quantitative descriptor, the Fukui function (f (r)), arising from finite difference approximation. Thus, the Fukui function was defined as

$$f^{+}(\mathrm{r}) = \rho\mathrm{N}{+}1(\mathrm{r}) - \rho\mathrm{N}(\mathrm{r}) \text{ for nucleophilic attack} \quad (1)$$

$$f^{-}(\mathrm{r}) = \rho\mathrm{N}(\mathrm{r}) - \rho\mathrm{N}{-}1(\mathrm{r}) \text{ for electrophilic attack.} \quad (2)$$

where ρN+1(r), ρN(r) and ρN−1(r) are the electron densities at a point r in the system with N+1, N and N−1 electrons, respectively, all with the ground state geometry of the N electron system.

They concluded, 'regions of a molecule where the Fukui function is large are chemically softer than the regions where the Fukui function is small and by invoking the HSAB principle in a local sense, one may establish the behaviour of different sites with respect to hard or soft reagents'.[32]



Scheme 3.

It was demonstrated that most of the frontier-electron theory of chemical reactivity can be well rationalized on the basis of density functional theory (DFT) of the electronic structure of the molecules.[36,37] Yang and Mortier[38] subsequently suggested the use of the gross charge (qr) at a particular atom r in a molecule obtained from Mulliken population analysis (MPA) to determine the condensed Fukui function (*fr*) at that atom. Thus,

$$f^{+}\mathrm{r} = \mathrm{qr}(\mathrm{N}+1) - \mathrm{qr}(\mathrm{N}) \text{ for nucleophilic attack} \quad (3)$$

$$f^{-}\mathrm{r} = \mathrm{qr}(\mathrm{N}) - \mathrm{qr}(\mathrm{N}-1) \text{ for electrophilic attack.} \quad (4)$$

As discussed earlier, no attempt has been made so far to investigate the reactions of secondary amines with maleic anhydride under kinetic and thermodynamic controls. Furthermore, in contrast to the reaction with an acyclic α,β-unsaturated carbonyl compound, in the present case, the possibility of an equilibrium between three species (**11**, **12**, **13**) exists (Scheme 3).

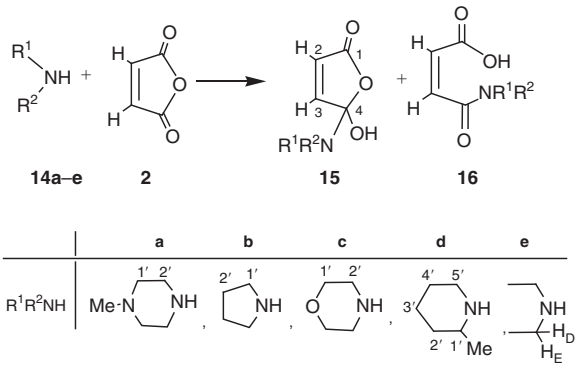
With this background, we investigated the reaction of some secondary amines with maleic anhydride under kinetic and thermodynamic controls and attempted to rationalize the observed regioselectivity on the basis of the condensed Fukui functions; the results are presented here.

Results and Discussion

Experimental Results

We investigated the addition of five secondary amines (**14**) with maleic anhydride under kinetic control, i.e. at low temperature (−78°C or −15°C) and under thermodynamic control at higher temperature (40°C) (Scheme 4).

In a typical experiment, to a cooled solution (−78°C or −15°C) of maleic anhydride in methylene chloride, 1 equivalent of amine was added and the reaction mixture was stirred at the same temperature for 0.5 h followed by removal of the solvent (at the same low temperature). In the case of the reaction at higher temperature, after adding the amine to the solution of maleic anhydride in methylene chloride, the reaction mixture was refluxed for 1 h followed by distilling off the solvent. The ^{1}H NMR spectra of the viscous mass so obtained were scanned in $CDCl_3$. These spectra are given in the Supplementary Material.



Scheme 4.

Formation of the product **15**, resulting from addition of amine across the C=O group of maleic anhydride, could be confirmed by the presence of two doublets in the ^{1}H NMR spectrum at δ ~6 ppm with a $^{3}J_{HH}$ of ~12 Hz resulting from an AB spin system constituted by two *cis*-vinylic protons. However, the presence of two doublets slightly further downfield with a $^{3}J_{HH}$ of ~11–15 Hz indicates the formation of the maleimic acid derivative **16**.[8] The structure of a representative compound **16a**, prepared in pure form as described later, was established unambiguously by the ^{1}H-^{13}C correlated 2D NMR spectrum (solvent: CD_3OD, given in Supplementary Material), wherein two proton signals at δ 6.7 and δ 6.9 ppm correlated with the ^{13}C NMR signals at δ 130.9 and δ 132.2 ppm, respectively, thereby confirming the vinylic nature of the protons. These NMR data rule out structure **13** for these products. We realise that in an earlier communication,[39] structure **13** was erroneously assigned to these products and this should be revised. Thus, in contrast to the acyclic α,β-unsaturated carbonyl compounds, in the present case, the initially formed product from the addition of a secondary amine across the C=O functionality of maleic anhydride isomerizes to N-substituted maleimic acid, rather than changing back to the reactants, and then to the C=C addition product under thermodynamic control, i.e. at higher temperature. The stabilisation of the maleimic acid derivative resulting from delocalization of the nitrogen lone pair of the amidic moiety appears to be responsible for the preferred formation of these compounds. The relative percentages of the products **15** and **16** were calculated on the basis of the intensities of doublets of the vinylic proton in **15** and **16** in the ^{1}H NMR spectra. The ^{1}H NMR signals between δ 6–8 ppm obtained from the products of the reaction of 1-methylpiperazine with maleic anhydride under different conditions are reproduced in Fig. 1.

It is noteworthy that the initially formed C=O addition product of amine does not completely change to maleimic acid even on heating the reaction mixture at 40°C for 1 h. As the removal of the solvent at −78°C took a prohibitively long time, except for the reaction with 1-methylpiperazine and pyrrolidine, the reactions with the other amines were studied only at −15°C and 40°C.

The percentages of the C=O addition products (**15**) and the corresponding maleimic acids (**16**) determined on the basis of the ^{1}H NMR spectra, as outlined earlier, formed from the reactions of amines with maleic anhydride under different conditions are given in Table 1. It was found that the doublets of the vinylic protons of the C=O addition product and those of the maleimic acid derivative obtained from the reaction of 2-methylpiperidine with maleic anhydride overlap, and therefore the relative percentages of the two products under different conditions could not be determined.

The reaction with piperazine afforded a polymeric substance which was found to be insoluble in common organic solvents but soluble in water.

It may be noted that, as expected, at low temperature (−78°C or −15°C), addition across the C=O functionality occurs exclusively or predominantly. On heating the reaction mixture at 40°C, i.e. on refluxing in methylene chloride, the initially produced major C=O addition products in the reactions with **14a**, **14b** and **14c** change into the corresponding maleimic acids to varying extents. Pure maleimic acid derivatives of these three amines could be obtained by refluxing the reaction mixtures in acetonitrile for ~2 h followed by column chromatography and recrystallization from methanol. However, similar efforts to obtain pure maleimic acid derivatives of 2-methylpiperidine and diethylamine were not successful.

Theoretical Results

The values of the global hardness (η) and global softness (s), and the condensed Fukui functions f^{+}r and f^{-}r, and local softness s^{+}r and s^{-}r at different atoms of maleic anhydride and at the donor nitrogen atom (NH) of amines used in the reactions are given in Tables 2 and 3, respectively.

It may be noted that condensed Fukui functions of many atoms, including those of the carbonyl carbon atoms in maleic anhydride and donor nitrogen atoms in amines, have negative values. The condensed Fukui functions with negative values have been often obtained while using MPA.[40,41] However, application of Hirshfeld population analysis (HPA),[42] based on the stock-holder idea, yields only positive condensed Fukui functions.[40,43] Later, negative condensed Fukui functions were rationalized by invoking orbital relaxation effects. Thus, theoretical calculation of the redox-induced electron rearrangement (RIER) revealed that although the molecule loses one electron, the electron density may increase in some regions leading to the negative condensed Fukui functions.[44,45] Gázquez and Mendez[32] also found negative values of the condensed Fukui function at the carbonyl carbon atoms of the substrates used in the reactions.

Unlike in simple α,β-unsaturated aldehydes or ketones, such as acrolein (Fig. 2), the -CH=CH- functionality in maleic anhydride (**2**) is encompassed by the carbonyl groups on both sides. Thus, in contrast to acrolein, in the maleic anhydride molecule, the C=O and C=C groups are locked in the s-*trans* conformation and the value of the condensed Fukui function for the nucleophilic attack (f^{+}r) at the carbonyl carbon atom in maleic anhydride (0.003) is much smaller than in acrolein (0.215), which shows the much harder character of the former. The β carbon atom (C3) in maleic anhydride is much softer compared with the carbonyl carbon atom. This difference (difference between the hardnesses of the carbonyl carbon atom and β carbon atom) in acrolein is much smaller. From this, it may be concluded that under kinetic control conditions, attack at the carbonyl carbon atom in maleic anhydride leading to addition across the C=O group will be much more preferred than in acrolein under similar conditions.

The LUMO and the electrostatic potential map of the maleic anhydride molecule are shown in Fig. 3.

It may be noted that the LUMO of the maleic anhydride molecule is composed of the π*C=O and π*Cα=Cβ orbitals merged together. In view of this, the attacking nucleophile has

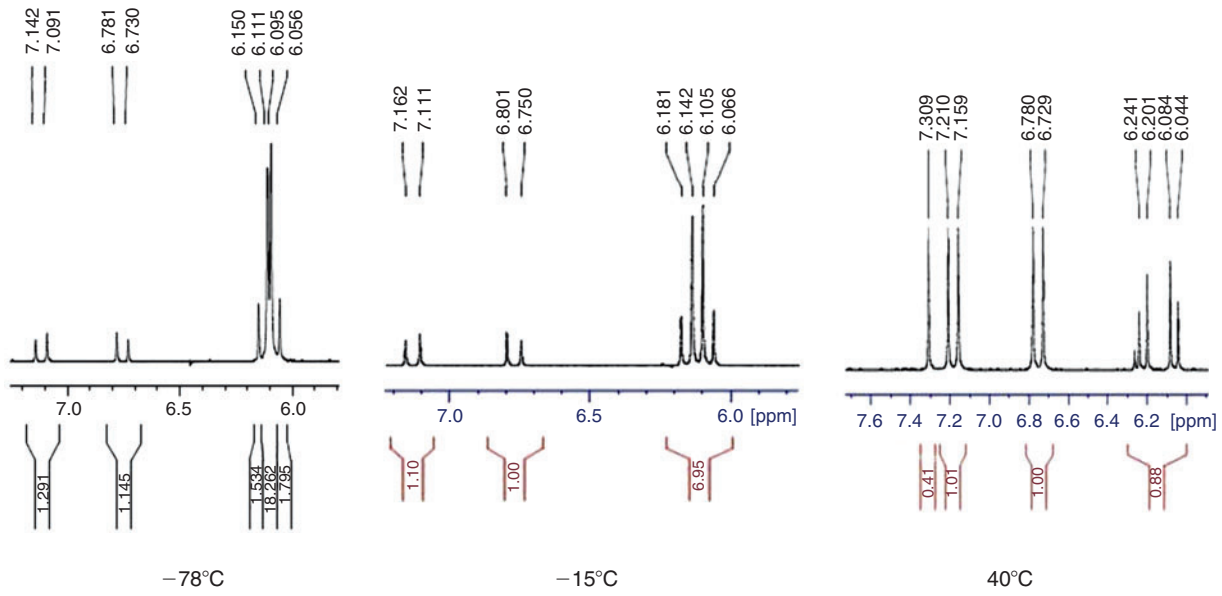


Fig. 1. Part of the ^{1}H NMR spectra of the products formed from the reaction of 1-methylpiperazine with maleic anhydride at different temperatures.

Table 1. Relative percentages of the products 15 and 16 in the reactions of secondary amines with maleic anhydride (solvent: methylene chloride)

Entry no.	Amine	Temp [°C]	Relative percentage [%]	
			C=O Addition product **15**	Maleimic acid derivative **16**
1	**1a**	−78	90	10
2		−15	77	23
3		40	30	70
4	**1b**	−78	72	28
5		−15	11	89
6		40	–	100
7	**1c**	−15	95	5
8		40	7	93
9	**1d**	−15	_[A]	_[A]
10		40	_[A]	_[A]
11	**1e**	−15	100	–
12		40	91	9

[A]Relative percentages could not be determined.

both opportunities, i.e. either to attack the carbonyl carbon atom or the Cβ atom of the C=C functionality. This preference will, however, be determined by the relative condensed Fukui functions for the nucleophilic attack ($f^{+}r$) at these two sites as well as the conditions. Amines are known to have intermediate hardness and can attack either of the two sites depending upon the conditions. Thus, under kinetic control, i.e. at low temperature, the carbonyl carbon atom, which is the harder site ($f^{+}r = 0.003$), is attacked giving the C=O addition product. The preferential attack of amine on the carbonyl carbon atom is in accordance with the electrostatic potential map which also shows the highest electron deficiency (highest intensity of blue colour) at this site.

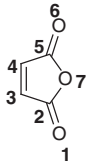
The HOMO and the electrostatic potential map of a representative amine, namely 1-methylpiperazine (**14a**), are given in Fig. 4. The HOMOs and electrostatic potential maps of other amines are provided in the Supplementary Material.

It may be noted that lone pairs on the two nitrogen atoms constitute the HOMO of 1-methylpiperazine. However, the lone pair on the nitrogen atom of NH (N18 in Fig. 4a), being sterically less hindered, attacks the maleic anhydride molecule. In the electrostatic potential map, the intensity of the red colour also indicates the high electron density on the nitrogen atom.

Conclusions

The reaction of secondary amines with maleic anhydride under kinetic control conditions occurs across the carbonyl group exclusively, which may be attributed to the much harder nature of its carbonyl carbon atom as compared with that in an acyclic α,β-unsaturated carbonyl compound, such as acrolein. It could be rationalized theoretically on the basis of the condensed Fukui function which reveals the hardest nature of the carbonyl carbon atom making it the preferred site for the nucleophilic attack. The

Table 2. Condensed Fukui functions f^+r and f^-r and local softness (s^+r and s^-r) values at different atoms of the maleic anhydride molecule calculated at the B3LYP/6–311++G//B3LYP/6–31+G* level**

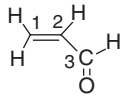


Global hardness η = −0.272 and global softness s = −1.836

Atom	f^+x	s^+x	f^-x	s^-x
O1	−0.069	0.127	−0.106	0.195
C2	−0.003	0.006	−0.012	−0.022
C3	−0.045	0.083	−0.047	0.086
C4	−0.158	0.290	−0.085	0.156
C5	−0.003	0.006	0.012	−0.022
O6	−0.191	0.351	−0.291	0.534
O7	−0.191	0.351	−0.290	0.532

Table 3. Condensed Fukui functions f^+r and f^-r and local softness (s^+r and s^-r) values at the donor nitrogen atom of amines calculated at the B3LYP/6–311++G//B3LYP/6–31+G* level**

Amine	f^+x	s^+x	f^-x	s^-x
1a (η = 0.123, s = 4.063)	−0.365	−1.483	−0.041	−0.167
1b (η = 0.148, s = 3.372)	−0.448	−1.511	0.448	1.511
1c (η = 0.143, s = 3.495)	−0.332	−1.148	−0.247	−0.854
1d (η = 0.141, s = 3.556)	−0.182	−0.647	−0.286	−1.017
1e (η = 0.145, s = 3.454)	−0.253	−0.874	−0.302	−1.043



Acrolein

η = 0.19

s = 2.65

	f_x^+	s_x^+	f_x^-	s_x^-
C1	−2.250	0.662	−0.097	−0.257
C2	0.061	0.161	−0.003	−0.008
C3	−0.215	−0.569	−0.029	−0.077

Fig. 2. Condensed Fukui functions at different carbon atoms of the acrolein molecule.

resulting carbonyl addition products isomerize to the N-substituted maleimic acid derivatives, which are stabilised due to amidic delocalization of the nitrogen lone pair. Thus, in contrast to the acyclic α,β-unsaturated carbonyl compound, no addition occurs across the C=C functionality of maleic anhydride.

Experimental

Materials

Commercially available amines, maleic anhydride and dichloromethane were purchased from Sigma-Aldrich. Dichloromethane was freshly dried and distilled.

Analysis and Characterisation of Products

IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. NMR spectra were recorded on a Bruker-DPX-300 MHz spectrometer. ^{1}H NMR were recorded at a frequency of 300.13 MHz and ^{13}C NMR at 75.48 MHz using tetramethylsilane (TMS) as the internal reference. High resolution mass spectra (HRMS) were recorded on a mass spectrometer, model Xevo G2-S Q Tof (Waters, USA) with UPLC.

General Method

A solution of **2** (1 g, 10.20 mmol) in dichloromethane (10 mL) was cooled to −78°C in a cryostat under anhydrous conditions. To it was added dropwise a solution of 1 equiv. of amine (**14a**, 1.021 g, 1.13 mL, 10.20 mmol; **14b**, 0.725 g, 0.83 mL, 10.20 mmol; **14c**, 0.888 g, 0.89 mL, 10.20 mmol; **14d**, 1.011 g, 1.19 mL, 10.20 mmol; **14e**, 0.745 g, 1.05 mL, 10.20 mmol) in methylene chloride (5 mL) with continuous stirring and the temperature was maintained at −78°C. After the addition was complete, the reaction mixture was stirred for another 0.5 h at the same temperature. The solvent was thereafter removed under vacuum with maintaining the temperature at −78°C. The viscous mass so obtained was dried under vacuum and the IR and ^{1}H NMR spectra were obtained. Similar experiments were also carried out at −15°C or at room temperature (~25°C) followed by refluxing in methylene chloride (boiling point 40°C) for 1 h for all the amines.

The reaction mixtures of the secondary amines and maleic anhydride in acetonitrile on prolonged refluxing followed by column chromatography and recrystallization from methanol afforded the corresponding maleimic acid derivatives (**16**) in a pure state.

*Compound **15a** (in mixture with **16a**)*: IR: υ_{max} (KBr, cm^{-1}) 3408 (O-H s), 1575 (C=O s), 1193 (C-O s); ^{1}H NMR (300 MHz, $CDCl_3$, TMS, δ ppm, *J* Hz): δ 8.43 (bs, OH), δ 6.13 (d, $^3J_{HH}$ 11.7, 1H, C(2)H), 6.08 (d, $^3J_{HH}$ 11.7, 1H, C(3)H), 5.30 (s, 3H, N-CH_3), 2.41 (t, $^3J_{HH}$ 4.8, 4H, C(2')H2), 2.27 (t, $^3J_{HH}$ 4.8, 4H, C(1')H2).

*Compound **16a***: Yield: 92 %; mp 168–170°C; IR: υ_{max} (KBr, cm^{-1}) 3450 (O-H s), 1611 (C=O s), 1100 (C-O s); ^{1}H NMR (400 MHz, [D4]methanol, TMS, δ ppm, *J* Hz): δ 6.34 (d, $^3J_{HH}$ 11.2, 1H, C(2)H), 6.07 (d, $^3J_{HH}$ 11.2, 1H, C(3)H), 4.90 (s, OH), 3.31(t, $^3J_{HH}$ 3.2, 4H, C(1')H2), 3.30 (t, $^3J_{HH}$ 3.2, 4H, C(2')H2), 2.74 (s, 3H, N-CH_3); ^{13}C NMR (75.48 MHz, [D4]methanol, δ ppm): 171.30 (C(1)=O), 170.11 (C(4)=O), 132.19 (C2), 130.97 (C3), 44.24 (C2′), 42.92 (C1′), 39.17 (CH_3); HRMS: *m/z* 198.21; $[M]^+$ requires 198.22 .

*Compound **15b** (in mixture with **16b**)*: IR: υ_{max} (KBr, cm^{-1}) 3416 (O-H s), 1555 (C=O s), 1216 (C-O s); ^{1}H NMR (300 MHz, $CDCl_3$, TMS, δ ppm, *J* Hz): δ 8.19 (bs, OH), 6.19 (d, $^3J_{HH}$ 11.9, 1H, C(2)H), 6.04 (d, $^3J_{HH}$ 11.9, 1H, C(3)H), 3.26 (t, $^3J_{HH}$ 4.8, 4H, C(1')H2), 2.69 (t, $^3J_{HH}$ 4.8, 4H, C(2')H2).

*Compound **16b***: Yield: 78 %; mp 162–164°C; IR: υ_{max} (KBr, cm^{-1}) 3400 (O-H s), 1585 (C=O s), 1163 (C-O s); ^{1}H NMR (400 MHz, [D4]methanol, TMS, δ ppm, *J* Hz): δ 7.34 (d, $^3J_{HH}$ 15.4, 1H, C(2)H), 6.74 (d, $^3J_{HH}$ 15.4, 1H, C(3)H), 4.95 (s, OH), 3.70 (t, $^3J_{HH}$ 6.4, 4H, C(1')H2), 3.55 (t, $^3J_{HH}$ 6.4, 4H, C(2')H2);

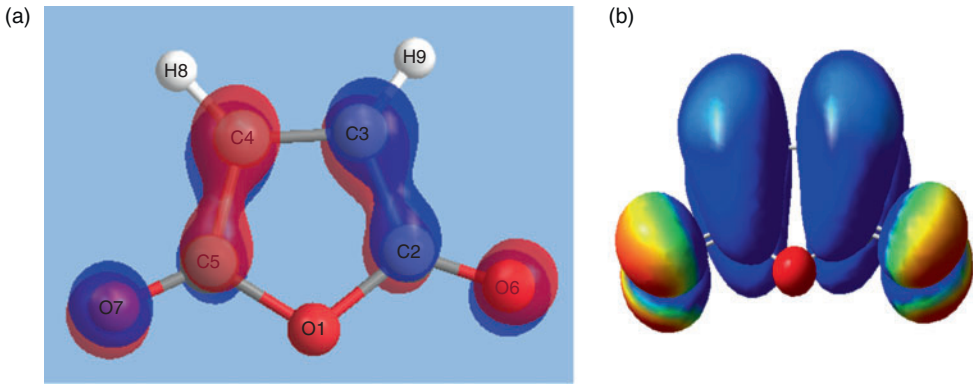


Fig. 3. (a) LUMO and (b) electrostatic potential map of the maleic anhydride molecule.

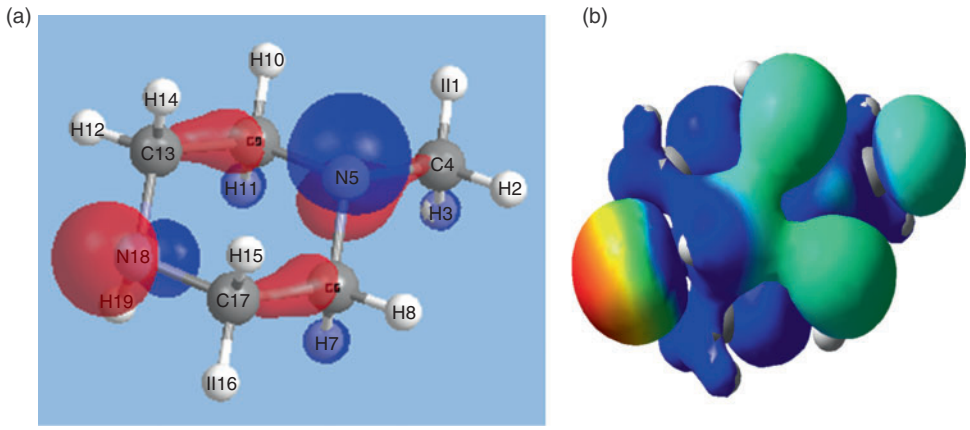


Fig. 4. (a) HOMO and (b) electrostatic map of 1-methylpiperazine.

^{13}C NMR (75.48 MHz, [D4]methanol, δ ppm): 167.73 (C(1)=O), 164.03 (C(4)=O), 134.94 (C2), 131.56 (C3), 26.22 (C1′), 24.45 (C2′); HRMS: *m/z* 170.18; $[M+H]^+$ requires 170.18.

Compound ***15c*** *(in mixture with* ***16c****)*: IR: υ_{max} (KBr, cm^{-1}) 3412 (O-H s), 1576 (C=O s), 1113 (C-O s); ^{1}H NMR (300 MHz, $CDCl_3$, TMS, δ ppm, *J* Hz): δ 8.58 (bs, OH), 6.23 (d, $^3J_{HH}$ 11.9, 1H, C(2)H), 6.14 (d, $^3J_{HH}$ 11.9, 1H, C(3)H), 3.87 (t, $^3J_{HH}$ 4.8, 4H, C(1')H2), 3.13 (t, $^3J_{HH}$ 4.8, 4H, C(2')H2).

Compound ***16c*** *(contains traces of* ***15c****)*: Yield: 82 %; mp 134–136°C; IR: υ_{max} (KBr, cm^{-1}) 3480 (O-H s), 1609 (C=O s), 1105 (C-O s); ^{1}H NMR (400 MHz, [D4]methanol, TMS, δ ppm, *J* Hz): δ 7.34 (d, $^3J_{HH}$ 15.2, 1H, C(2)H), 6.67 (d, $^3J_{HH}$ 15.2, 1H, C(3)H), 4.89 (s, OH), 3.82 (t, $^3J_{HH}$ 4.8, 4H, C(1')H2), 3.69 (t, $^3J_{HH}$ 4.8, 4H, C(2')H2); HRMS: *m/z* 186.18; $[M+H]^+$ requires 186.18.

Compound ***15d+16d***: IR: υ_{max} (KBr, cm^{-1}) 3430 (O-H s), 1586 (C=O s), 1181 (C-O s); ^{1}H NMR (300 MHz, $CDCl_3$, TMS, δ ppm, *J* Hz): δ 9.3 (bs, OH), 6.21 (d, $^3J_{HH}$ 12.0, 1H, C(2)H), 6.08 (d, $^3J_{HH}$ 12.0, 1H, C(3)H), 3.43 (t, $^3J_{HH}$ 6.9, 2H, C(5′)H2), 3.36 (t, $^3J_{HH}$ 6.9, 1H, C(1')H), 2.96 (q, $^3J_{HH}$ 7.2, 1H, C(2')H), 1.25 (m, 2H, C(3′)H2), (C(4')H2 merged), 1.14 (d, $^3J_{HH}$ 7.2, 3H, CH_3).

Compound ***15e+16e***: IR: υ_{max} (KBr, cm^{-1}) 3429 (O-H s), 1580 (C=O s), 1194 (C-O s); ^{1}H NMR (300 MHz, $CDCl_3$, TMS, δ ppm, *J* Hz): δ 8.9 (bs, OH), 6.23 (d, $^3J_{HH}$ 12.0, 1H, C(2)H), 6.09 (d, $^3J_{HH}$ 12.0, 1H, C(3)H), 3.43 (q, $^3J_{HH}$ 7.1,1H, $C\underline{H}_DH_ECH_3$), 3.36 (q, $^3J_{HH}$ 6.7, 1H, $CH_D\underline{H}_ECH_3$), 2.96 (q, $^3J_{HH}$ 7.2, 2H, CH_2), 1.28 (t, $^3J_{HH}$ 7.2, 3H, CH_3), 1.16 (t, $^3J_{HH}$ 7.2, 3H, CH_3).

Computational Methods

All calculations were carried out at the DFT level using the B3LYP hybrid functional.[46,47] All geometries were optimized in the gas phase at the B3LYP/6–31+G(d) level of the theory, using the *Gaussian 03* suite of programs.[48] Frequency calculations were performed at the same level to determine zero-point correction energies and to characterise the minima by the presence of no imaginary frequencies. The natural bond orbital (NBO)[49] analysis was employed for determining MPA.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

IR and ^{1}H NMR spectra of the products; Cartesian coordinates of the geometries optimized (Table S1) and energies of all the species in the gas phase at the B3LYP/6–311++G* level and zero-point correction at the B3LYP/6–31+G* level (Table S2); total energies, ionization potential, electron affinity, hardness and softness of **1a–e** (Table S3); Mulliken atomic charges and Fukui functions (Tables S4–S11); and FMOs and electrostatic

potential maps of maleic anhydride and amines are available on the Journal's website.

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