

AM1 and ESI/MS study of the Fragmentation of 4-Acyl Isochroman-1,3-Diones: Correlation between Electronic charges of Atoms and Fragmentations processes

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Abstract

Recently, it has been found a good correlation between the fragmentation processes of coumarins in electronic impact mass spectrometry (eims) and the electronic charges of the atoms of their hydrocarbon skeleton. The same results have been obtained with eims spectra of 4-acyl isochroman-1,3-diones and the electronic charges of their atoms. In this paper, the analytic method has been applied to ESI/MS mass spectra of a series of 4-acyl isochroman-1,3-diones to verify its reliability and extensibility. The results, which have been described for the very first time, show that fragmentations take place at the level of atoms bearing high positive charge, according to the nature of ionisation projectile. The results are in good agreement with the earliest studies.

Keywords: ESI/MS, 4-acyl isochroman-1,3-dione, electronic charges, fragmentation.

Introduction

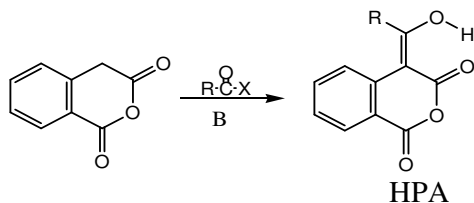
4-Acyl isochroman-1,3-diones are interesting compounds studied in our laboratories. It has been found several properties for these compounds. So, they exhibit fluorescence¹⁻² anti-oxydant³ and anti-bacterial properties⁴ among others. Some of their spectral properties, RMN⁵, mass⁶, UV-Visible³ and reactivity^{3,7-9} have been described. Their crystal structures are also been investigated¹⁰⁻¹². Recently it has been found a good correlation between the fragmentation of some organic compounds in electronic impact mass spectrometry (eims) and the charges of their atoms performed by AM1 semi empirical method. It has been found that fragmentation processes in eims take place mainly on the level of atoms bearing high negative charge¹³⁻¹⁵. It is then possible to predict and explain most of their fragmentations using electronic charges of atoms.

The same analytic method has been successfully applied to the eims spectra of title compounds¹⁶. So, for the very first time, we should like to apply the method using the electronic charges of atoms in the study of fragmentations of title compounds in ESI/MS. So, ESI/MS spectra of a series of 4-acyl isochroman-1,3-diones has been chosen to establish and confirm the reliability of the method and to evaluate its extensibility. Good results have been obtained.

Material and Methods

Preparation of 4-acyl isochroman-1,3-diones:The title compounds have been prepared as early described¹ by action of acid chlorides or acid anhydrides on homophthalic anhydride (HPA) in the presence of an appropriated base as shown below (scheme 1) ;

Scheme-1: Synthesis of 4-acylisochroman-1,3-diones



X = Cl or OCOR B = pyridine or triethylamine.

1a: R = CH₃; **1b:** R = C₂H₅; **1c:** R = C₆H₅;

1d: R = *p*-NO₂C₆H₄; **1e:** R = *p*-ClC₆H₄;

1f: R = *p*-(CH₃)₂NC₆H₄; **1g:** R = *p*-CNC₆H₄.

Recording spectra: ESI/MS mass spectra, described in the below table 1, are obtained with a 3200 QTRAP (Applied Bio systems SCIEX) mass spectrometer apparatus, equipped with an atmospheric pressure ionisation source (API). The sample is dissolved in 500 μL of chloroform and diluted at 1/100 in a 3mM methanolic solution of ammonium acetate. It is then ionized in positive electrospray mode in the follow conditions: electrospray tension (ISV) : 5500V ; Orifice tension (OR) : 20V ; pressure of nebulisation gas (air) : 20psi ; debit : 5 μL/min. The fragmentation spectra are obtained after dissociation induced by collision; collision gas is N₂ ; energy of collision 20eV ; two quadrupoles tandem mass analysers. Spectra presented two to six fragments with a significant relative abundance (>20) characterising their stability.

AM1 Calculation of electronic charges: All the electronic charges of atoms are performed by Austin Model 1 (AM₁) semi empirical method¹⁷ from "Chem3D Ultra8" software, using a "Pentium 4" computer. Results are reported in tables 2a, 2b and 2c.

Results and discussion

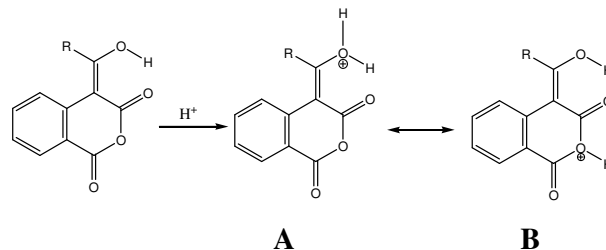
The acylated isochroman-1,3-diones **1** have been obtained by the described method with more than 70% yield¹. They have been identified by their melting point and by their ¹H, ¹³C and ¹⁷O NMR spectra^{3,5}.

General modes of fragmentations of 4-acyl isochroman-1,3-diones

Formation of the pseudo molecular ion [M+H]⁺

The pseudo molecular ion [M+H]⁺ has been described to be obtained by the follow reaction exposed in scheme 2. It is noticeable that the reaction takes place at the level of heteroatom under SP³ hybridization (O₂ and O₄), due to the easiest mobility of p electrons doublets and their best ability to react with acids (scheme 2).

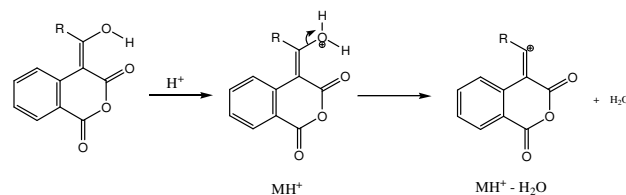
Scheme-2: Formation of pseudo-molecular ion



Formation of [M +H]⁺ – H₂O and [R-CO]⁺ or [Ar-CO]⁺ ions: So, the proton used in the ionisation pathway, react with O₂ or O₄ to give [M+H]⁺ The reaction leads to

[M+H]⁺ – H₂O and R-CO⁺ fragments by the following processes:- after protonation of O₄, the loss of a molecule of water by direct fragmentation leads to [M+H]⁺ – H₂O fragment as shown below (scheme 3):

Scheme 3: Formation of [M+H]⁺ – H₂O



1a: R=CH₃; m/z = 187;

1b: R = C₂H₅; m/z = 201;

1c: R = C₆H₅; m/z = 249;

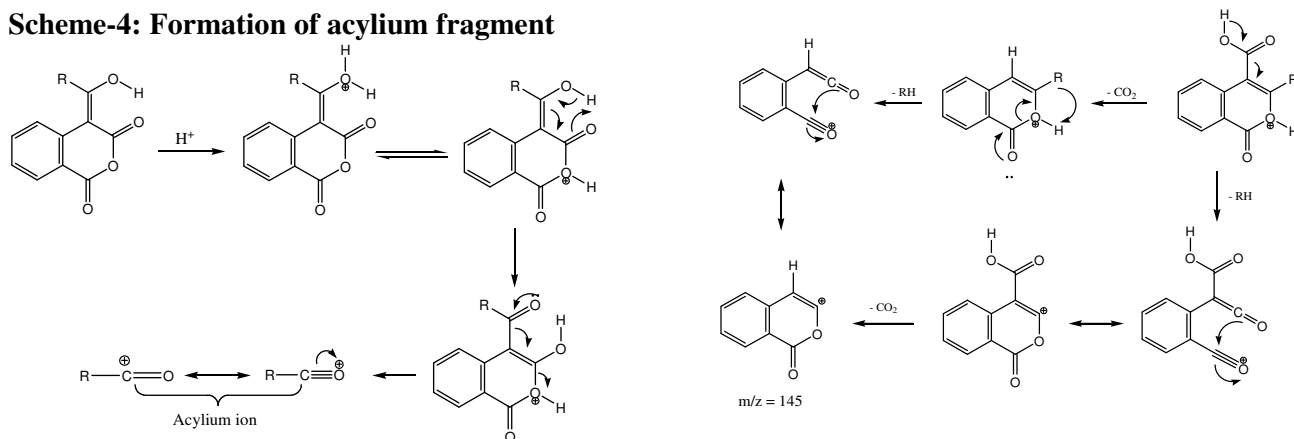
1d: R = *p*-ClC₆H₄; m/z = 283

1e: R = *p*-NO₂C₆H₄; m/z = 294;

1g: R = *p*-CNC₆H₄; m/z = 274

It is also possible, after formation of the pseudo molecular ions, to obtain a prototropy of this molecular ion as described in scheme 4^{7,9} which then, leads to the formation of acylium fragment (scheme 4)

Scheme-4: Formation of acylium fragment

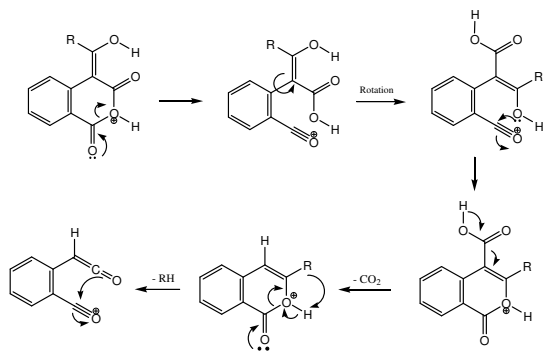


- 1a:** R = CH₃; m/z = 43; **1b:** R = C₂H₅ : m/z = 57;
1c: R = C₆H₅; m/z = 105;
1d: R = pClC₆H₄; m/z = 139-14;
1e: R = pNO₂C₆H₄; m/z = 150;
1f: R = p(CH₃)₂NC₆H₄; m/z = 148;
1g: R = pCNC₆H₄; m/z = 130.

These fragmentations take place at the level of C₁₁ and C₃. So, according to the nature of the charge of proton, which is the source of ionisation, the fragmentations processes seemed to take place at the level of atoms bearing a high positive charge as C₁₁ and C₃.

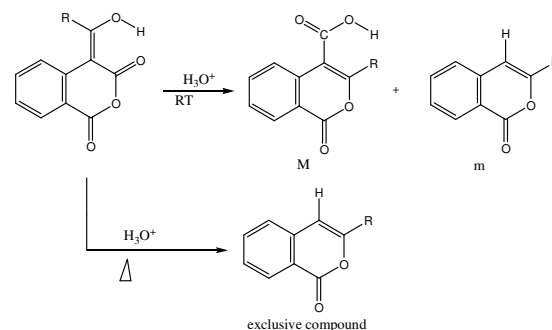
Formation of fragment m/z = 145: The formation of this fragment has been found to be particularly interesting. It has been described to be formed by the follow process⁶ described in the below scheme 5:

Scheme-5: Formation of fragment m/z = 145



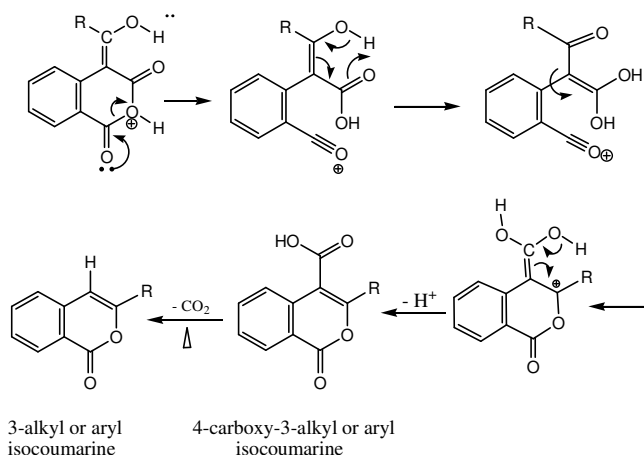
This fragment at m/z = 145 is known as 3-isocoumaryl cation. Its presence in the spectra of most of the compounds is conforming to the synthesis route to isocoumarins by the reaction described by R. N. Usgaonkar and al.⁸. Thus, under treatment of 4-acyl isochroman-1,3-diones by a 80% aqueous solution of sulphuric acid, the reaction lead to the formation of corresponding 3-alkyl isocoumarins. The authors found that when the reaction is run at room temperature, the 3-alkyl 4-carboxy isocoumarin is obtained as majority compound with a little portion of 3-alkyl isocoumarin. However, in high temperature, only the 3-alkyl isocoumarin is obtained, according to the follow scheme 6:

Scheme-6: Synthesis of isocoumarins from 4-acyl isochroman-1,3-diones



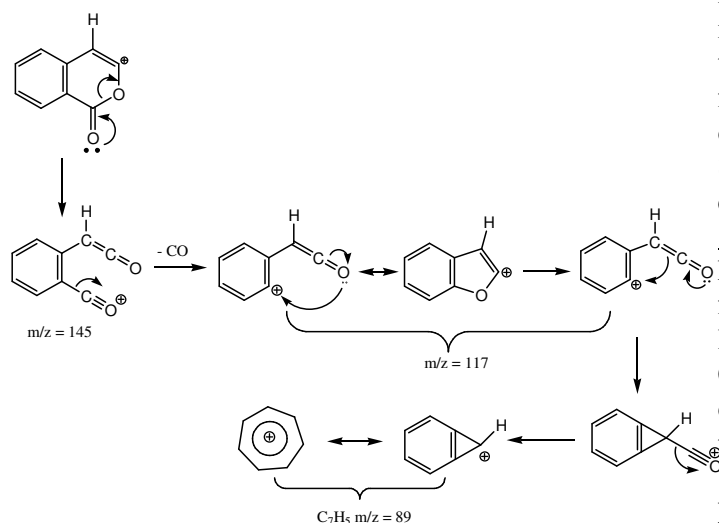
In this case of ESI/MS spectrometry, the results are comparables. So the conditions of recording spectra seemed to be very closes to those described by Usgaonkar and al.⁸. The mechanism proposed by the authors is reproduced below in scheme 7. It is once, noticeable that the fragmentations obtained are directed by C₁₁, C₃ and C₁. These atoms of carbon are bearers of high positive electronic charges.

Scheme-7: mechanism of formation of isocoumarin [8,9]



Formation of fragment $m/z = 117$ and 89 : These fragments take place from the precedent fragment $m/z = 145$. The process of its fragmentation is a well known process described to be two successive loss of a molecule of carbon monoxide^{6,17,18} to give the tropylium cation $m/z = 89$. In this process, the fragmentation takes place at the level of C_1 and C_3 which are bearers of the highest positive electronic charge (scheme 8).

Scheme 8: Formation of fragment $m/z = 117$ and 89 .

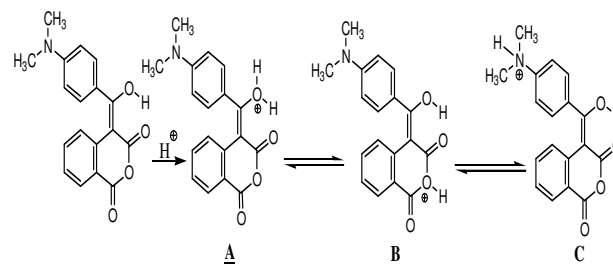


However, between the whole fragmentations described above, only the fragmentation leading to the acylium ion is observable in the spectrum of **1f**. The fragmentations of this compound follow an atypical pathway and will be considered below.

Atypical fragmentations of 1f

Formation of pseudo molecular ion: 1f [$R = p-(CH_3)_2NC_6H_4$], has never been studied in mass spectrometry. It is noticeable that this compound **1f** has an atypical behaviour in ESI/MS. The nitrogen atom of its amino group has a very significant influence in its behaviour. Due to the presence of the nitrogen atom, it is possible to assume many forms of the pseudo molecular ion as indicated below in scheme 9 and its fragmentations.

Scheme-9: Possible forms of pseudo molecular ion.

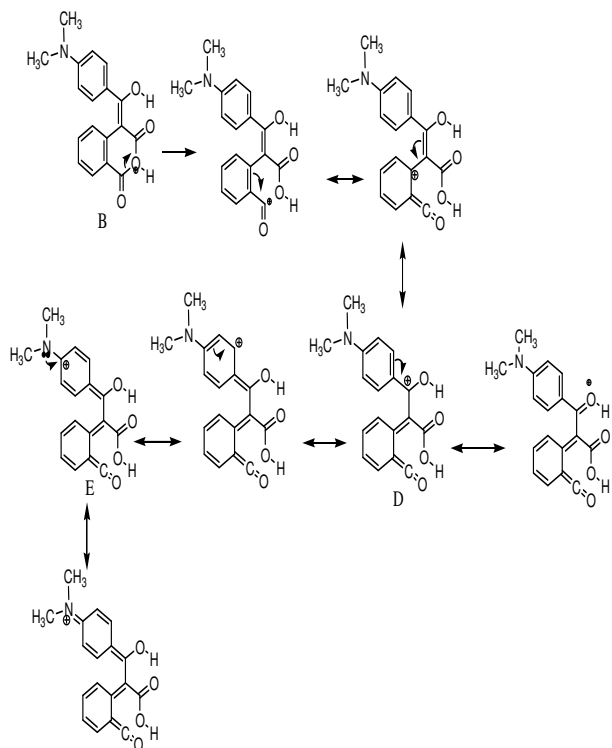


The lack of the fragments $m/z = 292$ and 265 , materializing respectively the loss of neutral molecules of water (H_2O) and dimethylamine $(CH_3)_2NH$ in the spectrum of **1f**, is indicative of non formation of the **A** and **C** types of pseudo molecular ions. Only pseudo molecular ion **B** is then formed, due to its best stability and lead to fragmentations giving the spectrum of **1f**. In the other hand, all the fragments $m/z = 145$, 117 and 89 , observed in all the spectra of the above compounds, are not observables in the spectrum of **1f**. According to the nature of the charge of the hydrocarbon skeleton of this compound, the fragmentation processes will take place at the level of atoms bearing high positive charge as C_1 , C_3 , C_{10} , C_{11} , and C_{15} . So the follow fragments are obtained. Their formations can be explained by the below mechanisms.

Formation of $m/z = 295$ and 267 fragments:

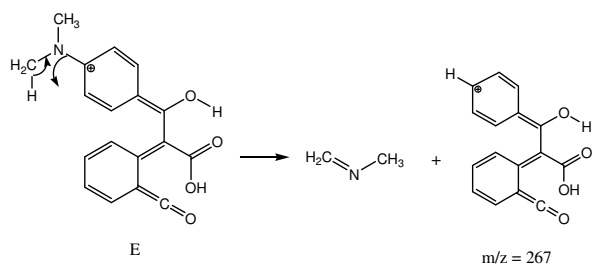
These fragments derive from the pseudo-molecular ion **B**. The fragmentations of **B** lead to fragments stabilized by electron donating effect of the nitrogen atom (scheme 10).

Scheme-10: mesomeric forms of pseudo molecular ion B.



This pseudo-molecular ion is the most stable than the others. It will be the parent peak leading to the formation of the most significant fragments. The first fragment is formed by the loss of a methyl group leading to the fragment $[M+H]^+ - 15$, ($m/z = 295$). The second fragment can be obtained from E as parent peak, after transposition of an atom of hydrogen from one of the methyl groups linked on the nitrogen atom, on the phenyl ring as shown below (scheme 11):

Scheme-11: Formation of fragment 267 ($[M+H]^+ - 43$)



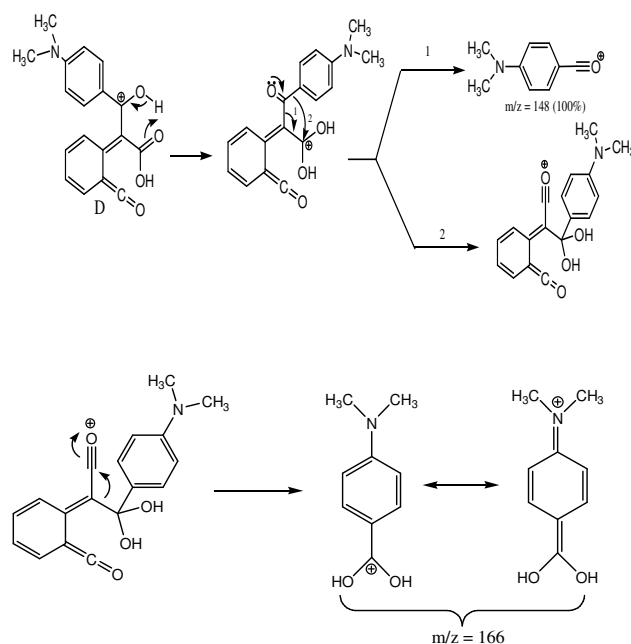
This transposition of the aliphatic proton is known and described several times¹⁸⁻²⁰ for alkyl and

dialkylaminophenyl moieties. In the compound **1f**, the atom C_{15} is bearer of a relative high positive charge and can control this fragmentation.

Formation of fragment $m/z = 166$ and 148:

According to the electronic charge of atoms, the formation of these fragments must take place at the level of carbons C_3 and C_{11} , bearing high positive charge. It is then possible to propose the follow mechanism as an explanation; the process starts from D as parent peak (scheme 12).

Scheme-12: Mechanism of formation of fragment $m/z = 166$ and 148

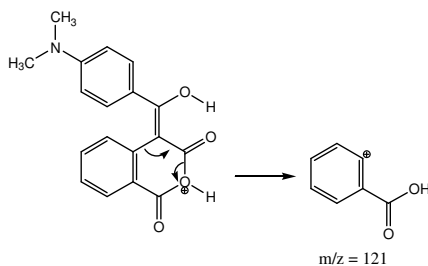


After the prototropy, the formation of the fragments $m/z = 148$ takes place by simple cleavage of C_4-C_{11} bond (way 1). The 1,3-migration of the phenyl group from C_{11} onto C_3 (way 2) leads to the fragment $m/z = 166$ by subsequent cleavage of the C_4-C_3 bond. It is necessary to assume this transfer of the phenyl group²⁰⁻²² as shown in the above scheme 12 to explain the formation of this fragment $m/z = 166$. The high positive charge of the atoms of carbon C_{11} and C_3 , can make possible this transfer between C_{11} and C_3 . Nevertheless, the process described in scheme 4 for the formation of fragment $m/z = 148$ remain possible.

Formation of fragment $m/z = 121$: This fragment comes directly from the pseudo

molecular ion by two successive cleavages as shown below. The formation of this fragment is controlled by oxonium atom O₂ and carbon atoms C₃ and C₁₀. These atoms of carbon are bearer of positive electronic charge (scheme 13), even if the charge of C₁₀ is weak.

Scheme-13: Formation of the fragment m/z = 121



Conclusion

In this study, it has been found that the fragmentations of 4-acyl isochroman-1,3-diones in ESI/MS spectrometry / positive electrospray mode, take place mainly at the level of atoms bearing a significant positive charge. So, according to the nature of the charge of ionisation projectile, the fragmentations processes take place mainly at the level of atoms bearing the same type of charge. In eims, it has been observed that fragmentations take place at the level of atoms bearing high negative charge. In this ESI/MS positive electrospray mode ionisation study, most of the important fragmentations take place at the level of atoms bearing high positive charge. It is then possible to predict the fragmentation processes of organic compounds using the electronic charge of the atoms of their hydrocarbon skeleton. The ESI/MS spectrum of a new compound **1f**, has been successfully analysed through this method. In the other hand, the behaviour of most of these compounds in ESI/MS in positive electrospray mode, is very close to their behaviour when they are treated by acid middle. In this case, the compounds are transformed into corresponding 3-alkyl or 3-aryl isocoumarins. In the present ESI/MS positive electrospray mode spectrometry, one of the fragmentations observed, lead to a fragment identified as 3-isocoumaryl cation; except for **1f**. This result suggests that, sometimes, it will be possible to predict the behaviour of an

organic compound in acidic condition, by studying its mass spectrum recorded in ESI/MS electrospray positive mode. At last, it will be interesting to study the behaviour of **1f** in the reaction described by Usgaonkar and al, transforming title compounds into isocoumarins by acidic treatment.

Aknowldgments

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Structure of 4-acylisochroman-1,3-diones

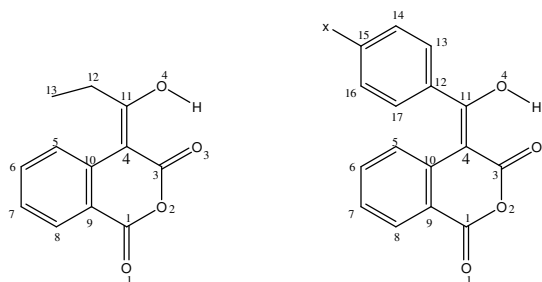


Table-1: ESI/MS Mass Spectra of 4-acylisochroman-1,3-diones

1a R = CH ₃		1b R = C ₂ H ₅		1c R = C ₆ H ₅		1d R = <i>p</i> -NO ₂ C ₆ H ₄		1e R = <i>p</i> -ClC ₆ H ₄		1f R = <i>p</i> -(Me) ₂ NC ₆ H ₄		1g R = <i>p</i> -CNC ₆ H ₄	
m/z	%	m/z	%	m/z	%	m/z	%	m/z	%	m/z	%	m/z	%
205	9.6	219	84.21	267	13.55	312	23.73	303	53.57	310	11.17	292	57
187	13.8	201	10.52	249	2	294	13.55	285	3.57	295	5.6	274	11.78
177	1	191	2	205	1	250	5	257	25	267	3.62	264	1
163	100	173	3	177	1	248	6.78	241	1.8	166	4.7	248	1
149	55.17	163	100	145	10.16	150	100	145	37.5	151	1	246	1
145	65.52	159	5.26	117	3	145	44	141	100	148	100	230	1
135	17.24	145	68.42	105	100	119	22	117	1	121	2.35	145	45.82
117	10.35	135	1	89	6.78	117	5	113	1	107	1	130	100
89	8.62	117	5	77	30.50	104	2.5	89	1	-	-	117	2.35
57	15.52	99	6	53	3.40	89	1	-	-	-	-	102	1
43	32.75	89	3	-	-	-	-	-	-	-	-	89	1
29	2.0	57	75.43	-	-	-	-	-	-	-	-	-	-
-	-	39	3.5	-	-	-	-	-	-	-	-	-	-

Table-2a: Electronic charges of atoms of 1

R	C ₁	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	C ₉	C ₁₀	C ₁₁
CH ₃	0.414	0.426	-0.321	-0.207	-0.149	-0.212	-0.109	-0.175	0.050	0.210
CH ₃ CH ₂	0.414	0.425	-0.319	-0.206	-0.145	-0.211	-0.110	-0.175	0.045	0.209
C ₆ H ₅	0.414	0.423	-0.328	-0.198	-0.157	-0.215	-0.109	-0.185	0.034	0.271
<i>p</i> ClC ₆ H ₄	0.412	0.426	-0.315	-0.202	-0.151	-0.214	-0.111	-0.176	0.047	0.265
<i>p</i> (CH ₃) ₂ NC ₆ H ₄	0.414	0.428	-0.334	-0.202	-0.151	-0.216	-0.112	-0.181	0.054	0.285
<i>p</i> NO ₂ C ₆ H ₄	0.406	0.417	-0.240	-0.139	-0.179	-0.086	-0.117	-0.151	0.030	0.364
<i>p</i> CNC ₆ H ₄	0.413	0.425	-0.300	-0.197	-0.150	-0.209	-0.112	-0.175	-0.038	0.247

Table-2b: Electronic charges of atoms of 1

R	C ₁₂	C ₁₃	C ₁₄	C ₁₅	C ₁₆	C ₁₇	O ₁	O ₂	O ₃	O ₄
CH ₃	-0.351	-	-	-	-	-	-0.301	-0.285	-0.355	-0.307
CH ₃ CH ₂	-0.254	-0.349	-	-	-	-	-0.300	-0.286	-0.354	-0.307
C ₆ H ₅	-0,112	-0,136	-0,203	-0,164	-0,199	-0,141	-0.319	-0271	-0.341	-0.299
pClC ₆ H ₄	-0.107	-0.132	-0.190	-0.057	-0.188	-0.135	-0.294	-0.271	-0.373	-0.306
P(CH ₃) ₂ NC ₆ H ₄	-0.180	-0.083	-0.273	0.152	-0.270	-0.091	-0.307	-0.286	-0.363	-0.308
pNO ₂ C ₆ H ₄	-0,159	-0,133	-0,144	-0,054	-0,147	-0,132	-0.210	-0.237	-0.292	-0.217
pCNC ₆ H ₄	-0.085	-0.151	-0.157	-0.007	-0.158	-0.147	-0.297	-0.284	-0.362	-0.299

Table-2c: Charge of atoms of substituent X

X	Cl	N	C	O	O
Cl	-0,0108	-	-	-	-
(CH ₃) ₂ N	-	-0.383	-0.188	-	-
NO ₂	-	0.518	-	-0.297	-0.305
CN	-	-0.061	0.068	-	-