

Fragmentation Study of Substituted Chalcones: Gas Phase Formation of Benz-1-oxin Cation

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Abstract

The mass spectra of a number of substituted chalcones have been observed to show intense M - X peaks (where X=Cl, Br, OH, OMe), which largely arise through the loss of an ortho-substituent from the ring-A of chalcones. The base peak is attributed to highly resonance stabilized benz-1-oxin cation, which would be formed via modified McLafferty rearrangement in gas phase (70 eV). The exact mass measurement of such fragments and DFT studies supports the formation and stability of benz-1-oxin cation. This protocol may also be conveniently used to distinguish among different positional isomers of substituted chalcones.

Keywords: Chalcone; Mass spectrometry; McLafferty rearrangement; Benz-1-oxin cation; Gas phase intramolecular substitutions

Introduction

Chalcones (1,3-diaryl-2-propen-1-ones) represent a diverse group of natural and synthetic compounds having an array of biological activities. These secondary metabolites serve as key precursors in the synthesis of many biologically important compounds such as benzothiazepine, pyrazolines, 1,4-diketones, and flavones. A longstanding scientific endeavor has demonstrated that chalcones display a broad spectrum of pharmacological activities including antimalarial [1], anticancer [2], antibacterial [3], anti-inflammatory [4], antifungal [5], antipyretic, antimutagenic [6], antioxidant [7], cytotoxic, antitumor [8], etc. Since chemical/biological (re) activities are associated with structural properties of a compound, a detailed structural profile has to be established in order to predict a compound's reactivity/structure before and after metabolism. Among all spectroscopic/spectrometric techniques, mass spectrometry is one of the most frequently employed structural elucidation techniques.

Mass spectrometry (MS) has been widely employed for the structural characterization of chalcones. The simplest chalcone has been reported to display a quite straight forward fragmentation pattern; however, surprisingly, the fragmentation pattern of chalcones changes dramatically with rather small changes in substituents [9]. Numerous efforts have been devoted to structural characterization of chalcones by employing soft-ionization techniques [10-16]. A few of such techniques include: ESI [17], ESI tandem MS [18], CI [19,20], FD [21], FAB [22] and DART [23]. Although a significant number of reports are available on use of the soft-ionization for MS of chalcones; the literature concerning use of harsh ionization techniques (like EIMS) for the study of fragmentation pattern of chalcones still remains to be sporadic [24].

Herein, we wish to report a detailed study of mass fragmentation pattern of substituted chalcones, benzylidene indanones and benzylidene tetralone under harsh EIMS conditions. The study also involves calculation of the relative free energy change of the possible fragments / ion structures of proposed benz-1-oxin cation based on computational evidence.

Experimental

The TLC was carried out on pre-coated silica gel (0.25 mm thick layer over Al sheet, Merck) with fluorescent indicator. The spots were visualized under UV lamps (365 nm and 254 nm λ) of 8 W power and/

or KMnO₄ dip upon heating. The compounds were purified either on a glass column packed silica gel (0.6 mm-0.2 mm, 60 Å mesh size, Merck) or by crystallization. All solutions were concentrated under reduced pressure (25 mmHg) on a rotary evaporator (Laborota 4001, Heidolph) at 35°C -40°C. Melting points were determined using a MF-8 (Gallenkamp) instrument and are reported uncorrected. The IR-spectra are recorded on Prestige 21 spectrophotometer (Shimadzu) as KBr discs. The ¹H (300 MHz, 400 MHz and 500 MHz) and ¹³C NMR (75 MHz) are recorded on AM-300 MHz, 400 MHz and 500 MHz instrument (Bruker) in CDCl₃ using TMS as internal standard.

The chalcones, arylidene tetralones and arylidene indanones were prepared by our reported procedure in excellent yields. All chalcones, arylidene tetralone and arylidene indanones were synthesized by Claisen-Schmidt condensation of the appropriate benzaldehyde and ketone under silica-H₂SO₄ catalyzed conditions [25].

General procedure for the silica sulfuric acid (SSA) catalyzed synthesis of chalcones

The SSA (0.02 g) was added to a well stirred suspension of ketone (7.53 mmol, 1 eq) and aromatic aldehyde (7.91 mmol, 1.05 eq) and the resulting mixture was heated at 65°C for 1.5 hr. The reaction mixture was cooled to ambient and partitioned between brine (25 mL) and CH₂Cl₂ (3 × 15 mL). The combined organic extract was washed with brine (3 × 25 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the chalcone in excellent yields (78%-93%).

Mass spectrometer experiments

The LR EI-MS studies were carried out on MAT312 machine by a heated inlet system or with a heated-cooled probe with the lowest feasible sample temperature and ionization was carried

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out under electron impact (70 eV) conditions. All the elemental compositions given for the $[M]^+$ and $[M-X]^+$ were obtained by exact mass measurements carried out by the peak-matching method. The perfluorokerosene (PFK) was used as reference for the determination of exact masses. The mass resolution was set at 10,000 (approx) with an external calibration mode.

The HR EIMS experiments were performed on a Thermo Finnigan MAT 95 XP double focusing mass spectrometer (Thermo Fisher Scientific, Germany). The N_2 was used as the sheath gas and auxiliary gas. The EI conditions were as follows: ion source temperature: 250°C; ion source vacuum: 3.4×10^{-6} mbar; analyzer vacuum: 4.1×10^{-7} mbar; DI probe temperature: 40°C up to 360°C; electron energy: 70 eV and accelerating voltage: 5759 V. Data acquisition and analysis were carried out with the Xcalibur software package (ver. 1.4 SR1; Thermo Fisher Scientific). The Gaussian 09 program package was used for all DFT calculations [26].

Results and Discussion

As a step towards green chemistry, the chalcones and benzylene indanone/tetralones were prepared under solvent free conditions by making use of silica- H_2SO_4 [25]. The condensation of aldehydes and ketones at 65°C in the presence of SSA afforded chalcones in high yields (Scheme 1, Table 1).

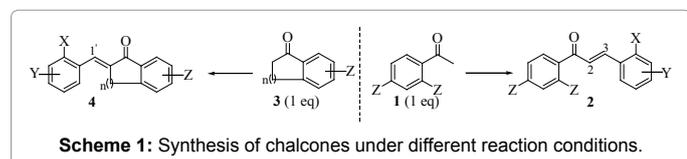
Reagent and conditions

ArCHO (1.05 eq), SSA, 65°C, 1.5 hr, neat

The formation of chalcones was indicated by a decrease in C=O stretching ν and a bathochromic shift in the UV spectra of products. The 1H NMR of the open chain chalcones showed the presence of olefinic protons exhibiting J_{trans} , whereas the benzylidene indanone/tetralone based chalcones displayed a single olefinic proton which appeared as a broad singlet in majority of the cases (Table 1).

The single crystal XRD of crystalline samples confirmed the structures of products beyond doubt (Figure 1) [27]. The Mass fragmentation pattern of simplest chalcone **5** has been studied extensively. It has been reported that in addition to the expected α -cleavage pattern, characteristic for carbonyl compounds, the fragmentation of **5** involve the formation of highly resonance stabilized benz-1-oxin radical **8** via loss of H radical (route a) [15,26] and phenylpropynone **8** through loss of a benzene molecule (route b) (Scheme 2) [15].

On the other hand, the fragmentation of 2-nitrochalcones has been reported to be very simple with suppressed characteristic fragmentation pattern of chalcones. Baldas et al. have explained in detail the effect of presence of NO_2 at C-2 that provides anchimeric assistance for the formation of benzoyl cation [15]. We have recently observed a quite surprising pattern in the fragmentation pathway of chalcones with substituents at C-2 of ring-A. Based on our current findings we wish to disclose that under EI conditions, the fragmentation pattern of chalcones derivatives is not only influenced by the presence of NO_2 group at C-2; any substituent at C-2 affects the fragmentation pattern in a similar manner. Such fragmentation pattern involves the loss of a substituent at C-2 and the resultant cation in turn, appears as a base peak in almost all cases [28].



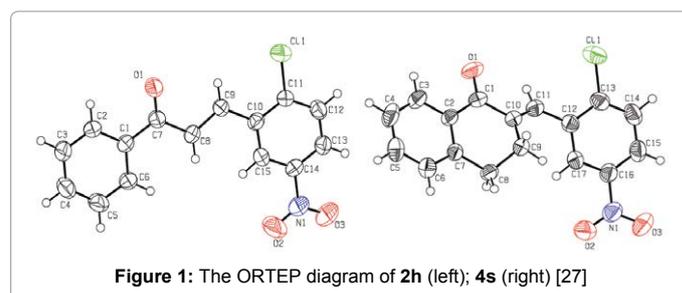
Entry	X	Y	Z	n	Product	Percentage yield (%)	δ_H^a (J in Hz)		
							H ^{2b}	H ^{3b}	H ^{1c}
1a	H	H	Cl	-	2a	87	7.15 (16.2)	7.49 (16.2)	-
1b	Cl	5-NO ₂	H	-	2b	95	7.70 (15.9)	8.20 (15.9)	-
1c	OMe	H	Cl	-	2c	83	7.15 (16.0)	7.77 (16.0)	-
1d	Cl	H	Cl	-	2d	88	7.37 (16.4)	7.97 (16.4)	-
1e	OMe	3-OMe	Cl	-	2e	88	7.14 (16.5)	7.78 (16.5)	-
1f	Cl	6-Cl	Cl	-	2f	91	7.31 (16.4)	7.62 (16.4)	-
1g	NO ₂	H	Cl	-	2g	89	7.03 (15.9)	7.92 (15.9)	-
1h	Cl	5-NO ₂	Cl	-	2h	93	7.66 (15.3)	8.19 (15.3)	-
3a	H	H	H	1	4a	87	-	-	7.93
3b	Br	H	H	1	4b	91	-	-	7.95
3c	Cl	H	H	1	4c	82	-	-	8.03
3d	H	3-Cl	H	1	4d	91	-	-	7.69
3e	H	4-Cl	H	1	4e	90	-	-	7.55
3f	Cl	4-Cl	H	1	4f	79	-	-	7.49
3g	Cl	6-Cl	H	1	4g	86	-	-	7.36
3h	Cl	5-NO ₂	H	1	4h	80	-	-	8.01
3i	OMe	H	H	1	4i	87	-	-	8.13
3j	H	3-OMe	H	1	4j	88	-	-	7.63
3k	OMe	3-OMe	H	1	4k	89	-	-	8.03
3l	H	3,4-(OMe) ₂	H	1	4l	85	-	-	7.18
3m	OH	3-Me	H	1	4m	81	-	-	7.85
3n	2-OH	H	H	1	4n	78	-	-	7.61
3o	H	4-OH	H	1	4o	82	-	-	7.58-7.63
3p	H	3-NO ₂	H	1	4p	85	-	-	8.53
3q	Cl	H	H	2	4q	92	-	-	7.82
3r	Cl	4-Cl	H	2	4r	93	-	-	7.94
3s	Cl	5-NO ₂	H	2	4s	91	-	-	8.71-8.73
3t	H	4-OMe	H	2	4t	92	-	-	7.83

^achemical shifts are reported in ppm & coupling constants are reported in Hz.

^bdoublet showing J_{trans}

^cbroad singlet was observed in majority of cases.

Table 1: The percentge yield and δ_H of olefinic protons in synthesized chalcones.

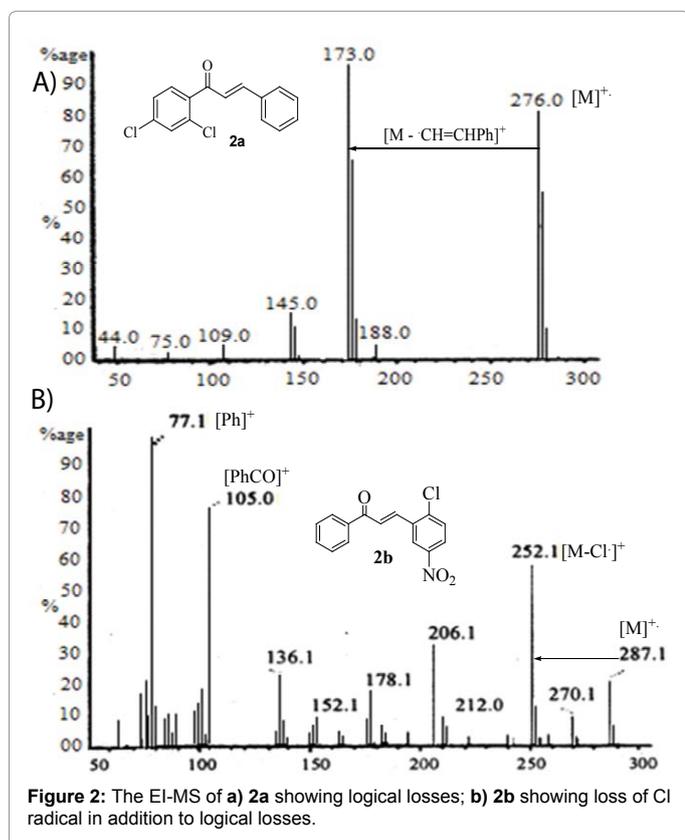
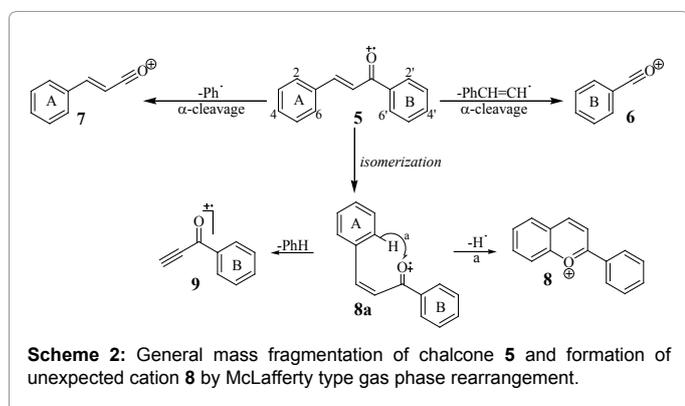


In order to ascertain the role of substituent on ring-B on the fragmentation pattern, compound **2a** (2',4'-dichlorinated derivative) was subjected to fragmentation under EI. The resulting spectrum seemed to be very simple with a prominent $[M]^+$. Along with a base peak, corresponding to 2,4-dichlorobenzoyl cation (m/z 173 amu, 175 amu, 177 amu) appearing in 9:6:1 (100%, 62%, 11% respectively), a characteristic pattern for the dichlorinated compounds. The lack of loss of Cl radical indicated that the substituent on ring B does not influence the fragmentation pattern of chalcones (Figure 2a).

The influence of ring-A substituents on the fragmentation pattern of chalcones derivatives was compared with ring-B substituted chalcones. To this end, chalcone **2b**, bearing 2-chloro-5-nitro groups on ring-A

was subjected to fragmentation under EI conditions. The resultant mass spectrum indicated a prominent $[M-Cl]^+$ peak. However, no significant loss corresponding to NO_2 was observed (Figure 2b), which indicated that only substituent at C-2 of ring-A influences the fragmentation pattern of such compounds.

The mass spectra of chalcones derivatives containing monosubstitution (at C-2) or disubstitutions (at C-2 and C-3 or C-2 and C-6) on ring-A and 2,4-dichlorosubstitutions on ring-B have revealed that the fragmentation pattern of these derivatives entirely depend on the location of the substituent on ring-A only (Figure 2). On the other hand, 2,4-dichloro substitutions on ring-B don't seem to be playing any significant role in the fragmentation pattern except the formation of fragment ion **6** by α -cleavage. The spectra of such chalcones display the formation of 2,4-dichlorobenzoyl cation (m/z 173 amu, 175 amu, 177 amu) in 9:6:1, appearing either as a base peak or a significant fragment ion. However, without any exception, loss of



substituent at C-2 of ring-A afforded either a significant fragment ion or base peak in almost all cases. In case of chalcones derivatives bearing monosubstitution at C-2 of ring-A, such as compounds **2c** (2-OMe) (Figure 3a), the $[M-OMe]^+$ fragment (m/z 275 amu, 277 amu, 279 amu) in 9:6:1 (43%, 28%, 5%) appeared as a prominent peak whereas in case of compound **2d** (2-Cl) (Figure 3b), $[M-Cl]^+$ fragment ion formed the base peak (100%, 70%, 12%) (Table 2).

Similarly, when compounds containing di substitutions on ring-A, for instance **2e** (2,3-dimethoxy substitutions) (Figure 3c) and **2f** (2,6-dichloro substitutions) (Figure 3d), were subjected to EI conditions, the same pattern was observed i.e., the cleavage of $[M-X]$ along with α -cleavage which resulted in a prominent 2,4-dichlorobenzoyl cation. However, no $[M-NO_2]$ loss was observed when chalcone **2g** was subjected to fragmentation under EI conditions. Likewise in case of compound **2h**, quite intense peaks due to $[M-Cl]$ were observed at 320, 322, 324 amu in 9:6:1 (97%, 62%, 11%) with the 2,4-dichlorobenzoyl cation forming the base peak (Table 2). In the cases of all disubstituted chalcones no further loss was observed after the first loss of substituent. In contrast to the findings of Baldas and Porter [15], no $[M-H]$ ion was observed in these cases.

The cleavage of a C-X (aryl-X) bond is not a frequently observed mode of fragmentation. Based on our findings, we propose that C-X cleavage occurs via gas phase isomerization of chalcone followed by

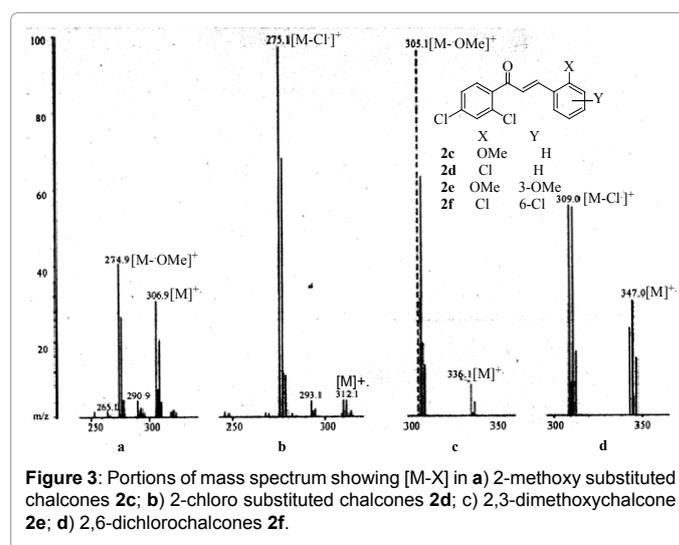


Figure 3: Portions of mass spectrum showing $[M-X]^+$ in **a) 2-methoxy substituted chalcones 2c**; **b) 2-chloro substituted chalcones 2d**; **c) 2,3-dimethoxychalcone 2e**; **d) 2,6-dichlorochalcones 2f**.

	X	Y	Z	$[M]^+$ amu, (%)	$[M-X]^+$ amu, (%)	A amu, (%)
2a	H	H	Cl	276 (82), 278 (55), 280 (9)	-	173 (100), 175 (62), 177 (11)
2b	Cl	5-NO ₂	H	287 (23), 289 (7)	252 (61)	105 (78)
2c	OMe	H	Cl	306 (32), 308 (21), 310 (4)	275 (43), 277 (28), 279 (5)	173 (100), 175 (69), 177 (11)
2d	Cl	H	Cl	310 (4), 312 (5), 314 (1), 316 (0)	275 (100), 277 (67), 279 (12)	173 (34), 175 (23), 177 (4)
2e	OMe	3-OMe	Cl	336 (7), 338 (4), 340 (0)	305 (100), 307 (64), 309 (14)	173 (45), 175 (34), 177 (8)
2f	Cl	6-Cl	Cl	344 (24), 346 (31), 348 (16), 350 (0), 352 (0)	309 (56), 311 (56), 313 (18), 315 (0)	173 (100), 175 (65), 177 (11)
2g	NO ₂	H	Cl	321 (0), 323 (0), 325 (0)	275 (15), 277 (10), 279 (2)	173 (100), 175 (68), 177 (12)
2h	Cl	5-NO ₂	Cl	355 (9), 357 (9), 359 (0), 361 (0)	320 (97), 322 (62), 324 (11)	173 (100), 175 (66), 177 (10)

Table 2: Logical fragments of chalcones formed under EI conditions.

a McLafferty type of rearrangement in which the oxygen of the C=O facilitates the C-X bond cleavage and hence the formation of benz-1-oxin cation (Scheme 3). The peak matching experiment confirmed the [M-X] assignment to be correct.

In order to justify our findings, several highly substituted chalcones were subjected to fragmentation under EI conditions which supported our observation and resulted in the formation of benz-1-oxin as a base peak in almost all cases (Scheme 4, Table 2).

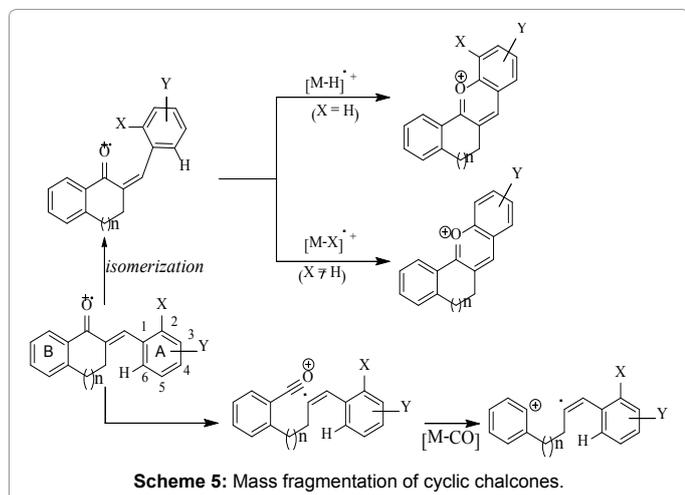
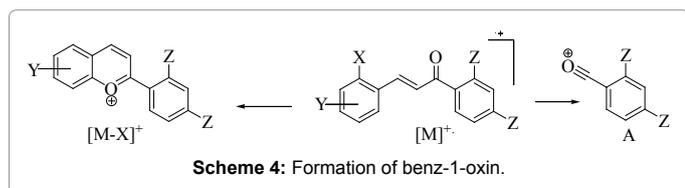
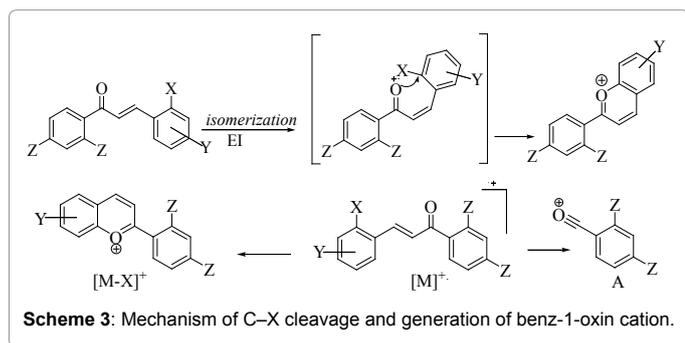
Inspired by the tendency of chalcones to undergo [M-X] cleavage forming benz-1-oxin cation in gas phase EI conditions, we studied the fragmentation behavior of various substituted cyclic chalcones (i.e., arylidene indanones and arylidene tetralones) under EI conditions. Surprisingly, arylidene indanone /tetralones substituted at C-2 exhibited the same pattern of [M-X] cleavage and the resulting cation formed base peak in almost all cases. However, when the substitution at C-2 becomes OH (2-OH), as in **4m**, the fragment ion [M-·OH] doesn't appear as a prominent peak.

In case of cyclic chalcones substituted at C-3 and/or C-4, [M-X] didn't appear as prominent peak; [M-H⁺] forms a reasonably stable fragment instead. The loss of neutral CO was also observed as a minor signal in few cyclic chalcones (Scheme 5, Table 3). In order to confirm that the loss of H radical does not originate from the aliphatic

methylene carbon or ring B, chalcone **4g** (2,6-dichloro substitution on ring A) was subjected to EI conditions. As was expected, no [M-H⁺] was observed which confirmed that the generation of [M-H⁺] does not takes place from ring B or the methylene carbon but rather occurs from ring A. In addition, it was also established that in case of **4a**, H at C-2 was lost, forming a benz-1-oxin cation; an observation consistent with the findings of Baldas et al. [15].

The peak matching results of some selected acyclic (**2b**, **2e**) and cyclic chalcones (**4b**, **4i**, **4q**, **4r**) were observed to be in close agreement with calculated values, assuring the formation of targeted chalcones. Furthermore, the peak matching results of their corresponding benz-1-oxin [M-X] cation also showed very minute difference (0.4-1.5 millimass unit) in calculated and observed values (Table 4), which confirmed the assignment to be correct.

The DFT calculations were performed by taking into consideration four hypothetical isomers (**9a-d**) of benz-1-oxin cations, which originates from **4d-4g**. The molecular ion of **4d-4g** shows poor abundance (means poor stability) while their corresponding benz-1-oxin cations (isomers **9a**, **9b** and **9d**) shows base peak/high abundance (Table 3), which reflects high stability. The structures of isomers (**9a-d**) were optimized in gas phase using B3LYP functional and 6-311+G(d) basis set. The HOMO (Highest Occupied Molecular Orbital)-LUMO (Lowest Unoccupied Molecular Orbital) analysis was carried out to locate the charge transfer place within the molecule. The visualization of the electron charge was obtained using the Gauss View program. The intramolecular charge transfer has also been confirmed by HOMO-LUMO analysis (Figure 4). The frontier molecular orbitals (HOMO-LUMO) and their properties, such as energy, are very useful for physicist and chemists and are of prime significance in quantum chemistry. The frontier molecular orbitals make use of frontier electron density for predicting the most reactive position in π-electron systems



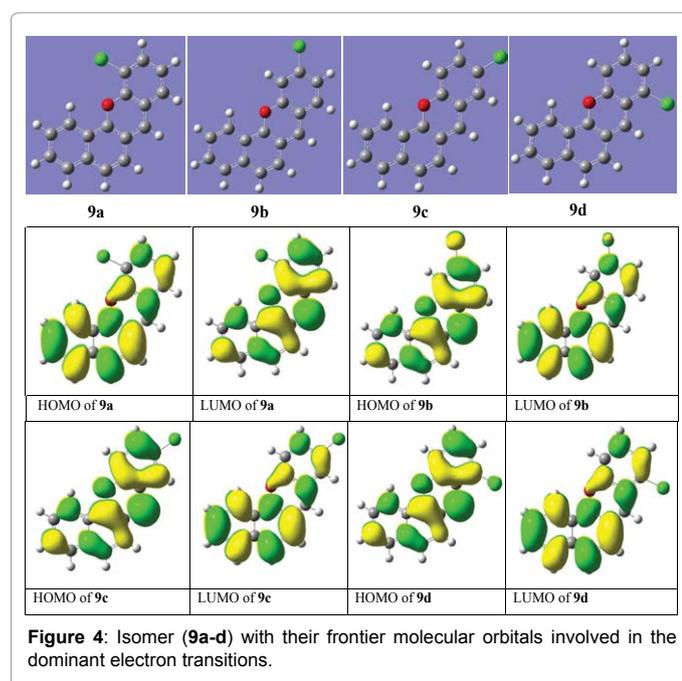
	n	X	Y	[M] ⁺ amu (% abundance)	[M-X] ⁺ amu, (%)	[M-H] ⁺ amu (% abundance)	[M-CO] ⁺ amu (%)
4a	0	H	H	220 (64)	-	219 (100)	192 (24)
4b	0	Br	H	298 (31), 300 (32)	219 (100)	-	-
4c	0	Cl	H	254 (3), 256 (1)	219 (100)	-	-
4d	0	H	3-Cl	254 (5), 256 (2)	219 (87)	-	-
4e	0	H	4-Cl	254 (33), 256 (13)	219 (25)	-	-
4f	0	Cl	4-Cl	288 (9), 290 (10), 292 (4)	253 (100), 255 (38)	-	-
4g	0	Cl	6-Cl	288 (4), 290 (3), 292 (0)	253 (100), 255 (45)	-	-
4h	0	Cl	5-NO ₂	299 (10), 301 (3)	264 (100)	-	271 (2), 273 (0)
4i	0	OMe	H	250 (5)	219 (100)	249 (2)	-
4j	0	H	3-OMe	250 (100)	219 (21)	249 (57)	-
4k	0	OMe	3-OMe	280 (17)	249 (100)	-	-
4l	0	H	3,4-(OMe) ₂	280 (100)	249 (41)	265 (39)	-
4m	0	OH	3-Me	266 (100)	251 (19)	265 (74)	-
4n	0	2-OH	H	236 (84)	219 (58)	235 (43)	208 (18)
4o	0	H	4-OH	236 (100)	-	235 (71)	208 (30)
4p	0	H	3-NO ₂	265 (42)	219 (35)	264 (24)	237 (2)
4q	1	Cl	H	268 (3), 270 (1)	233 (100)	267 (2)	-
4r	1	Cl	4-Cl	302 (4), 303(3), 304 (3)	267 (100), 269 (37)	-	-
4s	1	Cl	5-NO ₂	315 (21), 317 (6)	280 (81)	-	-
4t	1	H	4-OMe	264 (86)	233 (37%)	263 (100%)	-

Table 3: Logical fragments of cyclic chalcones formed under EI conditions.

Entry	[M] ⁺			[M - X] ⁺		
	Calculated (formula) ^A	Observed	Δ (mmu)	Calculated (formula) ^A	Observed	Δ (mmu)
2b	287.0349 (C ₁₅ H ₁₀ O ₃ NCI)	287.0343	0.6	252.0661 (C ₁₅ H ₁₀ O ₃ N)	252.0655	0.5
2d	336.0320 (C ₁₇ H ₁₄ O ₃ Cl ₂)	336.0322	0.2	305.0136 (C ₁₆ H ₁₁ O ₂ Cl ₂)	305.0145	0.9
4b	297.9993 (C ₁₆ H ₁₁ OBr)	297.9998	0.5	219.0810 (C ₁₆ H ₁₁ O)	219.0800	1.0
4i	250.0994 (C ₁₇ H ₁₄ O ₂)	250.0981	1.2	219.0810 (C ₁₆ H ₁₁ O)	219.0799	1.1
4q	268.0655 (C ₁₇ H ₁₃ OCl)	268.0664	0.9	233.0966 (C ₁₇ H ₁₃ O)	233.0970	0.4
4r	302.0265 (C ₁₇ H ₁₂ OCl ₂)	302.0256	0.9	267.0577 (C ₁₇ H ₁₂ OCl)	267.0592	1.5

^AOnly the peak matching results of most abundant isotope is reported here.

Table 4: Peak matching results of [M]⁺ and [M - X]⁺ of a few chalcones.



System	Point group (P)	Dipole moment (D)	Total energy (a.u.)
1	C ₁	2.0863	-1189.2479
2	C ₁	2.4483	-1189.2510
3	C ₁	2.3739	-1189.2509
4	C ₁	1.5970	-1189.2504

Table 5: Point group, dipole moment (Debye) and total bonding energy (a.u.) of 9(a-d).

and also explain several types of reactions in conjugated system. The conjugated molecules are characterized by a small HOMO-LUMO separation. Both the HOMO and LUMO are the main orbitals, which take part in chemical stability. The HOMO represents the ability to donate an electron, LUMO as an electron acceptor, represents the ability to gain an electron.

The HOMO and LUMO energy calculated by B3LYP/6-311+G(d) method is shown in Table 5. All isomers (9a-d) showed almost equal energy but isomer 9b may be considered relatively more stable among all (Table 5). It reflects that the presence of a substituent (Y) on variable positions of ring A of 4 does not make that big difference in the energies/stabilization of resulting benz-1-oxin cations. The

major contributor towards the high stability of benz-1-oxin cations is resonance stabilization. It supports our hypothesis as described in Scheme 5.

Conclusion

The gas phase loss/substitution of δ-substituent (substituent at C-2) of ring A of chalcones/arylidene indanones and tetralones has been confirmed to occur via a McLafferty type rearrangement. The hypothesis is supported by HR MS and DFT studies. This report of gas phase formation of benz-1-oxin from δ-substituted chalcones is an important breakthrough that can be employed to identify ortho-substituted chalcones from those with different substitution patterns.

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