JOC Article

Intrinsic Gas-Phase Reactivity of Ionized 6-(Oxomethylene)cyclohexa-2,4-dienone: Evidence Pointing to Its Neutral α-Oxoketene Counterpart as a Proper Precursor of Various Benzopyran-4-ones and Analogues

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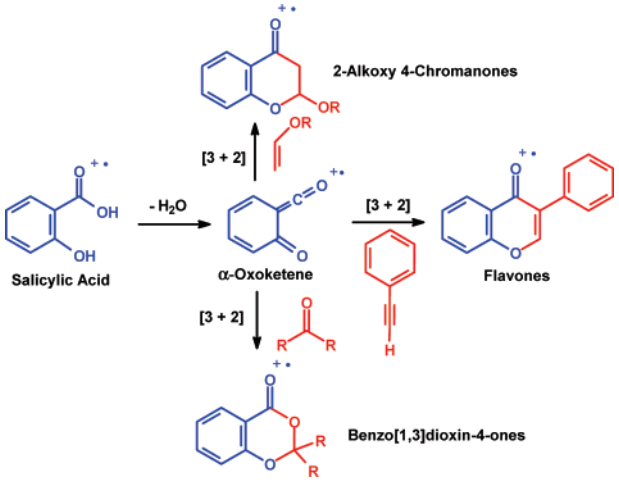

Despite its unique structure and potential use as an important building block in organic synthesis, the title α-oxoketene **1** has been formed mostly under very special conditions as a short-lived species. The reactivity of **1** is, therefore, nearly unexplored. In great contrast, it seemed that its ionized gaseous form $\mathbf{1}^{\bullet+}$ is stable and easily accessible. In this study, we used multiple-stage pentaquadrupole mass spectrometry to probe the formation of gaseous $\mathbf{1}^{\bullet+}$ and explore its stability and intrinsic reactivity. With water and methanol, gaseous $\mathbf{1}^{\bullet+}$ was found to react similarly to solvated **1**, which indicates that there is a close parallel between their reactivities. Gaseous $\mathbf{1}^{\bullet+}$ was also found to react promptly via polar [3 + 2] cycloadditons with various dienophiles including alkenes, alkynes, isocyanates, ketones and esters, thus forming a series of benzopyran-4-ones (flavones, 4-chromanones, 4-chromenones, benzo[1,3]dioxin-4-ones, and analogues) that are common structural units in many natural products. The present availability of **1** at room temperature and the gas-phase findings reported herein for gaseous $\mathbf{1}^{\bullet+}$ indicate that solvated **1** should undergo many [4 + 2] cycloadditions and functions as a versatile precursor of a variety of biologically active molecules.

Introduction

α-Oxoketenes are molecules of great synthetic utility.[1] Many of these rather reactive molecules have been found to act as versatile precursors and to participate promptly in a variety of reactions including nucleophilic additions, cycloadditions, unusual rearrangements, and DNA cleavage.[2] However, unless stabilized sterically or electronically,[1b] these interesting molecules are short-lived; hence, they are difficult to form and isolate in the condensed phase under ordinary reaction condi-

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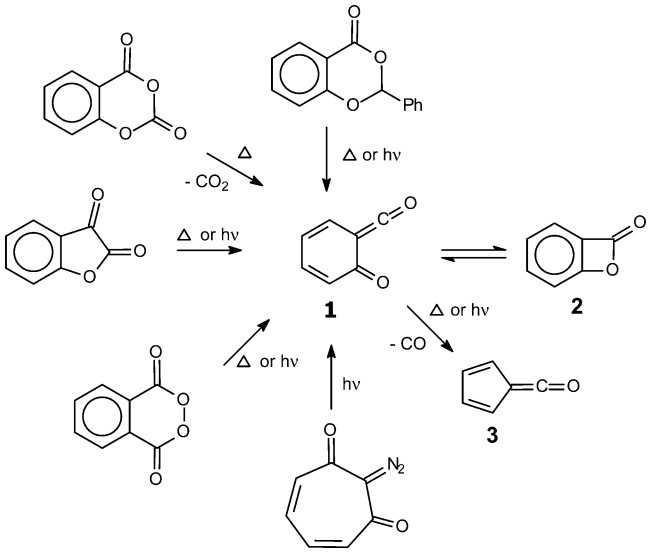
SCHEME 1



tions. The *o*-quinonoid α-oxoketene **1** with its cyclohexadiene ring is particularly attractive among the various α-oxoketenes owing to its unique restricted cyclic geometry and "nearly aromatic" nature and hence high reactivity that results from the aromaticity gain upon formation of salicylic acid derivatives.[1]

There have been, therefore, many attempts to form, trap, and study the reactivity of **1**.[1a] However, this interesting α-oxoketene had previously been trapped or characterized only under special conditions, and studies on the structure and reactivity of solvated **1** have been therefore only incidental. The successful efforts to prepare **1** employed pyrolysis or photolysis of proper precursors (Scheme 1) mainly under an argon matrix at 8−12 K.[3] Characterization of **1** has been restricted to IR spectroscopy,[4] whereas its trapping has been accomplished via simple nucleophilic addition of water and alcohols.[1a] More recently, however, the hope that **1** may become a useful and more readily accessible precursor in organic synthesis has greatly increased since Tidwell and collaborators showed, for the first time, that **1** can be formed at room temperature in an acetonitrile solution. They also measured the kinetics of the reactivity of solvated **1** with water, methanol, and diethylamine using time-resolved IR spectroscopy.[5]

In great contrast to the solvated **1**, gaseous $\mathbf{1}^{\bullet+}$ has long been known to be an easily accessible and apparently stable species.[6] In this work, we show that gaseous $\mathbf{1}^{\bullet+}$ is indeed easily accessible and stable in the gas phase and have screened its reactivity toward cycloadditions via a systematic series of gas-phase experiments. Our findings indicate that the reactivity of gaseous $\mathbf{1}^{\bullet+}$ parallels that of the short-lived solvated α-oxoketene **1** and that it may function as a versatile precursor for the preparation of molecules with high biological activity.

Experimental Section

The MS^2 and MS^3 experiments[7] were performed using an Extrel (Pittsburgh, PA) pentaquadrupole (QqQqQ) mass spectrometer.[8] The QqQqQ consists of three mass-analyzing quadrupoles (Q1, Q3, Q5), in which ion mass selection and mass analysis are performed, and two radio-frequency-only reaction quadrupoles (q2, q4). Reactions were then performed in q2 with neutral reactants. For the MS^2 experiments, $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 was generated by dissociative 70 eV electron ionization (EI) of salicylic acid and isolated by selection with Q1. After its ion/molecule reactions in q2 with the neutral reagents, Q5 was used to record the product ion mass spectrum, while Q3 and q4 were operated in the "full" ion-transmission rf-only mode.

For the MS^3 experiments, a reaction product ion of interest was selected in Q3 and dissociated by collisions with argon in q4, while Q5 was scanned across the desired *m*/*z* range to record the sequential product triple-stage (MS^3) mass spectra. Nominal sample and neutral gas pressures were typically 5×10^{-6} and 5×10^{-5} torr, respectively, as monitored by a single-ionization gauge located centrally in the vacuum chamber. The target gas pressure corresponds to a typical beam attenuation of 50−70%, viz., to multiple-collision conditions. However, lower reaction yields, but similar sets of products, were always observed at lower pressure, mainly single-collision conditions in q2. Instrument parameters such as quadrupole offset potentials and lens voltages were adjusted to maximize the abundance of the ion/molecule products. The collision energies, calculated as the voltage difference between the ion source and the collision quadrupole, were typically near 1 eV for ion/molecule reactions and 15 eV for collision-induced dissociation (CID).

Molecular orbital calculations were performed using GAUSSIAN98. The electronic energy after full structure optimization was obtained via unrestricted MP2/6-311G+(d,p) calculations. The geometry and energy of the investigated species are available from the authors upon request. All species have been characterized as energy minima by displaying only positive vibrational frequencies.

Results and Discussion

Generation of Gaseous $\mathbf{1}^{\bullet+}$. In the gas phase, $\mathbf{1}^{\bullet+}$ has been assumed to be formed as a major fragment ion via the dissociation of many ionized molecules, most particularly of salicylic acid and its derivatives.[6] We have therefore selected to form the putative $\mathbf{1}^{\bullet+}$ via 70 eV EI of salicylic acid, which is accompanied by dissociation of the molecular ion by water loss driven by an *ortho* effect (Scheme 2). Although the nascent ion of *m*/*z* 120 is easily rationalized to be the desired gaseous $\mathbf{1}^{\bullet+}$, we were concerned that it could isomerize promptly. This concern was based on the observation that solvated **1** has been reversibly transformed photochemically into its isomeric form **2** (benzodioxetane; Scheme 1).[3] Theoretical calculations also showed that the ring-closed lactone **2** is 2.8 kcal mol^{-1} more stable than neutral **1** (at the highest level considered).[1] Although offset by ring strain, the ring-closed form **2** gains stability due to aromatic stabilization.

In the gas phase and for the ionized forms, however, we found an opposite order; that is, $\mathbf{1}^{\bullet+}$ is more stable than $\mathbf{2}^{\bullet+}$ by 8.7 kcal mol^{-1} at the MP2/6-311(+)G(d,p) level of theory (see the Supporting Information). The greater stability of $\mathbf{1}^{\bullet+}$ as com-

(1) For reviews see: (a) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219. (b) Kollenz, G.; Heilmayer, W.; Kappe, C. O.; Wallfisch, B.; Wentrup, C. *Croat. Chem. Acta* **2001**, *74*, 815. (c) Sato, M.; Iwamoto, K. *J. Synth. Org. Chem.* **1999**, *76*. (d) Tidwell, T. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5778. (d) Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.

(2) Nakatani, K.; Shirai, J.; Sando, S.; Saito, I. *J. Am. Chem. Soc.* **1997**, *119*, 7626.

(3) Chapman, O. L.; McIntosh, C. C.; Pacansky, J.; Calder, G. V.; Orr, G. *J. Am. Chem. Soc.* **1973**, *95*, 4061.

(4) Chapman, O. L.; McIntosh, C. L. *J. Am. Chem. Soc.* **1970**, *92*, 7001.

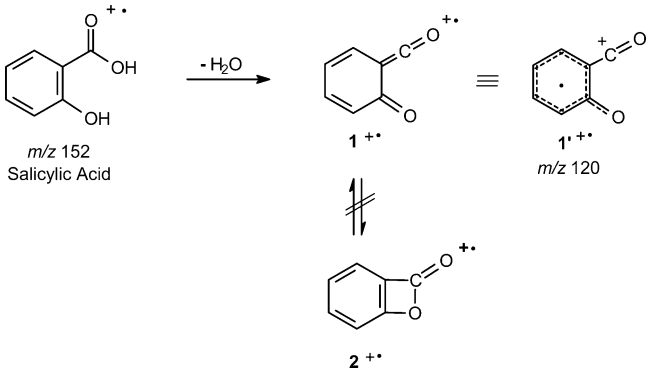
(5) Liu, R. C. Y.; Lusztyk, J.; McAllister, M. A.; Tidwell, T. T.; Wagner, B. D. *J. Am. Chem. Soc.* **1998**, *120*, 6247.

(6) (a) Emery, E. M. *Anal. Chem.* **1960**, *32*, 1495. (b) Aczel, T.; Lumpkin, H. E. *Anal. Chem.* **1961**, *33*, 386.

(7) Eberlin, M. N. *Mass Spectrom. Rev.* **1997**, *16*, 113.

(8) Juliano, V. F.; Gozzo, F. C.; Eberlin, M. N.; Kascheres, C.; doLago, C. L. *Anal. Chem.* **1996**, *68*, 1328.

SCHEME 2



pared to $\mathbf{2}^{\bullet+}$ may result mainly from a major contribution of distonoid[9] forms $\mathbf{1'}^{\bullet+}$ with the stabilizing effect of charge and spin separation and by extensive spin delocalization (Scheme 2). MP2/6-311(+)G(d,p) calculations corroborate this assumption since the ion is shown to display the positive charge mainly placed at the 6-oxomethylene group whereas the unpaired electron is substantially delocalized along the ring and the oxygen of the α-oxo group (see the Supporting Information).

Probing the Structure of Gaseous $\mathbf{1}^{\bullet+}$. To probe experimentally the structure of $\mathbf{1}^{\bullet+}$, we first dissociated the isolated gaseous ion via low-energy (10 eV) collisions with argon. The product ion mass spectrum (Figure 1) shows that $\mathbf{1}^{\bullet+}$ dissociates mainly by the loss of CO (Scheme $3c_1$)[10] to form an abundant fragment ion of *m*/*z* 92, likely the distonoid acylium ion $\mathbf{3}^{\bullet+}$. Note therefore that the "decomposition" behavior of gaseous $\mathbf{1}^{\bullet+}$ matches that of solvated **1**, which has been observed to undergo decarbonylation to carbonylcyclopentane **3** at 780 °C.[11] This matching of solution- and gas-phase decomposition behavior is evidence that points to similar reactivity between gaseous $\mathbf{1}^{\bullet+}$ and solvated **1**.

The distonoid acylium ion $\mathbf{1'}^{\bullet+}$ of *m*/*z* 120 may display a dual reactivity reflecting either its benzoyl cation or phenoxy radical nature, or both.[12] To explore the acylium ion nature of $\mathbf{1}^{\bullet+}$, two of the most characteristic reactions of gaseous acylium ions were tested: (a) polar transacetalization with 2,2-dimethyl-1,3-dioxolane[13] and (b) polar acetalization with vinylethylene glycol.[14] As Figure 2 exemplifies for polar transacetalization and Table 1 summarizes for both reactions (entries 1 and 2), the ion behaves exactly as expected if the predominance of the resonance form $\mathbf{1'}^{\bullet+}$ is considered. In reactions with 2,2-dimethyl-1,3-dioxolane, polar transacetalization occurs to a great

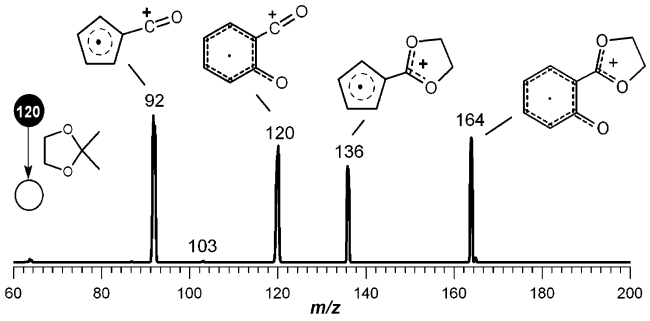
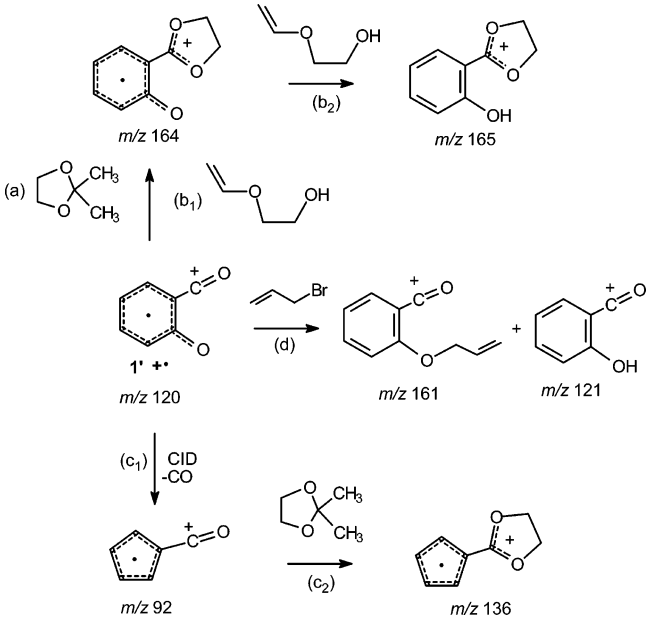


FIGURE 2. MS^2 for reactions of gaseous $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 with 2,2-dimethyl-1,3-dioxolane (102 Da).

SCHEME 3



extent at CO^+ to form the cyclic ionic acetal of *m*/*z* 164 (Scheme 3a). Another abundant product ion of *m*/*z* 136 is also formed concurrently owing to prompt transacetalization of the distonoid acylium ion $\mathbf{3}^{\bullet+}$ of *m*/*z* 92 (Scheme $3c_2$), which is the major fragment formed upon dissociation of $\mathbf{1}^{\bullet+}$ (Scheme $3c_1$ and Figure 1). Note that other competitive reactions, such as proton transfer that forms protonated 2,2-dimethyl-1,3-dioxolane of *m*/*z* 103, are nearly suppressed.

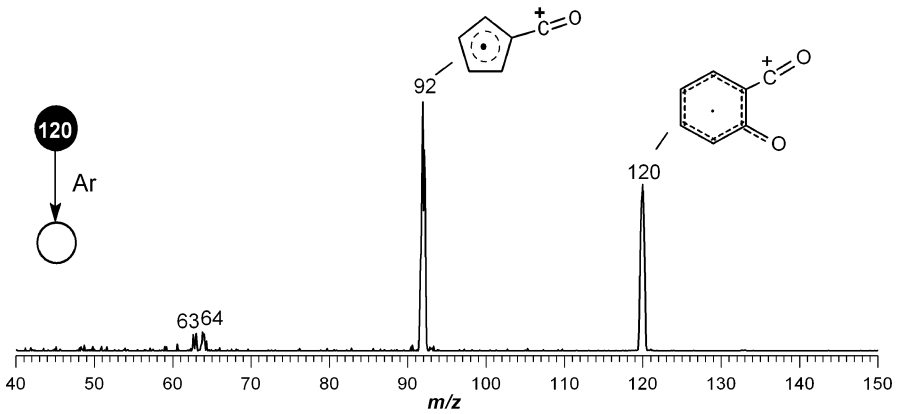
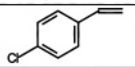
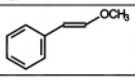
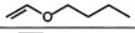
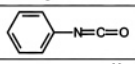
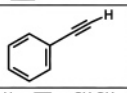
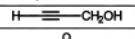


FIGURE 1. MS^2 for collision-induced dissociation of gaseous $\mathbf{1}^{\bullet+}$ of *m*/*z* 120.

TABLE 1. Major Product Ions Formed in Reactions of Gaseous $1^{\bullet+}$ of *m/z* 120 with Representative Neutral Reactants

Entry	Neutral Reactant	MW (Da)	Major Products[a] *m/z* (% relative abundance)[b]
1		102	164 (82), 103(1)
2		88	165(38), 164(100), 147(23), 73(62)
3		120	161(37), 121 (40), 81 (92), 79 (29)
4	H_20	18	138(100)
5	CH_3OH	32	152(100)
6	C_2H_5OH	46	166 (100)
7		104	104 (100), 208(92)[c]
8		138/140	138/140(100)
9		134	134(100)
10		53	173(2), 226(100)
11		72	192(88), 101(100)[d]
12		100	220(100), 185 (47), 159(32), 129(52)[e]
13		119	239(32), 119(100)
14		102	221(100), 204(99), 194(82), 102(37)
15		56	176(100), 131(12)
16		58	178(100), 163(5)
17		120	225 (100), 212(17)[f]
18		84	175(100)
19		84	204(76), 169(100)[g]
20		92/94	163(100)
21		88	208(100)
22		86	163(100)

[a] Under the low-energy (near zero) collisions used to favor bimolecular reactions, $1^{\bullet+}$ also dissociates to a major fragment ion of *m/z* 92, which sometimes appears to react further with the neutral reactant. These (usually minor) products most likely arising from this fragment ion are not reported. [b] Abundances of bimolecular products only. [c] Cycloaddition product of ionized styrene with neutral styrene. [d] The ion of *m/z* 111 is known to be formed via vinylation of ethyl vinyl ether due to self-reactions between the ionized and neutral molecule.[15] [e] The products of *m/z* 129, 159, and 185 appear to arise from reactions between the ionized and neutral butyl vinyl ether. [f] The nascent adduct of *m/z* 220 seems to lose CO to form the ion of *m/z* 212. [g] Proton-bound dimer of acetone[16] arising from a proton-transfer reaction.

In reactions with vinylethylene glycol (Table 1, entry 2), polar acetalization (Scheme $3b_1$) also occurs promptly to form the cyclic acetal of *m/z* 164 (the same product arising from polar transacetalization with 2,2-dimethyl-1,3-dioxolane, Scheme 3a), but the radical nature of $1^{\bullet+}$ also influences the reactivity of this distonoid acylium ion; hence, it reacts further with vinylethylene glycol, now as a radical, by H atom abstraction (Scheme $3b_2$). This dual charged-radical reactivity induces therefore the formation of an additional product ion of *m/z* 165.

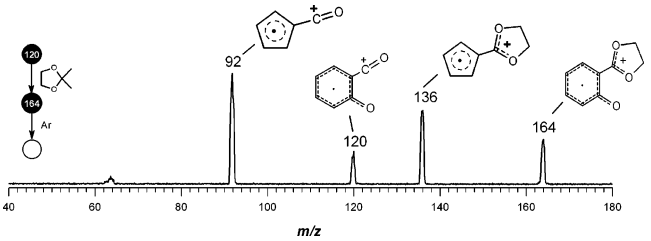
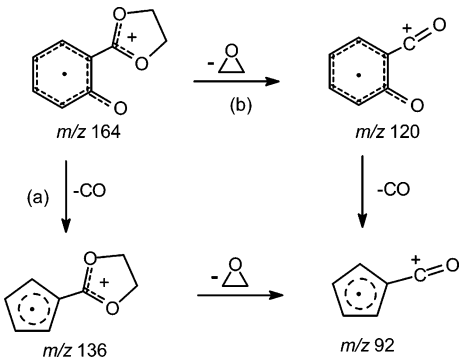


FIGURE 3. MS^3 of the product ion of *m/z* 164 formed by polar transacetalization of gaseous $1^{\bullet+}$ of *m/z* 120 with 2,2-dimethyl-1,3-dioxolane (102 Da).

SCHEME 4



With allyl bromide (Table 1, entry 3), $1^{\bullet+}$ reacts mainly as a radical by direct $Br^{\bullet}$ replacement (Scheme 3d)[17] to form the product ion of *m/z* 161 as well as by H abstraction to form the ion of *m/z* 121. This dual charged-radical behavior, which supports the distonoid nature of $1^{\bullet+}$, is similar to that observed in polar acetalization reactions of analogous distonic acylium ions.[12] Note that, as Table 2 summarizes, the structural assignments for the product ions just discussed are supported by their collision-induced dissociation chemistry. As a typical example, the cyclic ionic acetal of *m/z* 164 (Figure 3) dissociates by two structurally diagnostic routes [(a) consecutive CO plus ethylene oxide or (b) ethylene oxide plus CO losses], forming the major fragment ions of *m/z* 136, 120, and 92 (Scheme 4), whereas the cyclic ionic acetal of *m/z* 136 (Table 2) that misses the α-oxo group dissociates exclusively by ethylene oxide (Scheme 4b).

Both the characteristic dissociation and dual bimolecular chemistry of the ion of *m/z* 120 indicate therefore that, upon 70 eV EI of salicylic acid, the ionized form of the α-oxoketene $1^{\bullet+}$ is indeed formed as a stable, long-lived gaseous ion.

Reactions of Gaseous $1^{\bullet+}$ with Water and Methanol. In an acetonitrile solution and at room temperature, solvated **1** has been found to react promptly with water and methanol to form

(9) Tomazela, D. M.; Sabino, A. A.; Sparrapan, R.; Gozzo, F. C.; Eberlin, M. N. *J. Am. Soc. Mass Spectrom.* **2006**, *17*, 1014.

(10) Loss of CO from the α-oxo group of $1^{\bullet+}$ as opposed to that from the 6-oxomethylene group is predicted by MP2/6-311(+)G(d,p) calculations to be ca. −35 kcal mol^{-1} more energetically favored.

(11) Schulz, R.; Schweig, A. *Tetrahedron Lett.* **1979**, 59.

(12) (a) Moares, L. A. B.; Eberlin, M. N. *J. Am. Chem. Soc.* **1998**, *120*, 11136. (b) Moraes, L. A. B.; Eberlin, M. N. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 697.

(13) Cooks, R. G.; Chen, H.; Eberlin, M. N.; Zheng, X.; Tao, W. A. *Chem. Rev.* **2006**, *106*, 188.

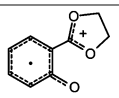
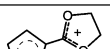
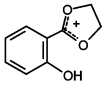
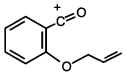
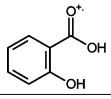
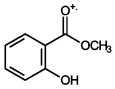
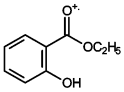
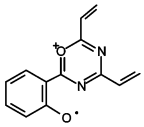
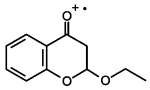
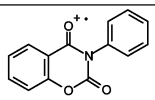
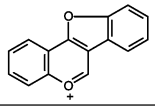
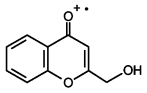
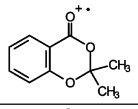
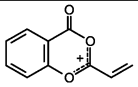
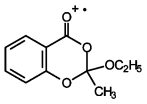
(14) (a) Moraes, L. A. B.; Pimpim, R. S.; Eberlin, M. N. *J. Org. Chem.* **1996**, *61*, 8726. (b) Morares, L. A. B.; Eberlin, M. N. *J. Am. Soc. Mass Spectrom.* **2001**, *12*, 150.

(15) (a) Kenttamaa, H. I.; Cooks, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 4122. (b) Augusti, R.; Gozzo, F. C.; Moraes, L. A. B.; Sparrapan, R.; Eberlin, M. N. *J. Org. Chem.* **1998**, *63*, 4889.

(16) Santos, L. S.; Catharino, R.; Eberlin, M. N. *J. Mass Spectrom.* **2005**, *40*, 127.

(17) Gozzo, F. C.; Moraes, L. A. B.; Eberlin, M. N.; Laali, K. K. *J. Am. Chem. Soc.* **2000**, *122*, 7776.

TABLE 2. Major Fragment Ions Formed upon Collision-Induced Dissociation of Products Arising from Reactions of Gaseous $1^{\bullet+}$ with Representative Neutral Reactants (See Table 1)

Entry in Table 1	Proposed Structure	*m/z*	Major Fragments *m/z* (relative abundance)
1		164	136(62), 120(31), 92(100), 64(3), 63(1)
1		136	92(100), 64(3), 63(1)
2		165	121(100)
3		161	133(42), 115(6), 105(8), 81(100), 79(43), 55(4)
4		138	120(100), 92(5)
5		152	120(100), 92(12)
6		166	120(100), 92(2)
10		226	186(78), 173(28), 120(100)
11		192	146(100), 120(52)
13		239	120(100), 92(4)
14		221	165(100), 164(11), 163(8), 149(4), 115(9), 89(8).
15		176	131(2), 120(100), 92(12)
16		178	163(12), 120(100), 92(3)
18		175	121(100), 55(22)
21		208	120(100), 92(3)

salicylic acid and methyl salicylate, respectively.[5] Via kinetic studies and theoretical calculations, hydration that forms salicylic acid has been proposed to involve in-plane attack of the water molecule on the 6-oxomethylene group through a "pseudopericyclic" transition state with assistance by coordination of the α-oxo group.[5] Similarly, we found that gaseous $\mathbf{1}^{\bullet+}$ displays prompt gas-phase reactivity with water, yielding ionized salicylic acid of *m*/*z* 138 (Figure 4). The ion also reacts promptly with

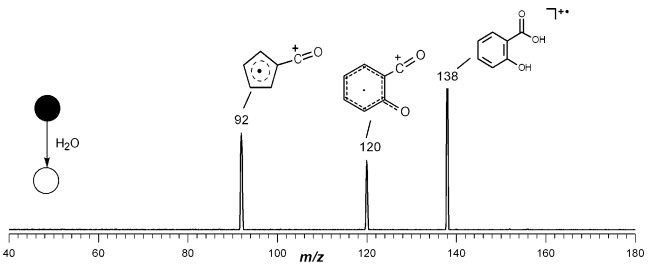
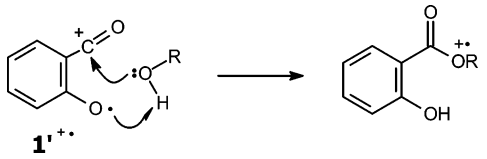


FIGURE 4. MS^2 for reactions of gaseous $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 with water (18 Da).

SCHEME 5



methanol and ethanol to yield methyl and ethyl salicylate of *m*/*z* 152 and 166, respectively (Table 1, entries 4−6).

As for solvated **1**, an analogous mechanism is also likely to operate for $\mathbf{1}^{\bullet+}$ (Scheme 5); that is, H abstraction may be assisted by coordination of ROH to the CO^+ group. Note in Figure 4 that, under the same reaction conditions, the distonoid fragment ion of *m*/*z* 92 ($\mathbf{3}^{\bullet+}$) seems to be inert toward water addition that would form a product ion of *m*/*z* 110.

Polar [3 + 2] Cycloadditions.[18]For α-oxoketenes with 1,3-oxadiene systems, [2 + 2] cycloadditions so common for other ketenes[19] are often overridden by [4 + 2] cycloadditions;[1] hence, other more (than **1**) easily accessible and stable α-oxoketenes are known to promptly undergo in solution many types of [4 + 2] cycloadditions with dienophiles.[20] We therefore screened the ability of gaseous $\mathbf{1}^{\bullet+}$ (as a probe for solvated **1**) to act as a diene and to undergo such synthetically relevant cycloadditions (either concerted or stepwise) with several dienophiles.

(i) Alkenes. With styrene, *p*-chlorostyrene, and methoxystyrene (Table 1, entries 7−9), unfortunately, $\mathbf{1}^{\bullet+}$ reacts solely by electron abstraction. This undesirable reactivity for the ionized molecule likely results from the low (likely lower than that of **1**) IE of these three neutral alkenes (the IE of **1** is apparently unknown). With these alkenes, therefore, gaseous $\mathbf{1}^{\bullet+}$ is an inadequate probe for the reactivity of solvated **1**, and cycloaddition reactivity of the neutral **1** with these alkenes is therefore not excluded.

In reactions with acrylonitrile (Table 1, entry 10), the monoaddition product ion of *m*/*z* 173 (as expected by [4 + 2] cycloaddition) is very minor, whereas a major product ion of *m*/*z* 226 from double addition is formed to a great extent. This great preference for double addition indicates that polar cycloaddition, across either the C═C or the CN bond, is precluded by double addition at CO^+, yielding aromatic 1,3,5-oxadiazinium ions (Scheme 6). This reactivity with nitriles is typical for acylium ions both in solution and in the gas phase.[21] The oxadiazinium ion of *m*/*z* 226 dissociates upon collisions with

(18) (a) Eberlin, M. N.; Sorrilha, A. E. P.; Gozzo, F. C.; Sparrapan, R. *J. Am. Chem. Soc.* **1997**, *119*, 3550. (b) Eberlin, M. N. *Int. J. Mass Spectrom.* **2004**, *235*, 263.

(19) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563.

(20) For an example see: Shumway, W. W.; Dalley, N. K.; Birney, D. M. *J. Org. Chem.* **2001**, *66*, 5832.

(21) Meurer, E. C.; Moraes, L. A. B.; Eberlin, M. N. *Int. J. Mass Spectrom.* **2001**, *212*, 445.

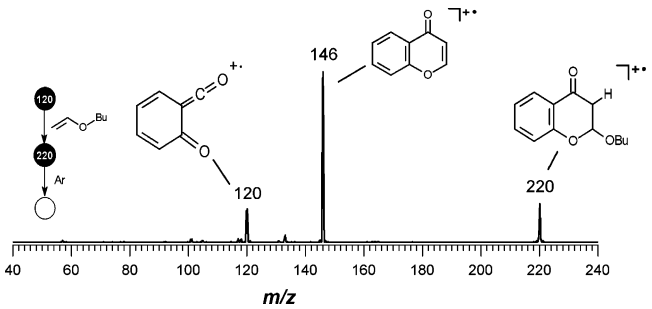
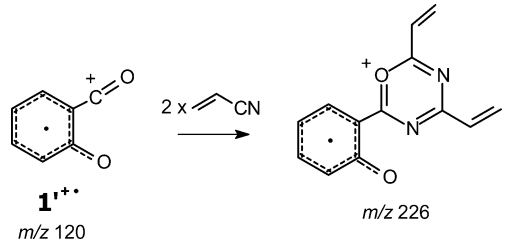
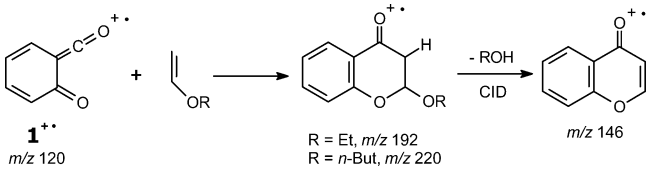


FIGURE 5. MS^3 for the [3 + 2] cycloadduct of *m*/*z* 220 formed in reactions of gaseous $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 with butyl vinyl ether (100 Da).

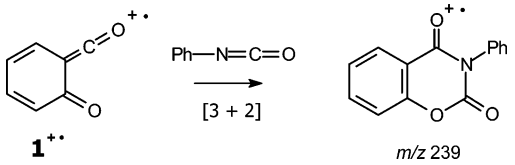
SCHEME 6



SCHEME 7



SCHEME 8

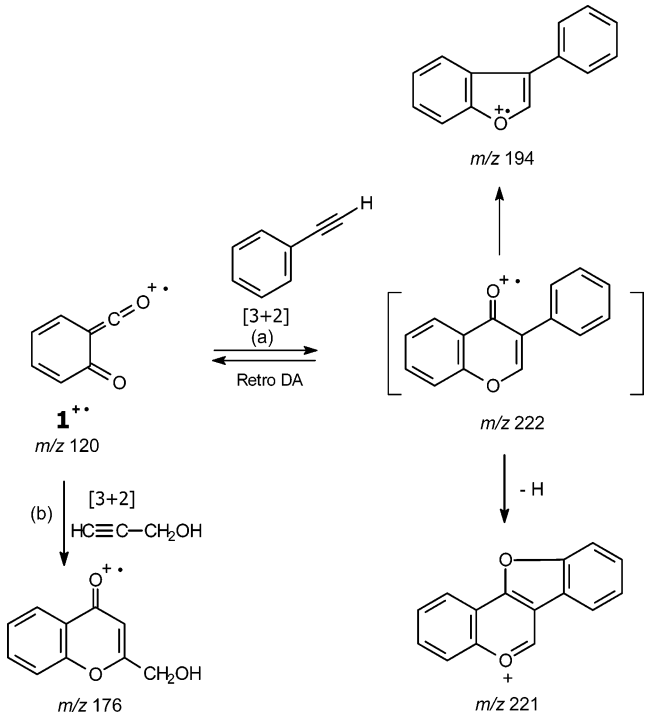


argon by sequential loss of two neutral acrylonitrile molecules, yielding the fragment ions of *m*/*z* 173 and 120 (as observed before for acylium ions),[18] but another unexpected dissociation route likely involving the unusual loss of a 40 Da species is also observed as a major process (Table 2).

Fortunately, however, when two alkoxy-substituted alkenes (enol ethers) were employed, gaseous $\mathbf{1}^{\bullet+}$ reacted promptly by polar [3 + 2] cycloaddition, yielding abundant intact cycloadducts of *m*/*z* 192 and 220, respectively (Table 1, entries 11 and 12). Ionized 2-alkoxy-4-chromanones are probably formed in these reactions and, as exemplified by the cycloadduct of *m*/*z* 220 from butyl vinyl ether in Figure 5, these ionized molecules dissociate in a structurally diagnostic fashion involving the loss of the corresponding ROH molecule to form ionized chromen-4-one of *m*/*z* 146 (Scheme 7).

(ii) Phenyl Isocyanate. With this dienophile, $\mathbf{1}^{\bullet+}$ also reacts promptly by electron abstraction to form ionized phenyl isocyanate of *m*/*z* 119 (Table 1, entry 13), but the expected polar [3 + 2] cycloaddition occurs competitively, thus yielding the product ion of *m*/*z* 239, that is, probably the ionized molecule of 3-phenylbenzo[*e*][1,3]oxazine-2,4-dione (Scheme 8). Double addition of a phenyl isocyanate molecule was not observed, which seems to indicate that cycloaddition precludes formation of 3,4-dihydro-2,4-dioxo-2*H*-1,3,5-oxadiazinium ions upon reactions at CO^{+}.[22] Dissociation of this cycloadduct occurs predominantly by retroaddition (Table 2).

SCHEME 9



(iii) Alkynes. Two alkynes were also tested. Phenylacetylene (Table 1, entry 14) reacts to a great extent by electron abstraction to form its ionized molecule of *m*/*z* 102 as well as its [2 + 1] self-cycloaddition product of *m*/*z* 204.[23] However, two abundant product ions of *m*/*z* 221 and 194, corresponding to the loss of a H and a CO from the intact cycloadduct, are also observed as major products. Probably, the simplest ionized flavone was formed as the nascent cycloadduct, and Scheme 9a proposes pathways for its favored dissociations by H and CO loss. These dissociations are also observed as major routes under 70 eV electron ionization of flavone (together with retro-Diels−Alder dissociation to $\mathbf{1}^{\bullet+}$ of *m*/*z* 120). Another alkyne, propargylic alcohol (Table 1, entry 15), reacts predominantly by [3 + 2] cycloaddition to form in this case the intact cycloadduct of *m*/*z* 176, likely ionized 2-(hydroxymethyl)-4-chromenone (Scheme 9b).

(iv) Carbonyl Compounds. Various ketones (Table 1, entries 16−20) and two esters (Table 1, entries 21 and 22) were tested, some displaying other functional groups along which cycloadditions could occur competitively. In general, as Figure 6 exemplifies for α-chloroacetone, [3 + 2] cycloadditions occur to great extents and preferentially along the C═O bond to form ionized benzo[1,3]dioxin-4-ones[24] as the nascent products (Scheme 10). However, as seen, for instance, for α-chloroacetone (Figure 7), the exothermicity of the gas-phase reaction often deposits an excess of energy on the product ions to cause prompt dissociation by the loss of an $R'^{\bullet}$ group. This dissociation

(22) Meurer, E. C.; Sparrapan, R.; Tomazela, D. M.; Eberlin, M. N.; Augusti, R. *J. Am. Soc. Mass Spectrom.* **2005**, *16*, 1602.

(23) Russell, D. H.; Gross, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 6279 and references therein.

(24) Cycloaddition across CO bonds is common for α-oxoketenes; see, for instance: Sato, M.; Ban, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689.

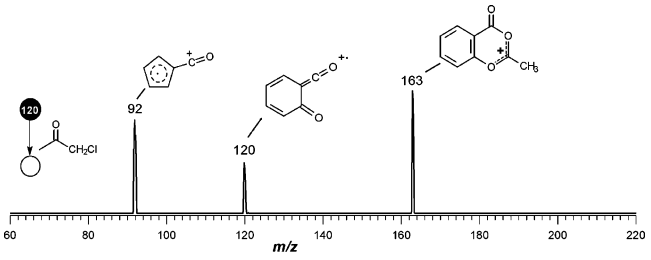
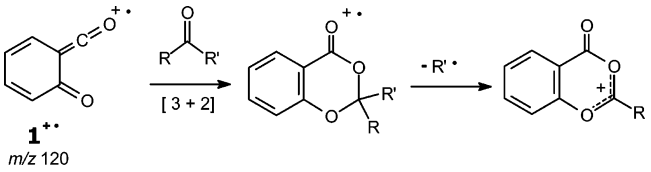


FIGURE 6. MS^2 for reactions of gaseous $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 with α-chloroacetone (92 Da).

SCHEME 10



dissipates some of the excess energy, and the intact cycloadducts of *m*/*z* 178 (Table 1, entry 16), *m*/*z* 204 (Table 1, entry 19), and *m*/*z* 208 (Table 1, entry 21) were observed only for acetone, cyclopentanone, and ethyl acetate.

The benzo[1,3]dioxin-4-one structures proposed for the final products (assuming preferential C═O cycloaddition) are corroborated by the dissociation chemistry of both the nascent cycloadducts (Scheme 10, R′ loss) and the observed products. For instance, the fragment of *m*/*z* 225 from ionized 2-methyl-2-phenylbenzo[1,3]dioxin-4-one (the putative cycloadduct of *m*/*z* 225 from acetophenone) dissociates to yield nearly exclusively the $PhCO^+$ ion of *m*/*z* 105 (Figure 7a), whereas the intact cycloadduct of *m*/*z* 294 from cyclopentanone (Figure 7b) dissociates by retroaddition to form $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 as well as by the loss of an ethyl radical to form an ion of *m*/*z* 175. The cycloaddition product of *m*/*z* 163 from both CH_2═CHO(CO)-CH_3 and α-chloroacetone (Figure 7c) dissociates readily by the loss of ketene of 42 Da.

Conclusion

The stable, long-lived, and easily accessible gaseous and ionized form of the α-oxoketene **1**, that is $\mathbf{1}^{\bullet+}$, has been formed, isolated, and characterized and its intrinsic reactivity investigated systematically in the gas phase via ion/molecule reactions with model reactants. Upon unimolecular dissociation and in reactions with water and methanol, gaseous $\mathbf{1}^{\bullet+}$ was found to display reactivity similar to that previously observed for solvated **1**. This similarity indicates therefore that gaseous $\mathbf{1}^{\bullet+}$ functions as a convenient substitute to access the reactivity of solvated **1**; hence, that a close parallel[25] can be drawn between the reactivity of gaseous $\mathbf{1}^{\bullet+}$ and solvated **1**.

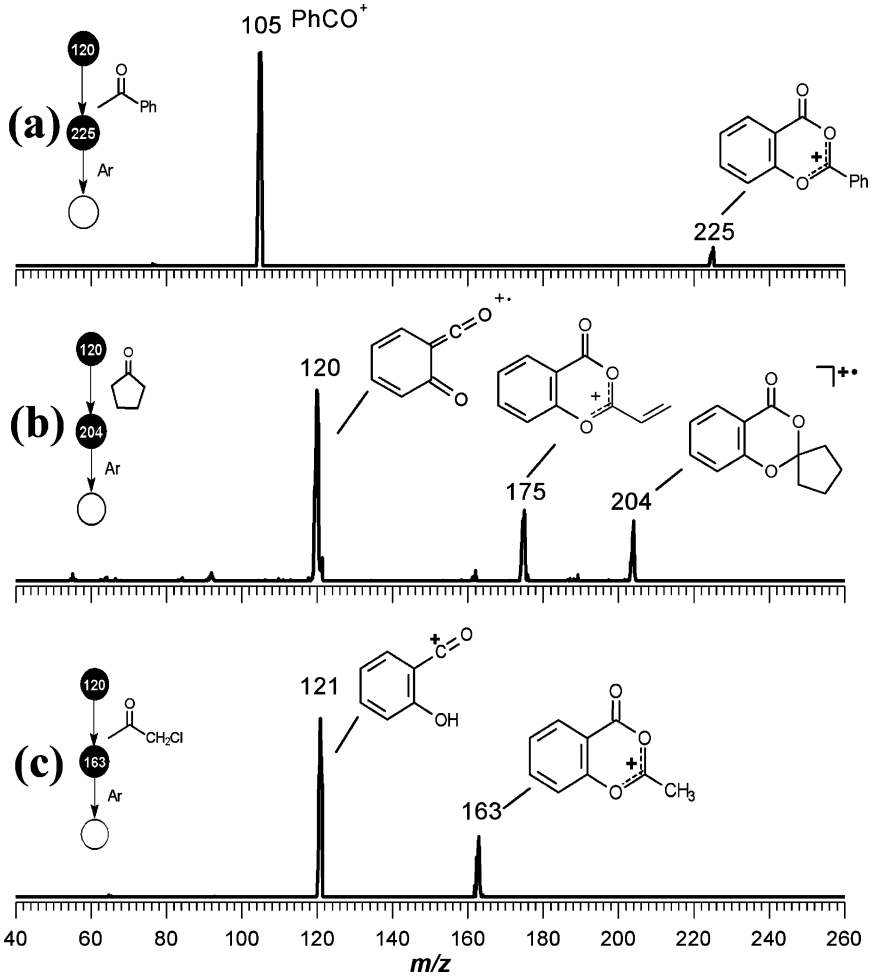


FIGURE 7. MS^3 for [3 + 2] cycloaddition products formed in reactions of gaseous $\mathbf{1}^{\bullet+}$ of *m*/*z* 120 with (a) methyl phenyl ketone, (b) cyclopentanone, and (c) α-chloroacetone.

The results described herein for reactions of $\mathbf{1}^{\bullet+}$ with various dienophiles including alkenes, akynes, isocyanates, and ketones anticipate that **1** is likely to display prompt and diverse [4 + 2] cycloaddition reactivity in solution. Benzopyrans and benzopyranones are widespread in nature and found in a variety of forms. Many of them are biologically relevant molecules such as those belonging to the plant pigments (anthocyanins and flavones) and the psychotropic constituents of hashish (tetrahydrocannabinol), the insecticidal ageratochromenes (precocenes) and rotenone, fungicidal phytoalexins, vitamin E, cournarin, and catechin.[26] The short-lived **1** (recently demonstrated to be easily accessible in solutions at room temperature)[4] may therefore become a versatile precursor of a variety of synthetic manipulations leading to highly biologically active 4-benzopyranones including flavones, 4-chromononones, 4-chromonenes, benzo[1,3]-dioxin-4-one, and analogues.

Acknowledgment. We thank the São Paulo State Research Foundation (FAPESP) and the Brazilian Research Council (CNPq) for financial support.

Supporting Information Available: Cartesian coordinates and energies (including S^2 spin contamination values) of species $\mathbf{1}^{\bullet+}$, $\mathbf{2}^{\bullet+}$, and $\mathbf{3}^{\bullet+}$ and spin and charge densities for $\mathbf{1}^{\bullet+}$. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070371Z

(25) For other similar examples in which a close parallel between gas-phase and solution-phase reactivity has been observed, see: (a) Queiroz, J. F.; Carneiro, J. W. M.; Sabino, A. A.; Sparrapan, R.; Eberlin, M. N.; Esteves, P. M. *J. Org. Chem.* **2006**, *71*, 6192. (b) Nibbering, N. M. M. *Mass Spectrom. Rev.* **2006**, *25*, 962. (c) Gronert S *Acc. Chem. Res.* **2003**, *36*, 848. (d) Uggerud, E. *Top. Curr. Chem.* **2003**, *225*, 3. (e) O'Hair, R. A. J. *Mass Spectrom. Rev.* **1991**, *10*, 133. (e) Wang, F, Tao, W. A.; Gozzo, F. C.; Eberlin, M. N,; Cooks, R. G. *J. Org. Chem.* **1999**, *64*, 3213.

(26) Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 247.