

Formal gas-phase polar [4 + 1⁺] cycloaddition of ionized methylene to α -dicarbonyl compounds: synthesis of 2-unsubstituted 1,3-dioxoles

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Ion/molecule reactions of $^+\text{CH}_2\text{OCH}_2$ with α -dicarbonyl compounds were performed via pentaquadrupole mass spectrometry. Besides the previously known [3⁺ + 2] 1,3-cycloaddition reaction that forms cyclic 1,3-dioxonium ions, an unprecedented reaction proceeding formally by [4 + 1⁺] cycloaddition of ionized methylene (CH_2^+) to the α -dicarbonyl compounds occurs competitively, leading to the gas-phase synthesis of several ionized 2-unsubstituted 1,3-dioxoles. This novel cycloaddition reaction may therefore be added to the set of methods available for the synthesis of 1,3-dioxoles. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: 1,3-dioxoles; ion/molecule reactions; gas-phase synthesis; distonic ions; α -dicarbonyl compounds; pentaquadrupole mass spectrometry

INTRODUCTION

Tandem^{1,2} and other multiple-stage mass spectrometric techniques (MS^n) have been widely used to elucidate the structures of gaseous ions via collision-induced dissociation (CID). Besides this major task, these techniques also provide elegant tools to perform reactions between gaseous ions and neutral molecules of many classes in an environment free from the influence of solvents and counterions. The study of such ion/molecule reactions, which has been summarized in several recent reviews from different perspectives,^{3–11} has proved to be valuable in many aspects including the discovery of new reactions and their synthetic and analytical applications.

An illustrative example of an interesting gas-phase ion/molecule reaction observed and efficiently performed via tandem mass spectrometry is that of ionized methylene (CH_2^+) transfer.^{12,13} This reaction, which provides carbon–carbon or, more often, heteroatom–carbon chain expansion, has been used to form several ionized ylides unavailable in their neutral forms. Reactions with the naked CH_2^+ ion are often ineffective (likely the product ions formed are too hot), so a common CH_2^+ transfer reactant is the α -distonic ion $^+\text{CH}_2\text{–O–CH}_2$ (**1**).¹⁴ In CH_2^+ transfer, **1** can be viewed as an ionized carbene (methylene) solvated by formaldehyde, which carries away a part of the heat liberated by the exothermic reaction. With ketones, CH_2^+ transfer from **1** forms ionized ketone ylides, $\text{R}^1\text{R}^2\text{C=O}^+\text{–CH}_2$, but we found that a [3⁺ + 2] 1,3-dipolar cycloaddition also occurs to form cyclic 1,3-dioxonium ions.¹⁵ Note that the term [3⁺ + 2]

is used to denote a cycloaddition reaction involving 3 + 2 π -electrons and that the 3- π -electron species is a radical cation.

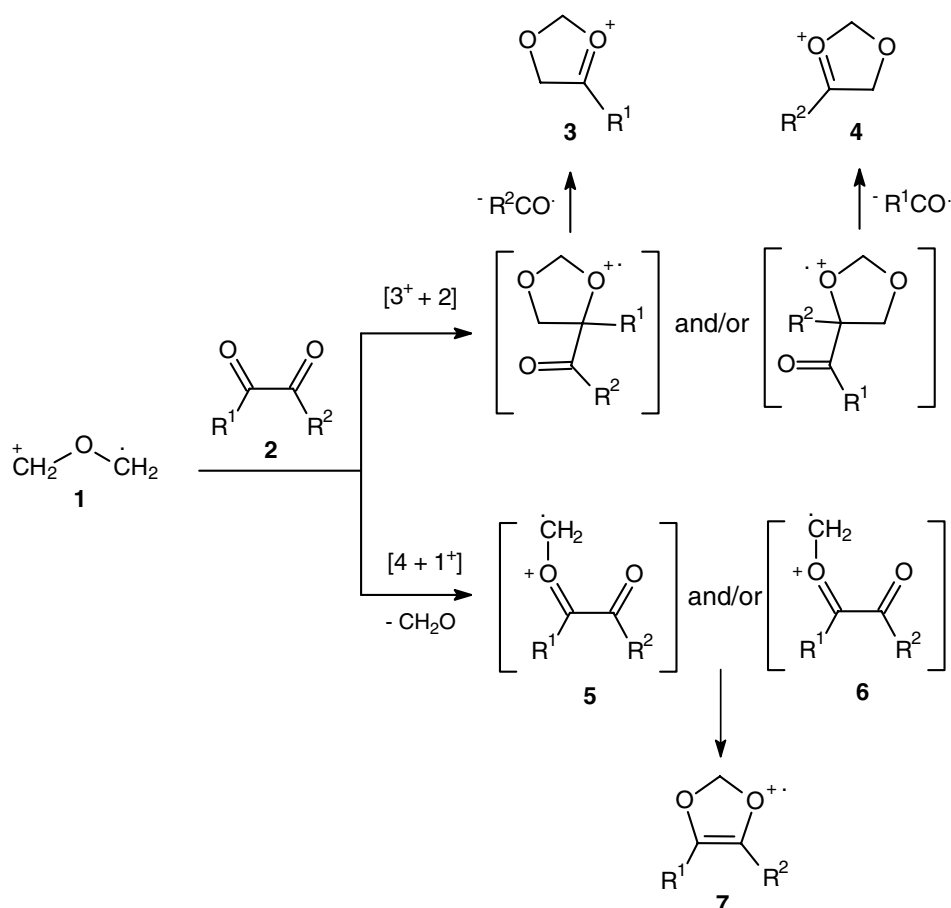
The initial goal of the present study was therefore to perform the gas-phase reactions of **1** with ‘asymmetrical’ α -dicarbonyl compounds **2** ($\text{R}^1 \neq \text{R}^2$). On the basis of our previous knowledge of this reaction,¹⁵ we planned to evaluate the competition between the two most likely reactions leading to four different products: either **3** or **4** (or both) via [3⁺ + 2] 1,3-cycloadditions across either one of the two carbonyl groups, and either **5** or **6** (or both) via CH_2^+ transfer to one of the two carbonyl oxygens (Scheme 1).

When performing such reactions, we observed that indeed CH_2^+ transfer occurs, but that it leads also to even more interesting products, i.e. ionized cyclic 2-unsubstituted 1,3-dioxoles **7** (Scheme 1). Formally, this reaction corresponds to a [4 + 1⁺] polar carbene–heterodiene (likely stepwise) cycloaddition and suggests a feasible synthetic entry to 2-unsubstituted 1,3-dioxoles. Here we report our initial findings on this novel and synthetically relevant gas-phase reaction.

EXPERIMENTAL

Ion **1**, formed by electron ionization of 1,3-dioxolane at 70 eV,¹⁵ was set to react with the α -dicarbonyl compounds **2**. These chemicals were purchased from Sigma-Aldrich and used as received. Glyoxal (**2a**) was sampled from the headspace of the commercial aqueous solution. The reactions were performed using a pentaquadrupole mass spectrometer¹⁶ via MS^2 experiments, in which **1** was mass-selected by Q_1 and further reacted in q_2 with the neutral α -dicarbonyl compounds. Ion translational energies were

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Scheme 1

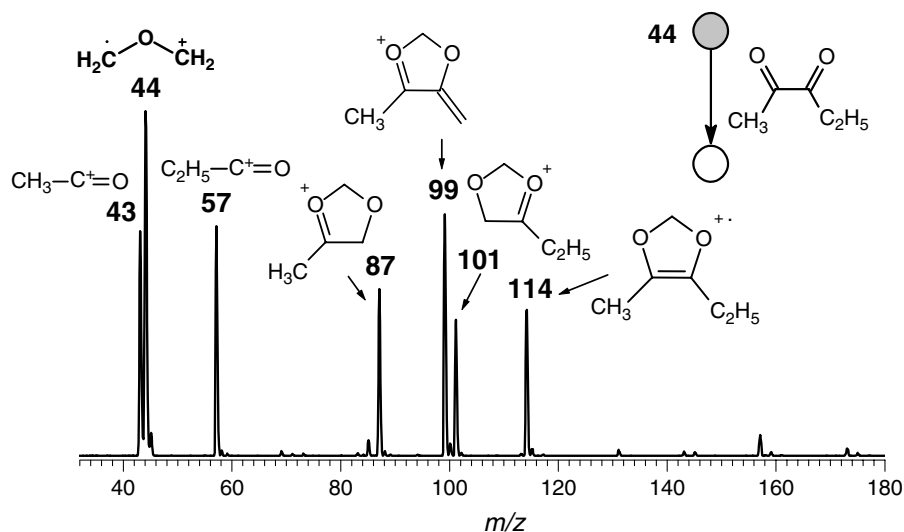


Figure 1. Product ion mass spectrum for reactions of **1** of m/z 44 with **2c** (2,3-pentanodione).

set to near 1 eV. To record the product ion mass spectra, Q_5 was scanned while operating Q_3 in the broadband r.f.-only mode. Multiple collision conditions that caused typical beam attenuations of 50–70% were used in q_2 so as to increase reaction yields and to help promote collisional quenching of both the reactant and product ions. For the MS^3 experiments, the product ions of interest formed in q_2 were mass-selected by Q_3 and further dissociated by 15-eV collision dissociation with argon in q_4 while scanning

Q_5 to acquire the spectra. The 15-eV collision energy was taken as the voltage difference between the ion source and the collision quadrupoles. The indicated pressures in each differentially pumped region were typically 2×10^{-6} (ion source), 8×10^{-6} (q_2), and 8×10^{-5} (q_4) torr, respectively.

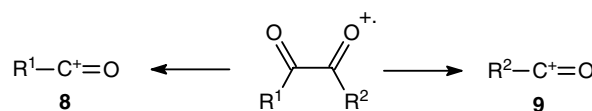
Optimized geometries and energies were obtained by theoretical calculations, with no symmetry constraints, using B3LYP DFT/HF hybrid functional and 6–311+G(d,p) basis sets, as implemented in Gaussian 98.

RESULTS AND DISCUSSION

α -Dicarbonyl compounds 2

As a typical example, Fig. 1 shows the product ion mass spectrum of the reaction of **1** with 2,3-pentanedione (**2c**, Table 1). Products of three major competing reactions are observed: (1) electron transfer that forms ionized 2,3-pentanedione, a labile electron-bound species¹⁷ that is not detected likely owing to its prompt and competitive dissociations to the acylium ions $\text{CH}_3\text{-C}^+=\text{O}$ (**8c**) of m/z 43 and $\text{C}_2\text{H}_5\text{-C}^+=\text{O}$ (**9c**) of m/z 57 (Scheme 2), (2) $[3^+ + 2]$ 1,3-cycloaddition¹⁵ across either carbonyl groups that forms the cyclic dioxonium ions **3c** of m/z 87 or **4c** of m/z 101 after prompt dissociation of the nascent cycloadducts by the loss of either the acetyl or propenyl radical, respectively (Scheme 1) and (3) an unprecedented formal $[4 + 1^+]$ polar cycloaddition of the nascent CH_2^+ that likely forms **7c**, i.e. ionized 4-ethyl-5-methyl-1,3-dioxole of m/z 114 (Scheme 1). As evidenced by MS³ experiments (see below), **7c** dissociates in part inside the q_2 reaction cell, (likely owing to the heat liberated in the exothermic reaction) by methyl radical loss to form the ion of m/z 99.

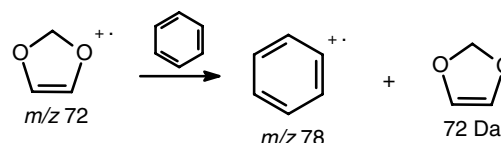
Table 1 summarizes data for reactions of **1** with the α -dicarbonyl compounds **2a–f**. Similar sets of product ions for the three competitive reactions just discussed are formed with all α -dicarbonyl compounds in variable abundance ratios. Therefore, the formation of the ionized 1,3-dioxoles



Scheme 2

7 via formal polar $[4 + 1^+]$ cycloaddition (Scheme 1) seems to be quite general and occurs competitively with $[3^+ + 2]$ cycloaddition.

Although ionized 1,3-dioxoles **7** have been formed, these heterocyclics could be converted to, or collected in, their neutral forms, using several MS approaches. Soft landing of ions¹⁸ on electron-rich surfaces is perhaps the most attractive and potentially effective alternative. Gas-phase electron-transfer reactions could also be performed; for instance, via an MS³ experiment **7a** was reacted with benzene (Fig. 2). Electron transfer occurred promptly, forming ionized benzene of m/z 78 and consequently the simplest 1,3-dioxole in its neutral form (Scheme 3).



Scheme 3

Table 1. Products (m/z with relative abundances in parenthesis) for reactions of **1** with α -dicarbonyl compounds **2a–f**

Neutral reactants	Products m/z (relative abundance)				
	[$3^+ + 2$] cycloaddition	[$4 + 1^+$] cycloaddition	Electron transfer		
2 Structures	3	4	7	8	9
a 		73(52)		72(100)	29 (15)
b 	87(54)	73(5)		86(100)	29(8) 43(52)
c 	101(56)	87(60)		114(58), 99(100) ^a	43 (86) 57 (97)
d 	87(22)	115(25)		128(20), 99(62) ^b	43(81) 71(100)
e ^c 	101(12)	89(0)		116(15)	45(4) 57(100)
f 	87(17)	103(8)		116(35)	43(100) 59(1)

^a Loss of a methyl radical from the $[4 + 1^+]$ cycloadduct.

^b Loss of an ethyl radical from the intact $[4 + 1^+]$ cycloadduct.

^c A minor product ion of m/z 131 corresponding to the loss of a methyl radical from the intact adduct is also observed.

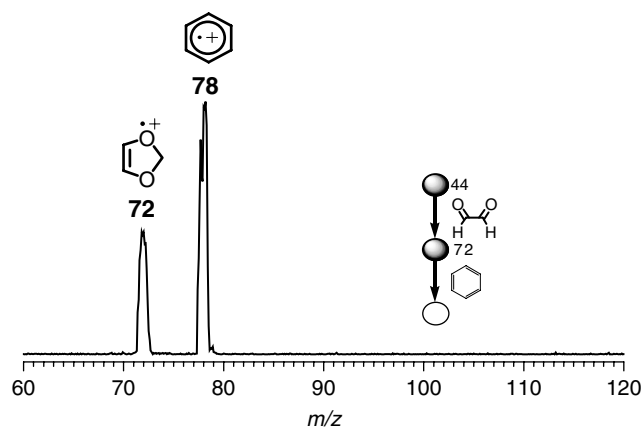
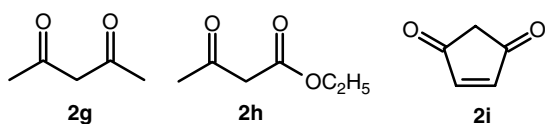


Figure 2. Triple-stage (MS^3) sequential product ion mass spectra for reactions of **7a** with benzene.

β -Dicarbonyl compounds and a cyclic α -dicarbonyl compound

Interestingly, reactions of **1** with two β -dicarbonyl compounds, i.e. **2g** and **2h**, as well as with the cyclic α -dicarbonyl compound **2i** (blocked in the *s-trans* conformation) are found to form no detectable amounts of CH_2^+ transfer products (spectra not shown). These reactions yield predominantly either the protonated molecules (for **2g** and **2h**) or the ionized molecule (for **2i**). These results indicate, therefore, that CH_2^+ transfer is favored particularly for α -dicarbonyl compounds, that can easily adopt the *s-cis* conformation that is required for cyclization and hence formation of the ionized 1,3-dioxoles **7**.



MS^3 Experiments

Table 2 summarizes the product ion mass spectra for the ionized 1,3-dioxoles **7a–f**, whereas Figs 3 and 4 show, as illustrative cases, the full spectra for **7a** of m/z 72 and **7c** of m/z 114, respectively.

Scheme 4 provides the rationalizations for the dissociation pathways of **7a–f**. The parent ion **7a** of m/z 72 (Fig. 3)

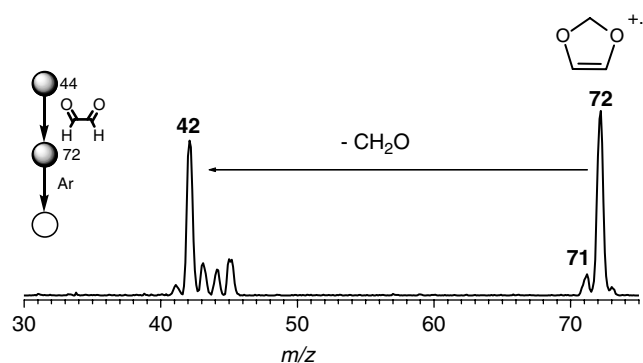


Figure 3. Triple-stage (MS^3) sequential product ion mass spectra of **7a**, i.e. the parent 1,3-dioxole in its ionized form of m/z 72.

Table 2. Major fragment ions (m/z with relative abundances in parenthesis) observed in the product ion mass spectra of the ionized 1,3-dioxoles **7**

Dioxoles	Structures	m/z	Major fragment ions
7a^a		72	71(16), 45(22), 44(19), 43(20), 42(100)
7b		86	85(78), 43(100)
7c^a		114	99(100), 69(7), 43(12) ^a
7d		128	99(100), 69 (3), 43(12)
7e		116	86(100), 58(35), 57(92)
7f		116	101(15), 45(20), 43(30)

^a For the full spectrum see Figs 3 or 4.

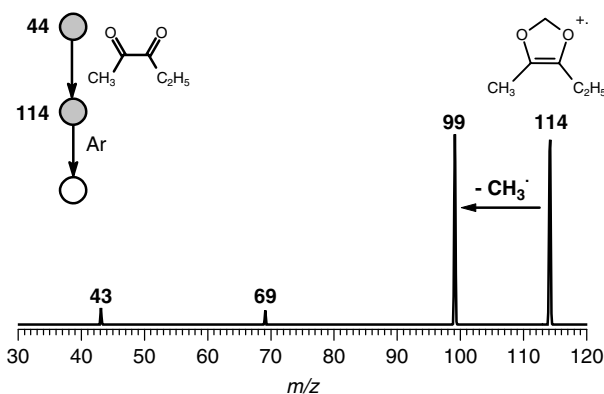
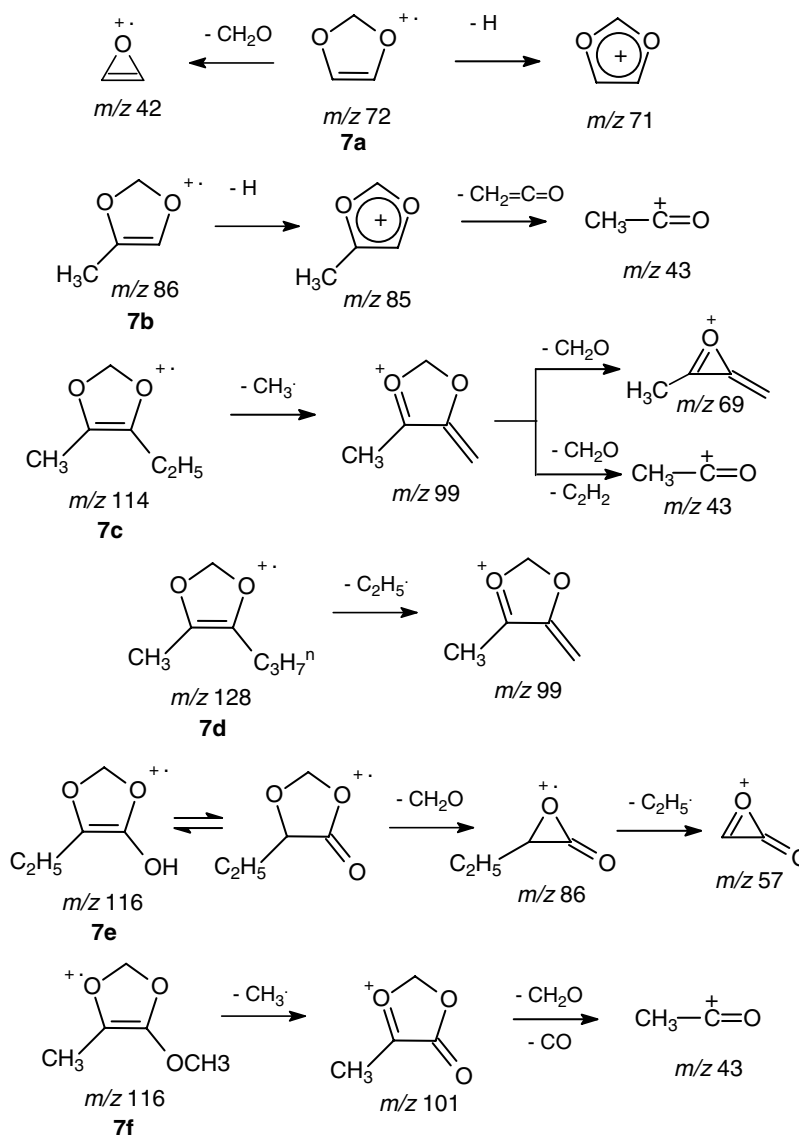


Figure 4. Triple-stage (MS^3) sequential product ion spectra for the ionized 1,3-dioxole, **7c**, of m/z 114.

dissociates predominantly by formaldehyde loss to form the fragment ion of m/z 42, whereas loss of an H that forms the ion of m/z 71, likely the aromatic [1,3]-dioxol-1-ylum ion, is also important. For the ionized 4-methyl-1,3-dioxole (**7b**) of m/z 86, loss of H that likely forms the aromatic 5-methyl-[1,3]-dioxol-1-ylum ion of m/z 85 is predominant, and this loss is followed by a ketene loss (42 Da) that forms the acetyl cation of m/z 43. Owing to the 4-ethyl substituent, loss of a methyl radical is predominant for **7c** forming the ion of m/z 99, a process that is also detected in the product ion mass spectrum (Fig. 1). Further dissociations of the



ion of m/z 99 yield the ions of m/z 69 and 43. Ionized 4-methyl-5-*n*-propyl-1,3-dioxole (**7d**) also dissociates predominantly by a similar major pathway to that of **7c**, i.e. by the loss of an ethyl radical, to form likely the same fragment ion of m/z 99. The dissociation of ionized 4-hydroxy-5-ethyl-1,3-dioxole (**7e**) is unique. Likely owing to keto/enol equilibrium, its keto form dissociates mainly by the consecutive loss of formaldehyde (m/z 86) and an ethyl radical (m/z 57). Ionized 4-methyl-5-methoxy-1,3-dioxole (**7f**) of m/z 116 is isomeric with **7e**, but dissociation of **7f** occurs very distinctively and predominantly by methyl radical loss (m/z 101) followed by formaldehyde and CO losses to form the acetylation of m/z 43. These dissociation pathways, rationalized in Scheme 4, can be conveniently linked to the proposed structures providing therefore evidence for the formation of the ionized cyclic 1,3-dioxoles **7**.

Theoretical calculations

To verify whether acyclic or cyclic products are more thermodynamically favored upon CH_2^+ transfer to **2**, calculations using B3LYP DFT/HF hybrid functional and

6-311+G(d,p) basis sets were performed starting from both **5** and **6** (Scheme 1). However, all the acyclic ions **5** and **6**, regardless of the addition site or input geometries, were found to collapse upon geometry optimization to the cyclic 1,3-dioxole structures **7a–f**. As an illustrative case, Fig. 5 shows a potential energy surface diagram for CH_2^+ transfer of **1** to glyoxal **2a** leading to either the cyclic ionized 1,3-dioxole **7a** or to the acyclic adduct **5a'** which was, for comparison, locked in the (otherwise unstable) *s-trans* form. Cyclization **5a'** \rightarrow **7a** is found to be as much as $-28.4 \text{ kcal mol}^{-1}$ exothermic, whereas the reaction pathway artificially interrupted at **5a'** is exothermic by just $-5.1 \text{ kcal mol}^{-1}$.

CONCLUSIONS

In gas-phase ion/molecule reactions of $^+\text{CH}_2\text{OCH}_2$ with α -dicarbonyl compounds, $[4 + 1^+]$ cycloaddition (formally of CH_2^+) occurs yielding ionized 2-unsubstituted 1,3-dioxoles. This novel cycloaddition reaction opens a feasible synthetic entry to straightforward gas-phase synthesis of these little

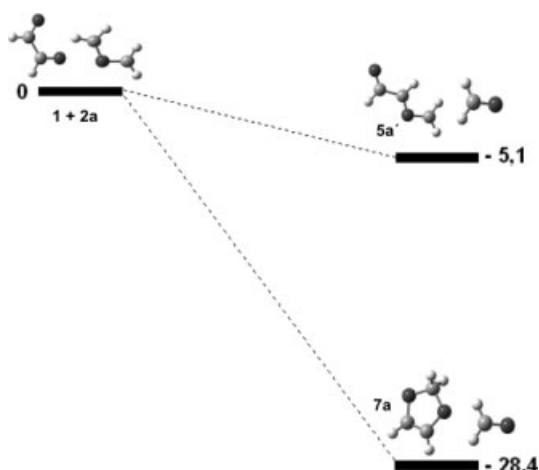


Figure 5. Potential energy diagram for the reaction of **1** with glyoxal (**2a**) leading either to the ionized cyclic 1,3-dioxole **7a** or the (otherwise unstable) acyclic CH_2^+ transfer product **5a'** locked at the *s-trans* conformation. Energies are given in kilocalories per mole. Total energies (au) are as follows: **1** (−153.42381), **2a** (−227.81947), **5a'** (−266.74448), **7a** (−266.78167), and formaldehyde (−114.50688). Transition state energies are not provided because attempts to locate their structures were all unsuccessful.

known heterocyclics (in their ionized forms), whereas MS approaches such as electron-transfer reactions or ion soft landing on electron-rich surfaces may be used to collect the products in their neutral forms. Since $^+\text{CH}_2\text{OCH}_2$ is accessible in the condensed phase,¹⁹ such reactions may also be attempted for the solvated ion. Therefore, this formal cycloaddition of the simplest ionized carbene may be added to the set of the few methods available for the synthesis of 1,3-dioxoles.^{20–22} It also shares some analogy with the solution cycloaddition of dicarbonyl carbenes to aldehydes and ketones, which was found to form polysubstituted 1,3-dioxoles.²⁰

Acknowledgements

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