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Gas-phase polar [4⁺ + 2] cycloaddition with ethyl vinyl ether: a structurally diagnostic ion–molecule reaction for 2-azabutadienyl cations

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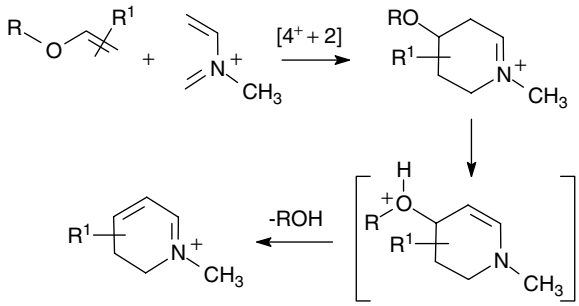
The intrinsic reactivity of eight gaseous, mass-selected 2-azabutadienyl cations toward polar [4⁺ + 2] cycloaddition with ethyl vinyl ether has been investigated by pentaquadrupole mass spectrometric experiments. Cycloaddition occurs readily for all the ions and, with the only exception of those from the *N*-acyl 2-azabutadienyl cations (*N*-acyliminium ions), the cycloadducts are found to dissociate readily upon collision activation (CID) both by retro-Diels-Alder reaction and by a characteristic loss of an ethanol (46u) neutral molecule. Ethanol loss from the intact polar [4⁺ + 2] cycloadduct functions therefore as a structurally diagnostic test: 72 u neutral gain followed by 46 u neutral loss, i.e., as a combined ion–molecule reaction plus CID 'signature' for *N*-H, *N*-alkyl and *N*-aryl 2-azabutadienyl cations. The two *N*-acyliminium ions tested are exceptional as they form intact cycloadducts with ethyl vinyl ether which dissociate exclusively by the retro-Diels-Alder pathway. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: gas-phase structurally diagnostic ion–molecule reactions; azabutadienes; azabutadienyl cations; cycloaddition reactions; pentaquadrupole mass spectrometry

INTRODUCTION

Cycloadditions are reactions of great importance in condensed phase chemistry and extremely useful in synthesis.[1] In these reactions, two unsaturated acyclic molecules combine in regioselective, site-selective and sometimes stereoselective ways to form cyclic or heterocyclic products. Cycloadditions are therefore highly selective, for molecular class and geometry, and are prime candidates for class-selective and structurally diagnostic reactions. In the gas phase, many polar cycloaddition reactions have been observed, and their mechanisms studied,[2] but the potential of such an ion–molecule reaction for structural elucidation and as a general structurally diagnostic ion–molecule reaction for gaseous ions and neutral molecules has not been yet fully explored.[3]

Azabutadienes and analogues, often under acid catalysis (hence in their *N*-protonated forms), or complexed cationized azabutadienes, have been vastly used in [4 + 2] and polar [4⁺ + 2] Diels-Alder cycloadditions, and these reactions are key steps in important strategies of heterocycle synthesis.[4] In the gas phase, many azabutadienes in protonated or cationized forms are readily formed upon ionization followed by dissociation of nitrogen-containing compounds. We have shown[5] that the simplest 2-azabutadienyl cation is formed by 70 eV electron ionization (EI) of piperidine, and that this ion readily undergoes gas-phase polar [4⁺ + 2] cycloaddition with ethyl vinyl ether followed by ready dissociation of the nascent cycloadduct by ethanol loss to form the *N*-protonated 2,3-dihydropyridinium ion. Later,[6] we found that the *N*-methyl 2-azabutadienyl cation reacts similarly, readily, and generally with several alkyl enolethers (Scheme 1), as well as with silyl and sulfur enolether analogues, to form intact polar [4⁺ + 2] cycloadducts.



Scheme 1

Collision-induced dissociation (CID) of the intact cycloadducts of the *N*-methyl 2-azabutadienyl cation occurs competitively by both retro-Diels-Alder (RDA) and a class-diagnostic loss of either a ROH (for alkyl enolethers), R_3SiOH (for silyl enolethers), or RSH (for thioenoleters) neutral molecule. Cycloadducts of acyclic enolethers that bear no double-bond substituents form, upon CID and R(Si)O(S)H loss, a characteristic fragment of *m*/*z* 96. For the cycloadducts

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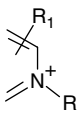
of enolethers bearing double-bond substituents (R^1), the mass of the R(Si)O(S)H loss fragment shifts proportionally to the mass of $[R^1 - H]$. Endocyclic enolethers also react readily by cycloaddition with the *N*-methyl 2-azabutadienyl cation, but, unless affected by ring substituents,[6] dissociation of their cycloadducts is dominated by RDA. Detailed structural information of the reactant enolethers and their analogues is therefore provided, and positional isomers can be easily distinguished. This interesting and efficient gas-phase polar $[4^+ + 2]$ cycloaddition reaction was therefore demonstrated to be class-selective, hence to function as a structurally diagnostic ion–molecule reaction for enolethers and their sulfur and silicon analogues.[6]

We now report that polar $[4^+ + 2]$ cycloaddition with enolethers (the simple, volatile and readily available ethyl vinyl ether was selected) is also selective and general for the reactant ions: the 2-azabutadienyl cations, and that the loss of an ethanol molecule from the cycloadduct functions as a structurally diagnostic test, i.e., as an ion–molecule reaction/CID 'signature' for *N*-H, *N*-alkyl and *N*-aryl 2-azabutadienyl cations. *N*-Acyl 2-azabutadienyl cations, more commonly known as *N*-acyliminium ions, are exceptional as they form intact cycloadducts with ethyl vinyl ether which dissociate upon CID exclusively by RDA.

EXPERIMENTAL

The gaseous ions were produced, reacted, and their products analyzed by double- and triple-stage (MS^2 and MS^3, respectively) mass spectrometric experiments performed with an Extrel (Pittsburgh, PA) pentaquadrupole ($Q_1q_2Q_3q_4Q_5$) mass spectrometer.[7] The reactant ions were formed by 70 eV EI of piperidine, *N*-methylpiperidine, 2-methylpiperidine, 3-methylpiperidine, *N*-ethylpiperidine, *N*-phenylpiperidine, oxopiperidine-1-acetonitrile, and carboxylic-1-piperidine acid methyl ester. For the MS^2 ion–molecule reactions, Q_1 was used to mass-select the ion of interest for further reactions in q_2 with neutral ethyl vinyl ether. Ion translational energies were set to near 1 eV. Product ion mass spectra were acquired by scanning Q_5, whereas operating Q_3 and q_4 in the broadband rf-only mode. Multiple collision conditions, which increase reaction yields and promote collisional quenching of both the reactant and product ions,[8] were used in q_2, as indicated by typical beam attenuations of 50–70%.



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a; R = R_1 = H, *m/z* 56
b; R = CH_3, R_1 = H, *m/z* 70
c; R = H, R_1 = 3-CH_3, *m/z* 70
d; R = H, R_1 = 4-CH_3, *m/z* 70
e; R = C_2H_5, R_1 = H, *m/z* 84
f; R = Ph, R_1 = H, *m/z* 132
g; R = COCN, R_1 = H, *m/z* 109
h; R = CO_2CH_3, R_1 = H *m/z* 114

For the MS^3 experiments,[8] a q_2 product ion of interest was mass-selected by Q_3 for further 15 eV CID with argon in q_4, whereas scanning Q_5 to record the mass spectrum. The 15 eV collision energies were taken as the voltage differences 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. Total energies of optimized geometries using no symmetry constraints were obtained by DFT calculations at the Becke3LYP/6-311+G(d,p) level of theory ran on GAUSSIAN98.[9] Details of the energies and optimized structures are available from the authors upon request.

RESULTS AND DISCUSSION

Ion–molecule reactions

Using a pentaquadrupole mass spectrometer ($Q_1q_2Q_3q_4Q_5$),[7] eight gaseous 2-azabutadienyl cations (**1a**–**h**) were formed by 70 eV EI of suitable precursors (see the Experimental section for details), mass-selected by Q_1, and then reacted under controlled and nearly identical conditions with ethyl vinyl ether in q_2, while scanning Q_5 to acquire the product ion mass spectrum. Table 1 summarizes the main products and yields (relative ion abundances) of these reactions. Note that readily available 2-azabutadienyl cations bearing different electron-donating and electron-withdrawing substituents have been formed and reacted so as to test the effect of such substituents on the polar $[4^+ + 2]$ cycloaddition reactivity of the ions. It should be emphasized here that although we assume that the reaction of 2-azabutadienyl cations with enol ethers is a concerted cycloaddition, in part by analogy with results for 2-azabutadienes in solution,[4,10] it is still an open issue whether these gas-phase reactions are really concerted or occur in a more stepwise

Table 1. Main ionic products observed in the product ion mass spectrum for the reaction of the mass-selected 2-azabutadienyl cations **1a**–**h** with neutral ethyl vinyl ether

	Ionic products *m/z* (% relative abundance)		
Ion[a]	Cycloadduct[b]	[Cycloadduct–C_2H_5OH[c]]$^+$	$CH_2{=}CH{-}O^+{-}(C_2H_5)_2$[d]
1a	None	82(100)	101(20)
1b	142(100)	96(7)	101(58)
1c	142(40)	96(1)	101(100)
1d	142(40)	None	101(100)
1e	156(100)	None	101(50)
1f	204(90)	None	101(100)
1g	181(60)[e]	None	101(100)
1h	186(4)[e]	None	101(10)

[a] For the structure of ions **1a**–**h**, see text. [b] See Scheme 2. [c] See Scheme 3. [d] Ethylated ethyl vinyl ether is a secondary product of proton transfer to ethyl vinyl ether, see text and Ref. 11. [e] Ions **1g** (HCN loss to form the ion of *m/z* 82) and **1h** (CO_2 loss to form the ion of *m/z* 70) dissociate readily upon collisions, even under the very low near 1 eV energy collisions used to performed ion–molecule reactions. The fragment ion of *m/z* 70 is the major product ion (100% relative abundance) in the product ion mass spectrum of **1h**.

fashion. Cycloadditions of closed-shell reactants usually have activation energies, which could anyway be surpassed by kinetic to internal energy conversion during collisions. In a two-step mechanism, a energy barrier is expected in the transition state for cyclization for conformational motion of the chain of the open-ring intermediate from the all-trans conformation (see Fig. 4) to a gauche conformation, but such a relatively small barrier should be more than compensated by the large exothermicity of the first addition step. In any case, however, what really matters for the structural diagnostic application explored herein is that cyclic products are formed which thus favor the class-selective ROH loss (see below) and that, if indeed a stepwise process dominates, the open-ring and cyclic structures are not in competition, but are linked in a consecutive and 'down-hill' pathway (see Fig. 4 and the 'Theoretical calculation' section below). We are currently conducting an extensive theoretical investigation on the energetics (including transition states) of both cycloaddition and the alternative stepwise cyclization process.

As Fig. 1 exemplifies for **1e**, all 2-azabutadienyl cations studied herein, which included *N*-H-, *N*-alkyl-, *N*-phenyl-, and *N*-acyl-substituted ions, react with ethyl vinyl ether to form the putative polar $[4^+ + 2]$ cycloadducts **2** (Scheme 2). A main and common secondary product ion is also that of m/z 101 (Table 1). This ion, ethylated ethyl vinyl ether, is known to be formed as a secondary product of proton transfer to ethyl vinyl ether.[11] The *N*-carboxymethyl-substituted ion **1h** also forms the adduct **2h** of m/z 186, but to a rather limited extent (Table 1) owing at least in part, if not exclusively, to its high lability towards CID which occurs mainly by CO_2 loss. The simplest 2-azabutadienyl cation **1a** reacts abundantly by $[4^+ + 2]$ cycloaddition,[5] but its intact cycloadduct **2a** of m/z 128 is not observed at all. The nascent **2a** dissociates promptly by ethanol loss (see Scheme 3) to form **3a** of m/z 82 (Table 1).[5] Ethanol loss also occurs to some extent for the **2b** and **2c** cycloadducts under the near 1 eV energy collisions used for the ion–molecule reactions, but such a loss is suppressed for the other cycloadducts.

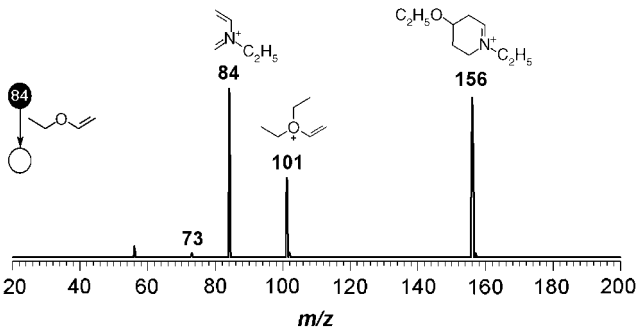
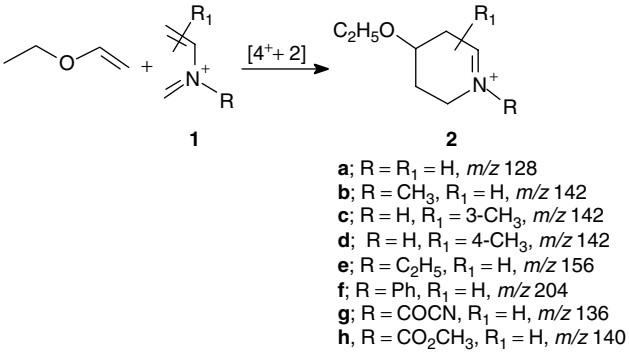
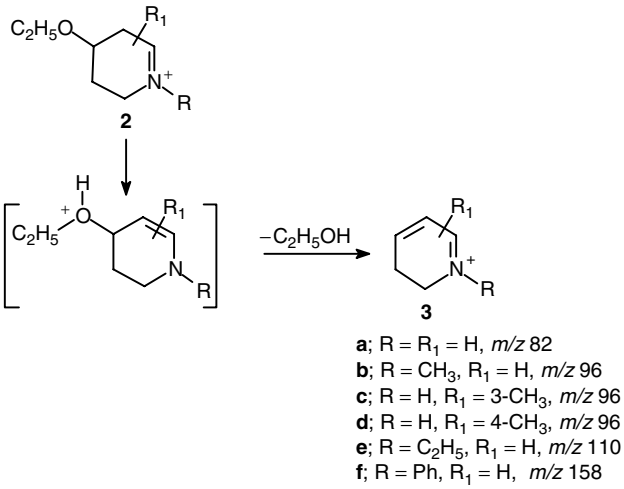


Figure 1. Product ion mass spectrum for the reaction of the *N*-ethyl 2-azabutadienyl cation **1e** with ethyl vinyl ether. Note the abundant polar $[4^+ + 2]$ cycloadduct **2e** of *m/z* 156, the proton transfer product (protonated ethyl vinyl ether of *m/z* 73), and the secondary product of proton transfer to ethyl vinyl ether of *m/z* 101 (ethylated ethyl vinyl ether, see Ref. 11).



Scheme 2



Scheme 3

Structural elucidation

To test whether cyclic or acyclic adducts are formed in these reactions, MS^3 experiments were performed in which the putative cycloadducts **2** were mass-selected by Q_3 and then dissociated by 15 eV collisions with argon in q_4, while scanning Q_5 to acquire the sequential product ion CID mass spectrum. As exemplified for **2c–f** in Fig. 2, the six putative *N*-H, *N*-alkyl and *N*-aryl cycloadducts **2a–f** dissociate to both RDA and, most interestingly, by the characteristic and common loss of an ethanol molecule of 46 u to form the 2,3-dihydropyridinium ions **3** (Scheme 3). Ethanol loss can be easily rationalized only for cyclic adducts,[5,6] and this loss serves therefore as a diagnostic for cyclic adducts. In contrast, however, and as Fig. 3 exemplifies for **2g**, the intact adducts **2g** and **2h** dissociate upon collision activation exclusively by RDA. Adducts **2g** and **2h** were formed from the *N*-carboxycyano (**1g**) and *N*-carboxymethyl (**1h**) 2-azabutadienyl cations, i.e., from the two *N*-acyliminium ions tested. In solution, *N*-acyliminium ions[12] are vastly used in Mannich-type condensation reactions, and their *N*-acyl groups[13] provide activation towards nucleophilic addition at the vicinal vinylic carbon. Hence, ions **1h** and **1g** could behave most pronouncedly as *N*-acyliminium ions

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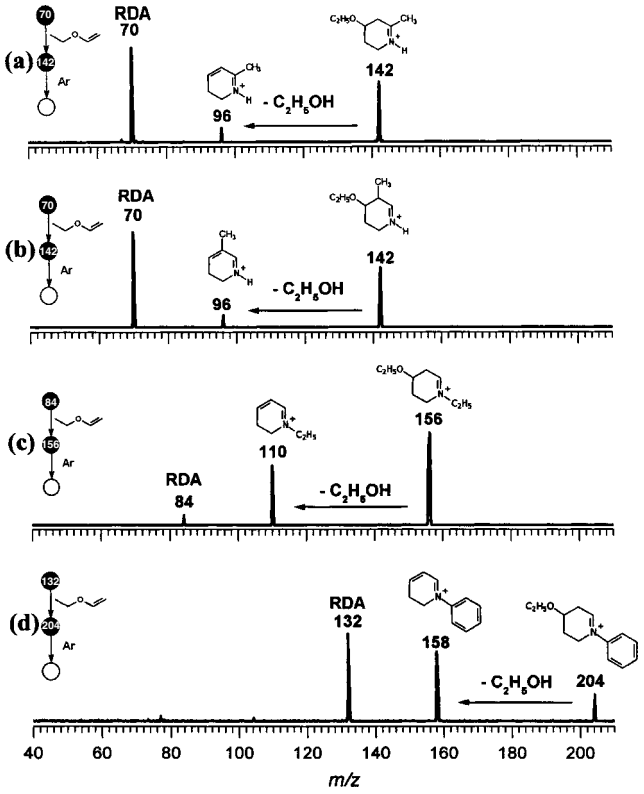


Figure 2. Triple stage product ion mass spectra for 15 eV CID with argon of the intact polar $[4^+ + 2]$ cycloadducts (2c–f) formed in reactions with ethyl vinyl ether of the 2-azabutadienyl cations (a) **1c**, (b) **1d**, (c) **1e**, and (d) **1f**. Note the characteristic dissociation by both RDA and ethanol loss displayed for all four cycloadducts exemplified herein.

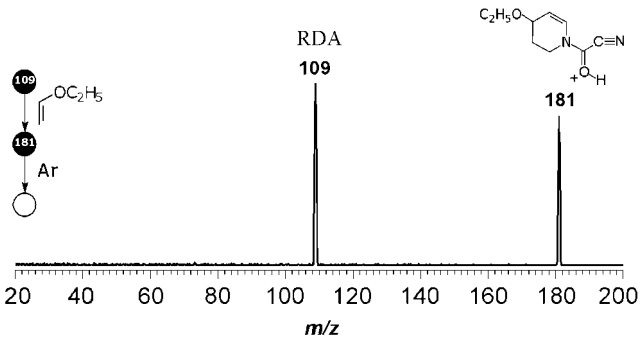
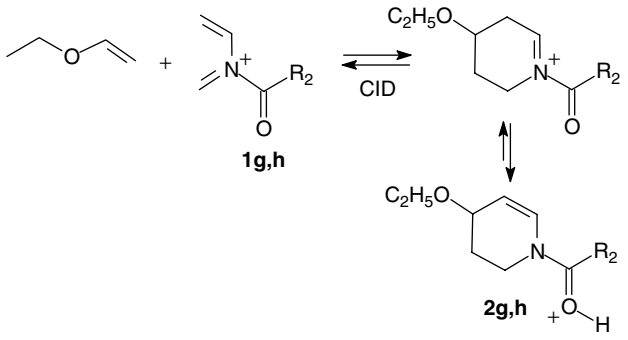


Figure 3. Triple stage product ion mass spectrum for 15 eV CID with argon of the intact acyclic adduct **2g** formed in reactions of the 2-azabutadienyl cation **1g** (an *N*-acyliminium ion) of *m/z* 109 with ethyl vinyl ether. Note the exclusive dissociation of **2g** by retro-addition to form *m/z* 109 owing likely to favored protonation at the *N*-acyl group.

(not 'typically' as 2-azabutadienyl cations), and they could then react with ethyl vinyl ether by simple addition to yield acyclic adducts. These acyclic adducts, upon CID, would be expected to dissociate predominantly, if not exclusively, by retro-addition. Another possibility is that the *N*-acyl groups compete more favorably for the proton with the ethoxy group thus suppressing the ethanol loss pathway (Scheme 4). The *N*-acyl protonated cyclic adducts **2g, h** should fail therefore



Scheme 4

to dissociate upon CID by ethanol loss making retro-addition dominant. The latter alternative is supported by theoretical calculations, see below.

Theoretical calculations

Figure 4 displays energy surface diagrams calculated at the B3LYP/6-311++G(d,p) level for reactions of the 2-azabutadienyl cations **1e** and **1g** with ethyl vinyl ether. For the *N*-ethyl-substituted ion **1e** (Fig. 4(a)), cycloaddition is far more thermodynamically favored (−45.8 kcal/mol) than simple addition (−11.9 kcal/mol), hence **1e** is predicted to behave much more pronouncedly as a by now 'typical' 2-azabutadienyl cation, i.e., as a positively charged activated diene, not as an *N*-acyliminium ion. For its cycloadduct **2e**, intramolecular proton transfer to the ethoxy group forms an unstable ion which undergoes, in the course of geometry optimization, spontaneous dissociation by ethanol loss to form the final 2,3-dihydropyridinium ion in an overall -40.6 kcal/mol process. The transition state (TS) energy for proton transfer within the **1e** cycloadduct has not been estimated, but we have shown for **2b**[6] that such a TS lies slightly above the reactants thus ethanol loss must be induced by collisions and compete with RDA. For the *N*-acyliminium ion **1g** (the *N*-carboxycyano 2-azabutadienyl cation), a similar picture is seen (Fig. 4(b)): cycloaddition is far more thermodynamically favored (−52.1 kcal/mol) than simple addition (−36.9 kcal/mol). Then for the **2g** cycloadduct, intramolecular proton transfer to the ethoxy group forms an unstable ion which undergoes, in the course of geometry optimization, spontaneous dissociation by ethanol loss to form the final 2,3-dihydropyridinium ion **3g** in an overall −48.4 kcal/mol process. The major difference for this *N*-acyl cycloadduct is related, however, to an alternative for intramolecular proton transfer to the *N*-carboxycyano group. Such a proton transfer forms an ion that lies −54.4 kcal/mol below the reactants, and which is therefore −2.3 kcal/mol more stable than the C-protonated isomer. Although the TSs for the two competitive proton transfers have not been estimated, they can again be roughly estimated from that of **2b**,[6] hence it is reasonable to assume from the thermodynamic stabilities and predicted TSs that proton transfer to the *N*-acyl group prevails for the **2g** cycloadduct which, upon CID, suppresses ethanol loss favoring the RDA dissociation.

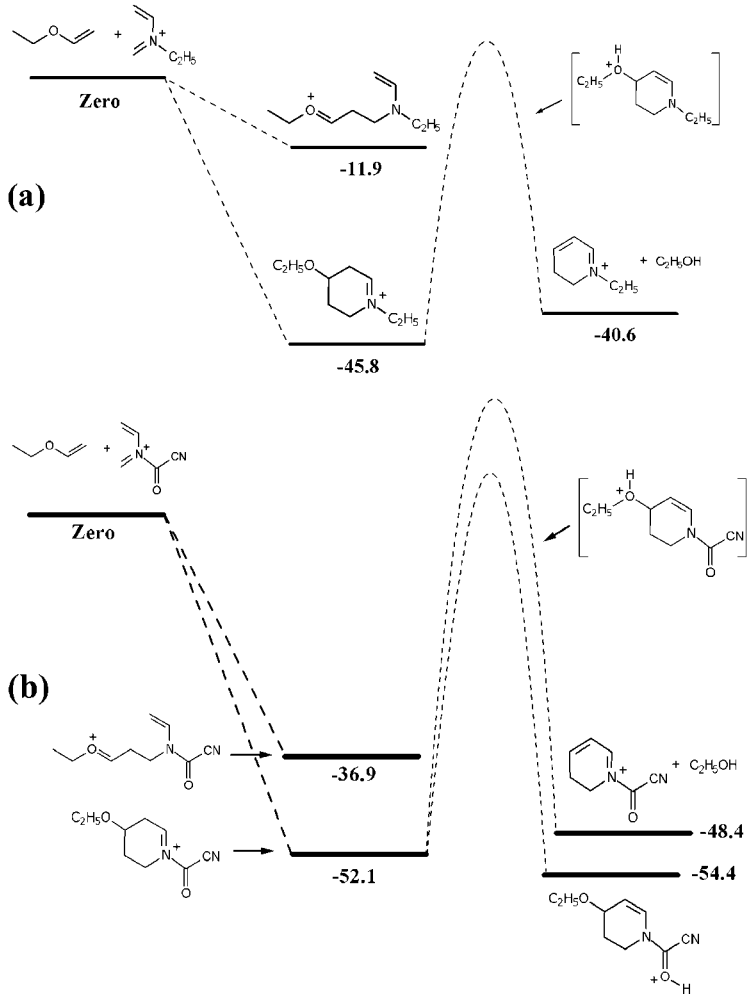


Figure 4. B3LYP/6-311++G(d,p) potential energy surface diagrams for the reactions of (a) *N*-ethyl and (b) *N*-carboxycyano 2-azabutadienyl cations with ethyl vinyl ether. Energies are given in kcal/mol. The energies of the transition states for intramolecular proton transfer have not been calculated, but they have been roughly estimated from the cycloadduct of the *N*-methyl analogue ion **1b**, see Ref. 6.

CONCLUSIONS

Gaseous 2-azabutadienyl cations react readily and generally with ethyl vinyl ether (and, as demonstrated previously,[6] also with a variety of other enolethers and their silicon and sulfur analogues) by polar $[4^+ + 2]$ cycloaddition. All the cycloadducts of the *N*-H, *N*-alkyl, and *N*-aryl 2-azabutadienyl cations tested dissociate upon CID both by RDA and by a class-selective loss of an ethanol neutral molecule. *N*-Acyliminium ions (and likely any other 2-azabutadienyl cation bearing relatively acidic *N*-substituents) do react by cycloaddition with ethyl vinyl ether but, upon CID, ethanol loss is suppressed by favored intramolecular proton transfer to the *N*-acyl group. Therefore, ethanol loss from the intact polar $[4^+ + 2]$ cycloadducts functions as a structurally diagnostic test (72 u neutral gain followed by 46 u neutral loss), an ion–molecule reaction/CID 'signature' for *N*-H, *N*-alkyl, and *N*-aryl 2-azabutadienyl cations. *N*-Acyliminium ions (likely any 2-azabutadienyl cation bearing relatively acidic *N*-substituents) are exceptional as their cycloadducts with ethyl vinyl ether dissociate upon CID exclusively by the RDA pathway.

Acknowledgements

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