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Theoretical study of the thermal isomerization of isoxazole and 5-methylisoxazole

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ABSTRACT: High-level *ab initio* and semi-empirical computations were carried out to investigate the mechanisms of thermal isomerization of isoxazole (**1a**) and 5-methylisoxazole (**2a**). The calculations were made over the whole isomerization potential energy surface at the MP2/cc-pVDZ and QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ levels. The predicted rate-limiting transition states were refined further at the QCISD(T)/aug-cc-pVDZ//QCISD/cc-pVDZ level. *Ab initio* results are in excellent agreement with available experimental results. Furthermore, they allow us to propose a detailed reaction mechanism and to exclude reaction paths proposed earlier. We also report the results from semi-empirical computations. The MNDO method predicts reasonable values for the heat of formation of the reactants but it fails for other isomers and overestimates the activation energies for most reaction steps. The AM1 method yields improved values for the activation energies, at the expense of less reliable heats of formation for the minima in the potential energy surface. In general, both methods produce results that are good when the simplicity of the model is considered; however, there is no simple way to determine in advance when the results are meaningful. Thermochemical and kinetic parameters obtained by the different theoretical methods are discussed and compared with experimental values. Copyright © 2004 John Wiley & Sons, Ltd.
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KEYWORDS: isoxazole; 5-methylisoxazole; FVT; flash vaccum thermolysis; isomerization

INTRODUCTION

Heterocyclic compounds, including isoxazole and its derivatives, are important structural units of many compounds of biological interest. In addition, five-membered heterocycles are recognized as compounds involved directly or as intermediates in the synthesis of new compounds that are potentially useful in a variety of different fields, including pharmaceuticals and medicinal chemistry.[1]

The Flash Vacuum Thermolysis (FVT) technique is becoming an increasingly important preparative synthetic method as well as a useful technique to study reaction mechanisms. A recent review surveys the most important reaction in the FVT of five-membered heterocycles.[2] Pérez *et al.* used this technique to investigate the reaction mechanism and kinetic parameters in the thermolysis of a variety of isoxazole derivatives,[3–5] including 5-methylisoxazole.[6] Based on these results they proposed a general reaction mechanism for isoxazoles, which is shown in Scheme 1. When $R_3 \neq H$ the oxazole isomer is obtained as the reaction product (and in some cases the isomerization stops in the intermediary azirine), whereas the nitrile is observed when $R_3 = H$.

Kinetic evidence led these authors to suggest that the rate-limiting step is the formation of the azirine isomer.[6] However, as can be observed in Scheme 1, a detailed reaction mechanism is not defined and the intermediacy of some compounds is uncertain. Early theoretical results using the MNDO method[7] shed some light on the reaction mechanism, suggesting the intermediacy of the vinyl nitrene (**h**), which was proposed earlier based on similar experimental results in the photolysis and thermolysis of vinyl azides.[8] In addition, MNDO results did not support the intermediacy of the ketenimine (**c**) in the isomerization process.[7]

More recently, Lifshitz and co-workers studied the thermal decomposition of isoxazole,[9] 5-methylisoxazole[10] and 3,5-dimethylisoxazole[11] in a shock tube reactor. The effective temperature obtained in these reaction conditions is substantially higher than those that can be reached in the FVT experiment, where the temperature can be regulated easily. Therefore, at these temperatures ($\sim$1000 K) they observed a variety of decomposition products and their simulations are also focused in finding decomposition channels, as is the *ab initio*/reaction-path dynamic study by Saito and Okada.[12] In both reports the authors seem to have missed the earlier results by Pérez

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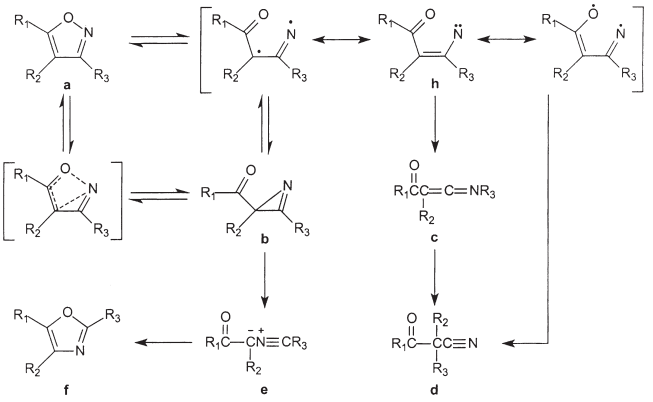


Scheme 1

showing that isoxazoles can isomerize to the products shown above at much lower temperatures (<800 K) before decomposition. Subsequently, Liu and co-workers[13] challenged the decomposition mechanism proposed by Lifshitz based on results obtained using density functional theory and proposed a concerted isomerization from isoxazole to the nitrile and then decomposition to $CH_3CN + CO$ and $HCN + H_2CCO$, the main decomposition products observed by Lifshitz.[9] However, as we show below, the concerted isomerization proposed by Liu is not the lower energy path in the potential energy surface.

In this paper we report a comprehensive, high-level *ab initio* computation of the thermal isomerization of isoxazole and 5-methylisoxazole. The results are in excellent agreement with the available experimental results. In addition, an updated reaction mechanism is proposed for 3-unsubstituted isoxazole derivatives.

COMPUTATIONAL METHODS

Semi-empirical MNDO[14] and AM1[15] calculations were performed with AMPAC (version 2.1) and MOPAC (version 6) on a personal computer. The original source codes for both packages were compiled and only minimal language adaptation and modifications were introduced. The test runs included in the program package were run also to verify the accuracy of the several values included in the output files.

Full geometry optimizations with no geometrical constraints were performed for compounds **2a**–**h** and true minima were confirmed through vibrational analysis. Hypersurfaces were calculated by assigning fixed values to the appropriate coordinates and optimizing all the others. Transition states were located by one-dimensional reaction paths or two-dimensional grid searches, and the resulting approximate transition-state geometries were refined by minimizing the scalar gradient of energy with respect to the geometry. These transition states were characterized as saddle points by diagonalizing the Hessian (force constant) matrix and establishing the presence of one, and only one, negative force constant. Unrestricted Hartree Fock computations were employed consistently in these methods.[7]

Ab initio calculations were carried out using the Gaussian 98 suite of programs.[16] A quick survey of the potential energy surfaces using density functional theory for compounds **1** and **2** was carried out at the B3LYP/6–31G** level, using the AM1 results as starting points. For some transition states the AM1 optimized geometries were not even a good starting geometry. Geometries then were reoptimized at the MP2/cc-pVDZ level, followed by QCISD(T)/aug-cc-pVDZ single-point calculations. An exhaustive and comprehensive transition states search was carried out between all minima found in the potential energy surface. In a few cases optimization at the QCISD/cc-pVDZ level coupled with single-point calculations at the QCISD(T)/aug-cc-pVDZ level were performed. Frequencies at the MP2/cc-pVDZ level were calculated for each stationary point and the number of negative eigenvalues in the Hessian matrix was used to determine if the structure was a minimum or transition state. These frequencies were used also to calculate the zero-point vibrational energy (not scaled). Intrisinc Reaction Coordinate (IRC) calculations at the B3LYP/6–31G** or MP2/cc-pVDZ level were carried out for all transition states to ensure that they connected the reported minima.

RESULTS AND DISCUSSION

The results from the *ab initio* calculations for the isomerization of **1a** and **2a** are presented in Table 1 and the potential energy surfaces are plotted in Figs 1 and 2, respectively.

The *ab initio* results show that the vinyl nitrene structures **1h** and **2h** are not minima in the potential energy surfaces, in contrast to results obtained using semi-empirical methods (see Supplementary material). All *ab initio* methods fail to find a minimum in the singlet potential energy surface. Attempts to optimize such a structure collapsed to the corresponding isoxazole or azirine minima, including attempts of optimization at the QCISD/cc-pVDZ level. However, the triplet nitrene is a minimum in the surface and was included in Table 1 despite the fact that we do not think that proposing a singlet–triplet surface crossing is reasonable in this case, particularly because it would have to occur twice. Vinyl nitrenes have been postulated as intermediates in the thermolysis and photolysis of vinyl azides to azirines;[8,17,18] however, our results suggest that when a carbonyl group is present such that an isomerization to the very stable isoxazole is conceivable (as in this case), proposing the intermediacy of a singlet vinyl nitrene species is unsuitable. Because the vinyl nitrenes (**h**) are not involved in the reaction mechanisms, the proposed azirine isomers (**b**) are being formed directly from their corresponding isoxazole in a concerted way, as shown

Table 1. *Ab initio* results for isoxazole (**1**) and 5-aminoisoxazole (**2**)

Isomer	Symmetry	State/ N_{imag}[a]	MP2/cc-pVDZ			QCISD(T)/aug-cc-pVDZ[b]		QCISD(T)/aug-cc-pVDZ[c]	
			Energy[d]	ZPVE[e]	Relative E[f]	Energy[d]	Relative E[f]	Energy[d]	Relative E[f]
1a	C_s	$^1A'/0$	−245.34826	36.49	0	−245.44963	0	−245.44991	0
1b	C_1	–/0	−245.31728	34.06	17.01	−245.42087	15.61		
1c	C_1	–/0	−245.34666	34.17	−1.31	−245.45355	−4.78		
1d	C_s	$^1A'/0$	−245.38564	34.37	−25.57	−245.48544	−24.59		
1e	C_1	–/0	−245.30528	33.86	24.34	−245.41031	22.04		
1f	C_s	$^1A'/0$	−245.38573	36.91	−23.10	−245.48532	−21.98		
1g	C_s	$^1A'/0$	−245.34172	34.34	1.96	−245.44992	−2.34		
1h	C_s	$^3A''/0$	−245.25090	33.93	58.53	−245.38552	37.66		
1TSab	C_1	–/1	−245.23143	32.71	69.53	−245.35914	53.00	−245.37220	44.97
1TSac	C_s	$^1A'/1$	−245.23806	30.98	63.64	−245.35470	54.05	−245.35614	53.33
1TScd	C_1	–/1	−245.25220	31.46	55.24	−245.35393	55.02		
1TSbg	C_1	–/1	−245.25365	31.44	54.31	−245.35801	52.44		
1TSad	C_1	–/1	−245.22944	31.98	70.05	−245.34794	59.30		
1TSef	C_1	–/1	−245.29839	33.73	28.53	−245.40601	24.61		
1TSbf	C_1	–/1	−245.24184	32.67	62.96	−245.34806	59.91		
1TSbe	C_1	–/1	−245.22373	31.74	73.39	−245.34320	62.03		
1TSdg	C_1	–/1	−245.27776	32.81	40.56	−245.38965	33.95		
2a	C_s	$^1A'/0$	−284.53757	54.10	0	−284.66442	0	−284.66475	0
2b	C_1	–/0	−284.50932	51.78	15.41	−284.63841	14.01		
2c	C_1	–/0	−284.53753	51.79	−2.28	−284.67003	−5.82		
2d	C_s	$^1A'/0$	−284.57754	51.98	−27.19	−284.70296	−26.30		
2e	C_1	–/0	−284.49545	51.33	23.67	−284.62600	21.35		
2f	C_s	$^1A'/0$	−284.57476	54.52	−22.91	−284.69918	−21.38		
2g	C_1	–/0	−284.53387	51.95	0.17	−284.66737	−4.00		
2h	C_s	$^3A''/0$	−284.44434	51.68	56.08	−284.60245	36.47		
2TSab	C_1	–/1	−284.41885	50.45	70.86	−284.57274	53.89	−284.58639	45.53
2TSac	C_s	$^1A'/1$	−284.42768	48.71	63.57	−284.57011	53.79	−284.57162	53.05
2TScd	C_1	–/1	−284.44326	49.07	54.16	−284.57001	54.22		
2TSbg	C_1	–/1	−284.44605	49.13	52.47	−284.59060	41.36		
2TSad	C_1	–/1	−284.41864	49.71	70.24	−284.56337	59.02		
2TSef	C_1	–/1	−284.48820	51.36	28.24	−284.62135	24.29		
2TSbf	C_1	–/1	−284.43220	50.44	62.47	−284.56327	59.82		
2TSbe	C_1	–/1	−284.41471	49.35	72.35	−284.55911	61.34		
2TSdg	C_1	–/1	−284.47023	50.65	38.81	−284.60721	32.46		

[a] Number of imaginary frequencies.
[b] Values obtained at QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level.
[c] Values obtained at QCISD(T)/aug-cc-pVDZ//QCISD/cc-pVDZ level.
[d] In atomic units.
[e] Zero-point vibrational energy in kcal mol^{-1}.
[f] Relative energy in kcal mol^{-1}, including ZPVE.

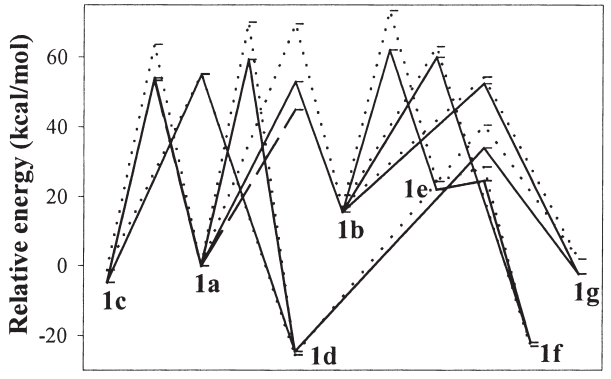


Figure 1. Schematic energy profile for the thermal isomerization of **1a** at the MP2/cc-pVDZ level (dotted line), QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level (solid line) and QCISD(T)/aug-cc-pVDZ//QCISD/cc-pVDZ level (dashed line)

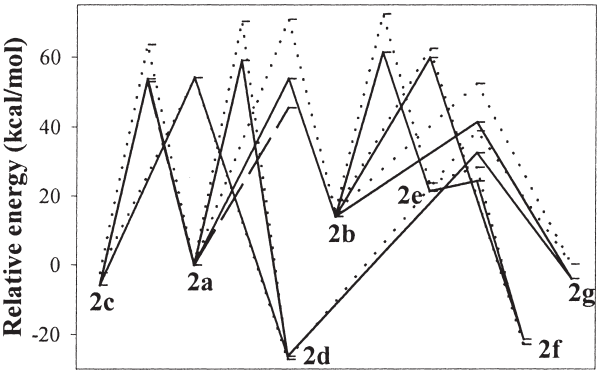
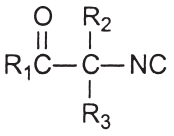


Figure 2. Schematic energy profile for the thermal isomerization of **2a** at the MP2/cc-pVDZ level (dotted line), QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level (solid line) and QCISD(T)/aug-cc-pVDZ//QCISD/cc-pVDZ level (dashed line)

also in Scheme 1. A similar situation is also found for the ketenimine (**c**) and nitrile (**d**) isomers. Extensive attempts to find transition structures connecting the azirines (**b**) with either ketenimine (**c**) and nitrile (**d**) isomers failed. Our failure to find a transition structure connecting the azirines with the ketenimines is consistent with experimental data. Experiments do not find ketenimines as a product in the thermolysis of any isoxazole reported to date. A simple inspection of the potential energy surface in Fig. 1 shows that if such a transition structure were energetically available (i.e. lower in energy than **1Tsab**), the ketenimine isomer should be isolated in the thermolysis of isoxazole for two reasons: the ketenimine is thermodynamically very stable; and further isomerization from ketenimine involves transition states that are higher in energy than **1Tsab**. However, this might not be the case for different substituted azirines. The presence of the carbonyl group attached to C-3 of the azirine ring represents a significant perturbation with respect to other groups. For a different substitution, such as an alkyl group, the potential energy surface potentially could be quite different without perturbation of the very stable isoxazole minima, and in some situations a pathway between the azirines and ketenimines has been demonstrated experimentally.[19,20] The mechanism for this step could be either concerted or through a singlet nitrene structure; however, evidently such situations are not contemplated in this report because the isomerizations start from the isoxazoles.

Finally, an additional pathway involving the isonitrile isomer (**1g**) was included. The isomerization from isonitriles to nitriles is a very well-known process[21–24] and it is included here because the formation of the isonitrile seems to be possible, showing activation energies from the azirine that are lower than the other competing paths, namely isomerization to the oxazole through either a concerted or stepwise mechanism involving the nitrile ylide,[25] in strong contrast to the semi-empirical results in which this process involves the highest energy transition state (see Supplementary material).



1g: $R_1=R_2=R_3=H$
2g: $R1=CH_3$, $R_2=R_3=H$

As can be observed in Table 1 and Figs 1 and 2, the relative energies of the minima in the potential energy surface do not change appreciably for the different computational levels reported here. For both substrates there is only a small change (1–2 kcal mol^{-1}; 1 kcal = 4.184 kJ) in the nitrile, nitrile ylide and oxazole isomers, and $\sim$4 kcal mol^{-1} in the case of the isonitriles, whereas the change in the other isomers is insignificant. This is an indication that the relative energy values for these minima at our highest computational level should be reasonably accurate.

In contrast, and to some extent as expected, the relative energy values for the transition states change more dramatically for the different computational methods. For isoxazole (Fig. 1), the energy values for all transition structures are observed to decrease to some extent. Some structures, such as the transition state connecting the ketenimine and nitrile (**1TScd**), do not change appreciably, whereas for others the relative energy decreases substantially. The implications of these differences are very important because results obtained at the MP2/cc-pVDZ level suggest that the first reaction step is the formation of the ketenimine (**1c**), whereas results at the QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level predict it to be the formation of the azirine (**1b**), in agreement with experimental evidence. It is clear that an accurate account of the electron correlation is very important for some of these transition states; transitions states **1TSab**, **1TSac** and **1TSad** have similar relative energies at the MP2/cc-pVDZ level, whereas the first one experiences a more important drop in moving to the QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level, yielding an activation energy of 53.0 kcal mol^{-1} (see Table 1). The fact that the energy of the competing pathway transition state, **1TSac**, is only $\sim$1 kcal mol^{-1} lower than that of **1TSab** and there is no experimental evidence of the formation of the ketenimine isomer, as discussed above, coupled with the difference in the energy changes in going to the better theoretical model, led us to suspect that further relative stabilization of **1TSab** can be obtained by using a more sophisticated level of theory. Furthermore, better accounting for electron correlation might also have some effect on the structures of these transition species. Reoptimization of structures **1a**, **1TSab** and **1TSac** at the QCISD/cc-pVDZ level, followed by single-point energy computations at the QCISD(T)/aug-cc-pVDZ level, shows that although **1TSac** is already converged (its relative energy drops by $<$1 kcal mol^{-1}); the same value for **1TSab** decreases by $>$8 kcal mol^{-1}. These results clearly indicate that isomerization to the azirine (**1b**) is the rate-limiting step in this reaction and the ketenimine isomer (**1c**) is not involved in the reaction mechanism. In addition, the activation energy calculated at this level is $\sim$45 kcal mol^{-1}, which is more in line with experimental results. Furthermore, we should point out that the nitrile isomer (**1d**) could not be formed directly from **1a**.

After **1b** is formed, it cannot further isomerize to **1f** either through a concerted mechanism or through involving **1e** as an intermediate in a stepwise mechanism, because the energy required for both of these processes is higher that that of the initial step. However, further isomerization of **1b** to **1d** with **1g** as an intermediate is possible when results obtained at the MP2/cc-pVDZ level are considered. The transition structure **1TSbg** is only

Table 2. *Ab initio* thermochemical results[a]

Method	Compound				ΔH_{rxn} (kcal mol^{-1})
	5	**4**	**1a,2a**	**3**	
$R_1 = H$ (1a)					
MP2/cc-pVDZ + ZPE	−209.44313	−229.28204	−245.29011	−193.38049	34.24
Exp. ΔH_f^0 (kcal mol^{-1})[b]	25.88 ± 0.10	−8.33 ± 0.16	18.78 ± 0.13	32.12 ± 0.28	33.35 ± 0.36
$R_1 = CH_3$ (2a)					
MP2/cc-pVDZ + ZPE	−248.59064	−229.28204	−284.45136	−193.38049	25.62
Exp. ΔH_f^0 (kcal mol^{-1})[b]	24.65 ± 0.13	−8.33 ± 0.16	8.14 ± 0.18	32.12 ± 0.28	23.94 ± 0.40

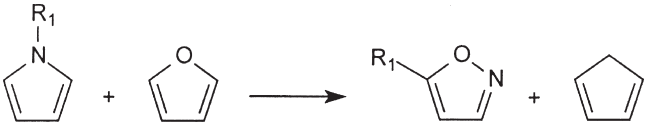
[a] Energies in atomic units, unless otherwise noted.
[b] From Ref. 30.

$\sim$0.5 kcal mol^{-1} lower than that of **1Tsab** at this level of theory, whereas **1TSdg** is very accessible. Nevertheless, as with **1TSac**, **1TSbg** seems to be already converged at the QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level, and it is expected that it will not show such a decrease in energy as in the case of **1Tsab** when going to the QCISD(T)/aug-cc-pVDZ//QCISD/cc-pVDZ level. As a consequence, these results suggest that the flash vacuum thermolysis of **1a** should produce **1b** as the major product.

The potential energy surface for the isomerization of **2a** is not much different from that of **1a**, with the exception that transition state **2TSbg** in this case also sustains a decrease in energy when going from the MP2/cc-pVDZ to the QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ level. The energy of this transition state is substantially lower than that of **2TSab**, the rate-limiting step, even at the MP2/cc-pVDZ level. Thus, the nitrile (**2d**) is predicted as the reaction product in the thermolysis of 5-methylisoxazole (**2a**), in agreement with experimental results. In addition, our results also support a reaction mechanism that involves **2b** and **2g** as intermediates. Although **2b** has been considered before as an intermediate in this reaction,[6,26] the intermediacy of **2g** has never been proposed in the thermolysis of isoxazoles. However, it has been shown that the FVT of isonitriles produces nitriles in quantitative yields[27] and early low-level *ab initio* computations[28] proposed the intermediacy of isonitrile in the isomerization of azirine to nitrile in the C_2H_3N potential energy surface.

For 5-methylisoxazole our best theoretical level predicts an activation barrier for the rate-limiting step in the isomerization of $\sim$45.0 kcal mol^{-1} (Table 1). This value is in very good agreement with the experimental value of 41.8 ± 0.4 kcal mol^{-1} reported by Pérez *et al.*[6]

Some comparisons between the values for the heats of formation obtained with our *ab initio* results, experiments and semi-empirical methods also were carried out. To calculate the heats of formation from our MP2/cc-pVDZ-level computations, we used the isodesmic reaction shown in Eqn (1). We note that even though this reaction is not rigorously an isodesmic reaction, it has been used successfully in the past to obtain the heats of formation of oxazole and other five-membered aromatic heterocyclic compounds.[29] Therefore, we used Eqn (2) and the approximation that $\Delta H \approx \Delta E$ to calculate the heats of formation (corrections to ΔE to obtain ΔH_f^0 are small enough to be considered in this case and should partially cancel each other) of **1a** and **2a** using the *ab initio* energies (including zero-point vibrational energy) and experimental heats of formation of cyclopentadiene (**3**), furan (**4**) and the appropriate pyrrole derivative (**5**), as shown in Table 2. The heats of formation for the other isomers (**1b–h**, **2b–h**) can be calculated easily once those for the corresponding isoxazoles are obtained. The results are listed in Table 3, which also includes results from semi-empirical computations (see Supplementary material), showing excellent agreement between the *ab initio* results and the few available experimental values. In addition, the relative figures should not be that different if the values from the more computational intensive QCISD(T)/aug-cc-pVDZ//MP2/cc-pVDZ method are used instead because, as shown before, the changes in their relative energies are only marginal.



(1)

$$\Delta H_f^0(\mathbf{1a},\mathbf{2a}) = \Delta H_{rxn}^0(\text{theory}) - \Delta H_f^0(\mathbf{3}) + \Delta H_f^0(\mathbf{4}) + \Delta H_f^0(\mathbf{5}) \quad (2)$$

A more comprehensive comparison of the heats of formation obtained between the different theoretical levels is feasible at this point. The agreement between the *ab initio* results and experiments for **1a** and **1b** is only matched by the MNDO results. Although the former seems to overestimate the experimental values by $\sim$1 and $\sim$1.5 kcal mol^{-1}, respectively, the errors in the MNDO figures are even smaller, emphasizing the accuracy of this method in these five-membered heterocyclic compounds. However, the situation is slightly different

Table 3. Thermochemical results on isoxazole (**1**) and 5-aminoisoxazole (**2**)

Isomer	Heat of formation[a]			Isomer	Heat of formation[a]			
	MNDO[b]	Isodesmic[c]	Exp.[d]		MNDO	AM1	Isodesmic[c]	Exp.[d]
1a	19.13	19.67	18.78 ± 0.13	2a	8.15	35.35	9.82	8.14 ± 0.13
1b	36.12	36.68		2b	30.34	40.45	25.43	
1c	12.34	18.36		2c	5.41	2.43	5.04	
1d	−7.66	−5.90		2d	−14.82	−15.08	−14.77	
1e	38.70	44.01		2e	32.30	28.06	31.86	
1f	−8.30	−3.43	-3.71 ± 0.13	2f	−19.43	5.32	−12.16	
1g	32.39	21.63		2g	25.94	15.57	7.48	
1h	42.75			2h	35.00	42.13		
1TSah	84.63			2TSah	74.05	79.75		
1TShc	89.85			2TShc	79.10	76.54		
1TScd	93.94			2TScd	90.91	115.17		
1TSbg	115.52			2TSbg	109.54	105.72		
1TShd	74.02			2TShd	67.90	59.83		
1TShb	55.98			2TShb	50.60	63.63		
1TSbe	62.52			2TSbe	55.24	65.65		
1TSef	59.20			2TSef	51.10	42.40		

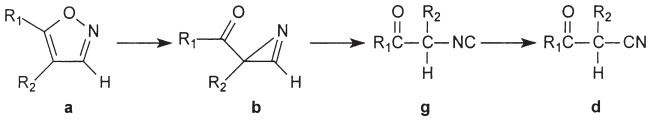
[a] In kcal mol^{-1}.
[b] From Ref. 7.
[c] Derived from *ab initio* results at the MP2/cc-pVDZ level using Eqns (1) and (2); see Table 2.
[d] Experimental values from Ref. 30.

for the oxazole **1f**, in which the *ab initio* results are more accurate than those from MNDO, with a deviation from experiment of ~ 0.5 kcal mol^{-1} in the former but MNDO overestimates its stability by almost 5 kcal mol^{-1}. As discussed in the supplementary material, the AM1 method yields unrealistically high values for these compounds. Assuming that the *ab initio* method produces more consistent values, i.e. with deviation from experiments similar for all isomers, it can be concluded that, with a few exceptions, the MNDO method yields good results considering its simplicity. However, predicting in which cases it produces reasonable results is very difficult. For example, it is surprising that MNDO yields very accurate results for the heat of formation of the small, highly strained azirine ring **1b**, whereas in **2b** the deviation is ~ 5 kcal mol^{-1}. For the open linear ketenimine (**c**), nitrile (**d**) and nitrile ylide (**e**) isomers, MNDO predicts reasonable values, underestimating the stability of **1c**, **1d** and **1e** by a few kcal mol^{-1}. In contrast, MNDO overestimates the heat of formation of both isonitriles, **1g** and **2g**, by ~ 10 and ~ 18 kcal mol^{-1}, respectively. In the latter, AM1 seems to produce a value closer to the *ab initio* results, while yielding reasonable values for **2c**, **2d** and **2e**.

CONCLUSIONS

Ab initio results at the MP2/cc-pVDZ level yield reasonably good relative energies for the minima, based on the fact that these values do not change substantially when compared with QCISD(T)/aug-cc-pVDZ-level results, suggesting energy convergence at this level. In addition, heats of formation obtained at the MP2/cc-pVDZ level using an isodesmic reaction are reasonably accurate for minima, with deviations from experiments of ≤ 1.5 kcal mol^{-1}. A different situation is found for the transition states. The activation energies at both the MP2/cc-pVDZ and QCISD(T)/aug-cc-pVDZ/MP2/cc-pVDZ levels are overestimated. Moreover, the former method yields the wrong rate-limiting step and/or the wrong reaction mechanism. These results stress the crucial importance of accounting for electron correlation, not only in computing the energy but also in obtaining an accurate molecular structure in some of these transition states.

The semi-empirical methods reported in the supplementary material support the existence of the singlet vinylnitrenes (**1h** and **2h**); however, our high-level *ab initio* computations indicate that they are not stationary points in the potential energy surface, suggesting that they are not intermediates in the thermal isomerization of these isoxazoles. We also discard the involvement of the triplet vinylnitrene in these reactions based on spin symmetry conservation. Our highest level *ab initio* calculations suggest a different reaction mechanism in the thermal isomerization of **2a** from the one proposed by Pérez *et al.*[6] This mechanism, which is shown in Scheme 2, can be generalized to the thermal isomerization of 3-unsubstituted isoxazoles and is in full agreement with known experimental results. The rate-limiting step is the concerted isomerization of the isoxazole (**2a**) to the corresponding azirine (**2b**), as proposed before, with further isomerization to the observed nitrile (**2d**) through the isonitrile (**2g**). In the case of compound (**1a**), the isomerization stops at the azirine (**1b**).



For 3-substituted isoxazoles, the 1,2-shift of the substituent to yield **g** should be less accessible and group migration should require a higher energy, which exposes the isomerization channel to the oxazole (in a concerted or stepwise mechanism) as a possible competing mechanism.

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Supplementary material

Results and discussion of the MNDO and AM1 results on the isomerization potential energy surface of **1a** and **2a**. Table including Gaussian 98 archive type files for the optimized structures of compounds **1a**–**h**, **2a**–**h** and the transition states. This material is available in Wiley Interscience.

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