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Computational studies on the asymmetric induction in intramolecular 1,3-dipolar cycloaddition of (*S*)-5-phenyl-morpholin-2-one

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Abstract

The intramolecular 1,3-dipolar cycloaddition reactions of chiral morpholinone-derived azomethine ylides with tethered alkenes and alkynes have been investigated by semi-empirical methods and ab initio quantum mechanics. The observed efficient direction of the asymmetric induction in the 1,3-dipolar cycloaddition has been modelled from a comparison of the energies of the four possible transition states arising from addition to either face of *E*- or *Z*-configured ylides. In the reaction of morpholinone with hex-5-enal, the most favourable transition state is shown to be the *anti*-addition to the *E*-ylide (E_{act} ~12 kcal/mol by HF/3-21G). By contrast, reaction with hex-5-ynal led to *anti*-addition from the *Z*-ylide (E_{act} ~19 kcal/mol by HF/3-21G) exhibiting the lowest transition state energy. The resulting trends of relative transition state energy are in excellent agreement with the experimental observations. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: 1,3-dipolar cycloaddition; semi-empirical; ab initio; activation barrier; transition state.

Azomethine ylides provide the organic chemist with a most flexible and general method of constructing pyrrollidine ring systems through a [3+2] addition to a suitable dipolarophile.[1] Thus, cycloaddition of azomethine ylides to olefinic and acetylenic dipolarophiles leads to pyrrolidines and Δ^3-pyrrolines, respectively, the latter being easily converted into pyrroles. We have shown that the 5-phenyl-morpholin-2-one system is an efficient precursor for generating chiral azomethine ylides which undergo [3+2] cycloadditions with good stereocontrol and, using the above two features, synthetic methods for generating enantiomerically pure proline derivatives have been developed.[2]

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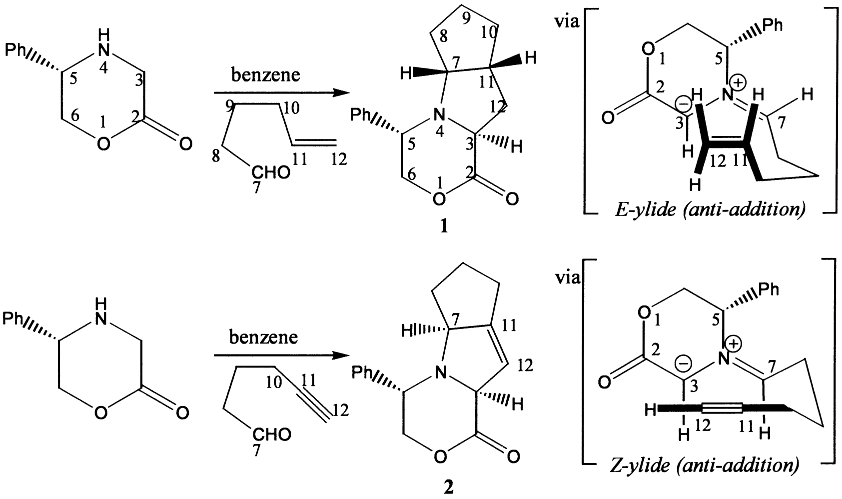
In recent publications, we have reported the synthesis of enantiomerically pure bicyclic proline derivatives.[3] The reactions of 5-phenyl-morpholin-2-one with 5-hexenal and 5-hexynal produce cleanly and efficiently cycloadducts **1** and **2**, respectively, which have different relative stereochemistry at C7 (Scheme 1). To rationalise the observed stereoselectivity a qualitative transition state model has been proposed in which diastereofacial controlled cycloadditions of either *E*- or *Z*-configured ylides give rise to the observed products. In this paper we report a validation of this proposal by ab initio quantum mechanics calculations.



Scheme 1.

Here we report the results of semi-empirical and ab initio calculations with possible reaction intermediate ylides and transition states, and describe a quantitative rationale of the different stereoselectivities. All calculations were carried out using the MOPAC in CS Chem3D version 5.0[4] and the Gaussian-94 package.[5] The initial structures of the ylide intermediates were built up using the half-chair conformation of the ring in the ylides with tethered alkenyl and alkynyl carbon chains. The transition state structures were generated from these intermediates. The structures of the intermediates and transition states were then fully optimised using the default convergence criteria at HF/3-21G as well as AM1 and PM3. Frequency calculations were subsequently carried out for the transition state structures and in each case one imaginary frequency was found confirming that the structures obtained were indeed transition states.

Four different intramolecular cycloaddition routes are possible: *E*-ylide with addition to the face *anti* to the C5-phenyl group on the morpholine ring (designated as **Ea**); *E*-ylide and *syn*-addition (**Es**); *Z*-ylide and *anti*-addition (**Z*a***); and *Z*-ylide and *syn*-addition (**Z*s***).[6] Optimised energies of the ylide intermediates (**YEa**, **YEs**, **YZa** and **YZs**), transition states (**TEa, TEs**, **TZa** and **TZs**) and products (**PE*a***, **PE*s***, **PZ*a*** and **PZ*s***) are summerised in Table 1 for the 5-ene and 5-yne reaction systems.

We have investigated TS energy from semi-empirical methods (AM1 and PM3) as shown in Table 1. One can immediately notice that the relative TS energy differences from semi-empirical calculations are too small to expect the high level of asymmetric induction in the 1,3-dipolar cycloaddition. The calculation with AM1 for the 5-ene system, for example, predicts **eTEa** to be slightly more favourable than **eTEs** by only 1.07 kcal/mol. In addition, PM3 calculation predicts

Table 1
Calculation results of cycloaddition of the 5-ene and 5-yne systems

	Cycloaddition of 5-ene system Energy a), b)					Cycloaddition of 5-yne system Energy a), b)			
	AM1	PM3	HF/3-21G	E_{act} c)		AM1	PM3	HF/3-21G	E_{act} d)
eYEa	-6.16 (0.00)	-15.35 (0.00)	-816.4732614 (0.00)		**yYEa**	30.85 (0.04)	18.65 (0.06)	-815.2760911 (0.37)	
eYEs	-5.75 (0.41)	-15.25 (0.10)	-816.4731605 (0.06)		**yYEs**	30.81 (0.00)	18.59 (0.00)	-815.2766829 (0.00)	
eYZa	-1.72 (4.44)	-12.45 (2.90)	-816.4633282 (6.23)		**yYZa**	35.18 (4.37)	22.54 (3.95)	-815.2649288 (7.37)	
eYZs	-2.54 (3.62)	-12.07 (3.28)	-816.4623292 (6.86)		**yYZs**	34.89 (4.08)	22.23 (3.64)	-815.2647553 (7.48)	
eTEa	7.67 (0.00)	5.97 (0.45)	**-816.4535898** **(0.00)**	**12.34**	**yTEa**	54.55 (2.57)	48.37 (2.80)	-815.2397552 (3.30)	23.17
eTEs	8.74 (1.07)	5.52 (0.00)	-816.4474429 (3.86)	16.20	**yTEs**	56.16 (4.18)	49.33 (3.76)	-815.2347475 (6.44)	26.31
eTZa	9.91 (2.25)	9.12 (3.60)	-816.4440495 (5.99)	18.33	**yTZa**	51.98 (0.00)	45.57 (0.00)	**-815.2450120** **(0.00)**	**19.87**
eTZs	15.13 (7.46)	12.44 (6.92)	-816.4276566 (16.27)	28.61	**yTZs**	56.96 (4.98)	49.95 (4.38)	-815.2316383 (8.39)	28.26
ePEa e)	-55.80	-67.34	-816.5805131		**yPEa**	-16.44	-35.66	-815.3835511	
ePEs	-54.63	-65.99	-816.5714821		**yPEs**	-15.88	-35.19	-815.3748979	
ePZa	-55.38	-66.80	-816.5789993		**yPZa** f)	-16.98	-36.20	-815.3814309	
ePZs	-52.73	-64.64	-816.5670418		**yPZs**	-14.59	-33.18	-815.3702532	

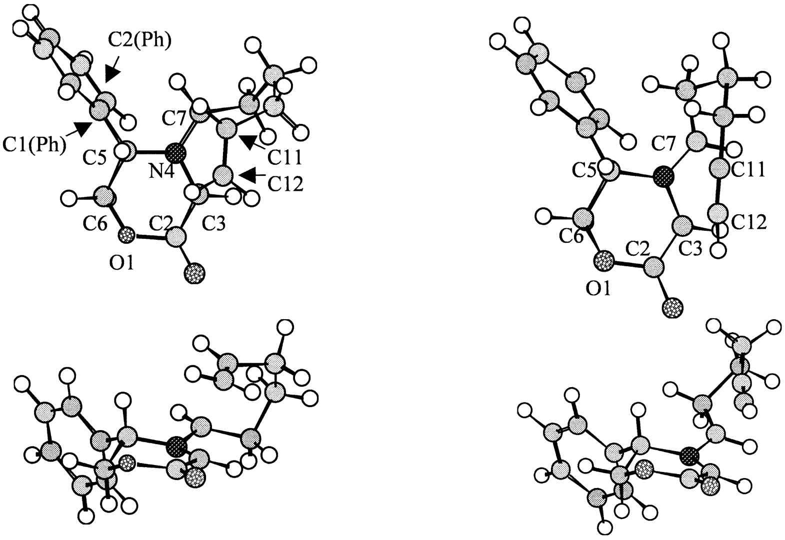
a) Units in hartrees for HF/3-21G, kcal/mol for AM1 and PM3, whose values are from heat of formation.
b) Values in parentheses are relative energies in kcal/mol.
c) Units in kcal/mol; E_{act} = E(**eT**) – E(**eYEa**).
d) Units in kcal/mol; E_{act} = E(**yT**) – E(**yYEs**).
e) Compound **ePEa** corresponds to product **1**.
f) Compound **yPZa** corresponds to product **2**.

the process via **eTEs** to be more favoured than the other processes, which conflicts with experimental observations.

We have also calculated with ab initio methods (HF/3-21G) as shown in Table 1. With the alkene dipolarophile, the four possible transition state structures were optimised and **eTE*a*** was found to be 3.8–16.2 kcal/mol lower in energy than the other three indicating that the most favourable process is *anti*-addition with *E*-ylide. In contrast with the alkyne dipolarophile, **yTZa** is the lowest transition state by 3.3–8.4 kcal/mol showing that *anti*-addition from *Z*-ylide is the most preferable process. The above trends of computational results are in excellent agreement with the experimental observations that **1** and **2** are the only products.

In both cases, the *anti*-diastereofacial selection is more favoured than the *syn*-addition. The repulsive interaction of the C5-phenyl group is increased during the *syn*-addition, which is the main reason for the preference of *anti*-additions. Regarding the possible reaction pathways, the most reactive intermediate, as measured by the lowest energy transition state in the 5-yne system is the Z-ylide **yYZa** and this indicates the favoured reaction path despite the product having a higher energy than the corresponding *E*-ylide. In contrast to the 5-ene system the *E*-ylide **eYEa** not only has the lowest energy as a reactive intermediate but also has the lowest energy transition state **eTEa** and this leads to cycloadduct **1** as the sole product. It should be noted, however, that whereas the energies of *E*-ylides are ca. 6–7 kcal/mol lower than *Z*-ylides, the products are determined by the relative energy of transition states. It therefore seems likely that there is a pre-equilibrium between the *E*- and *Z*-ylide intermediates, but the actual process for *E*–*Z* ylide isomerisation has not yet been established. However, the above theoretical results in both systems correctly explain the directions of the asymmetric reaction of 5-phenyl-morpholin-2-one with 5-hexenal and 5-hexynal.

The transition structure geometries (**eTE*a*** and **yTZ*a***) and their representative parameters are shown in Fig. 1. Here the ylides are shown by half-chair ring geometries with C6 atom directed downwards (C3-N4-C5-C6; –37.0 and –27.0°C for **eTE*a*** and **yTZ*a***, respectively) and *equatorial* 5-phenyl groups (C7-N4-C5-C1(Ph); 47.5 and 60.4°C for **eTE*a*** and **yTZ*a***, respectively). We also investigated the geometries in which the C6 atom is directed upwards (C3-N4-C5-C6; 26.2 and 26.4°C for **eTE*a*′** and **yTZ*a*′**, respectively) with a pseudo-*axial* 5-phenyl group (C7-N4-C5-C1(Ph); 95.4 and 99.7°C for **eTE*a*′** and **yTZ*a*′**, respectively. Transition state geometries were obtained via optimisation with Gaussian-94, but their energies are significantly higher than those of **eTE*a*** and **yTZ*a*** by 1.92 and 1.84 kcal/mol, respectively.[7] Presumably, the reaction should occur via **eTE*a*** and **yTZ*a***, which are the most favoured transition states in the 5-ene and 5-yne reaction systems.



eTEa

C7-C11	2.328 Å
C3-C12	2.379 Å
C3-N4-C7	120.9 °
C3-N4-C5-C6	-37.0 °
C7-N4-C5-C1(Ph)	47.5 °
N4-C5-C1(Ph)-C2(Ph)	–132.8 °

yTZa

C7-C11	2.205 Å
C3-C12	2.376 Å
C3-N4-C7	116.0 °
C3-N4-C5-C6	-27.0 °
C7-N4-C5-C1(Ph)	60.4 °
N4-C5-C1(Ph)-C2(Ph)	–144.8 °

Figure 1. Transition states of **eTEa** and **yTZa** (above for top-view and below for side-view)

In conclusion, we have investigated the energy of possible transition states in intramolecular 1,3-dipolar cycloaddition of azomethine ylides by RHF/3-21G calculation, and the results are in good agreement with the experimental results. According to the most favoured transition state geometry, the 5-phenyl group is sited in an equatorial environment and the reaction then proceeds via *anti*-addition to *E*-ylide with the alkene dipolarophile (E_{act} ~12 kcal/mol), and *syn*-addition to the *Z*-ylide with the alkyne dipolarophile (E_{act} ~19 kcal/mol). The *E*-and *Z*-ylides can be isomerised during the reaction, although the mechanisms are not clear, with an energy barrier of less than ~19 kcal/mol.[8]

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