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An ab initio and X-ray study of morpholinone derivatives: the intermolecular 1,3-dipolar cycloaddition of a derived ylide with maleimide

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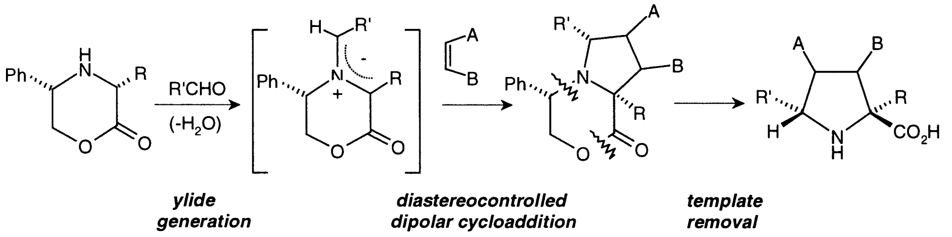
Abstract—Conformational analysis of *N*-acetyl 5-phenyl-morpholin-2-one, shows two main conformers. That which is also observed in the crystal structure determination contains the *C*(5)-phenyl substituent in a pseudo-axial position. The favored conformations of the paraformaldehyde-derived ylide, **1**, were similarly established and two conformers were also found distinguished by the position of the *C*(5)-phenyl group either in a pseudo-axial or equatorial position. Four reaction pathways for the cycloaddition of maleimide with each ylide conformer, have been examined by ab initio methods (HF/6-31+G* and B3LYP/6-31+G*) and our calculated transition state energies are in good agreement with the ratio of products observed experimentally. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

In recent years much attention has been focused on the development of chiral auxiliaries which are useful in synthetic chemistry. In particular, the morpholin-2-one system has been fully tested as an effective template for asymmetric reactions. In this system, the rigid geometry of the six-membered ring template allows for a diastereocontrolled carbon–carbon bond-formation process, which provides a useful tool for constructing α-amino acid derivatives in homologation reactions.[1,2]

It has been found that 5-phenyl-morpholin-2-one reacts with aldehydes under both thermal and catalysed conditions[3] generating an azomethine ylide species capable of undergoing highly diastereocontrolled cycloadditions. Subsequent removal of the chiral template permits the generation of proline derivatives in high enantiomeric purity (Scheme 1). Intramolecular reactions in which the dipolarophile is tethered to the aldehyde used to generate the ylide, proceed with high control of the reacting ylide geometry; whilst intermolecular reactions of alkene dipolarophiles with aldehydes other than formaldehyde show good selectivity for reaction via the *E*-azomethine ylide.

It has been previously been proposed that the six-membered ring system in morpholin-2-ones adopts a boat conformation with the axial phenyl group at C(5) playing a major role in stereocontrol.[4] In contrast, we have recently reported the results from ab initio calculations for intramolecular



Scheme 1.

Keywords: azomethine ylide; morpholin-2-one; proline; intermolecular 1,3-dipolar cycloaddition; ab initio.

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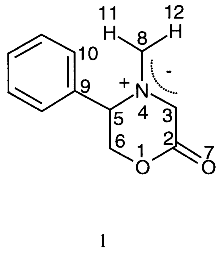

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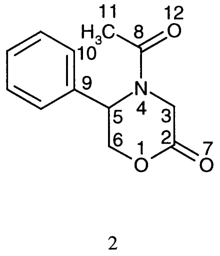

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Scheme 2.

1,3-dipolar cycloaddition reactions of (*S*)-5-phenylmorpholin-2-one with tethered alkenes and alkynes and showed that only conformations in which the *C*(5)-phenyl substituent was in an equatorial environment led to results consistent with experimental results,[5] in keeping with our predictive model.[3]

Ab initio calculations have been widely used to determine the basic reaction mechanisms[6] and the origins of stereoselectivity in 1,3-dipolar cycloadditions[7] and other pericyclic reactions such as the Diels–Alder reaction.[8] Here, we describe the origin of facial stereoselectivity in such a system by carrying out an ab initio transition state geometry calculation of the 1,3-dipolar cycloaddition[7,9,10] of the azomethine ylide,[11] **1**, to provide a quantitative explanation of experimental results. Ylide, **1**, is derived from 5-phenylmorpholin-2-one and paraformaldehyde. In order to obtain experimental data on the conformation of **1** we have carried out an X-ray analysis of *N*-acetyl morpholin-2-one (**2**), which has an equivalent [1,4]-oxazone ring system with a partially delocalised nitrogen lone-pair and the remaining ring atoms with similar hybridisation (Scheme 2).

2. Results and discussion

2.1. Conformational studies of *N*-acetyl morpholin-2-one (2)

The structure of *N*-acetyl morpholin-2-one (**2**) as determined by X-ray crystallography is shown in Fig. 1 together with the atomic numbering scheme. The known chirality at C(5) was used to select the correct enantiomorph. There are some minor differences in the torsion angles of the two molecules, but equivalent angles are within 15°. Both X-ray analysis and ab initio calculations lead to the adoption of a boat conformation. As expected N(4) is trigonal with the acetyl group in the trigonal plane (torsion angles C(3)–N(4)–C(8)–O(12) 2.3(6), 0.6(7)°). In keeping with the results of others,[12] the phenyl ring attached to C(5) is in an *axial* position and the ring plane intersects the trigonal plane of the nitrogen atom (atoms N(4), C(5), C(41) and C(3)) at angles of 86.0, 86.7°). Important torsion angles are shown in Table 1 for comparison with theoretical structures. For **2**, a detailed conformational analysis was carried out using molecular dynamics as described below. The experimental structure was used as the starting model and two distinct minima **2a** and **2b** were obtained after molecular mechanics minimisation with an energy difference of 13.72 kJ mol^{-1}. These structures were then optimized by ab initio Quantum Mechanics using the 6-31+G* basis set. The conformation of **2a** is a slightly twisted boat similar to that observed in the crystal structure (indeed when the crystal structure was used directly as a starting model the same **2a** conformation was obtained), while the conformation of **2b** is a boat (Fig. 2). Torsion angles are compared in Table 1. The energy of the two conformers showed that **2b** is more stable by 0.84 kJ mol^{-1}. A comparison with optimized geometries

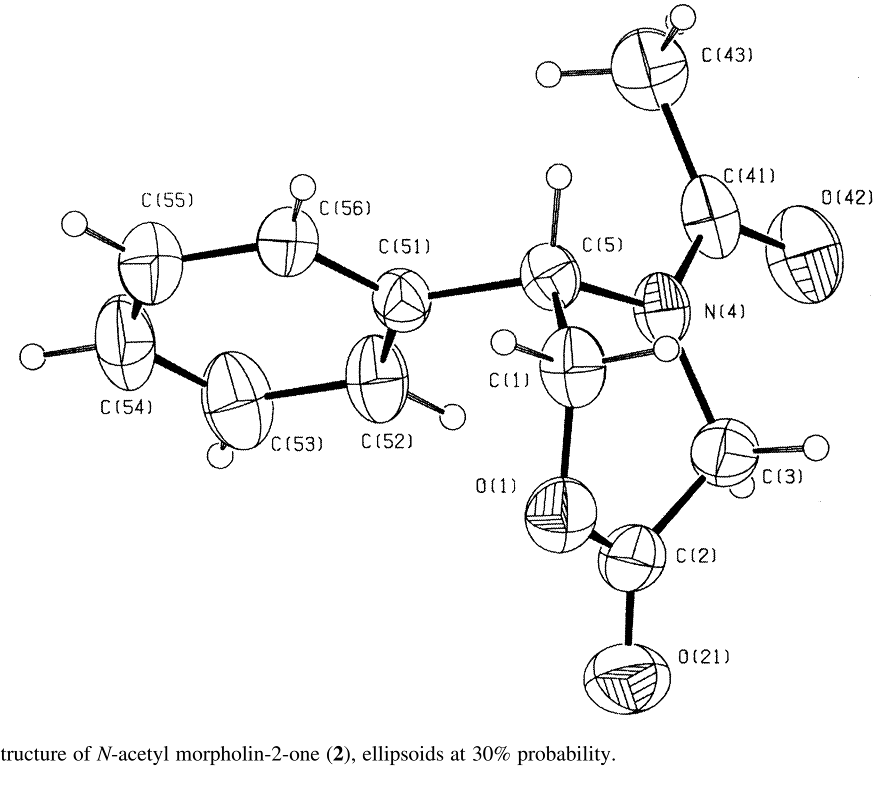


Figure 1. X-Ray crystal structure of *N*-acetyl morpholin-2-one (**2**), ellipsoids at 30% probability.

Table 1. Selected geometric parameters (Å, °) for **2a**, **2b** and X-ray structure of **2**

	HF/6-31+G*		Experimental
	2a	**2b**	Molecules A, B
Energy (hartree)	−741.066666	−741.067028	–
Relative energy (kJ mol^{-1})	0.00	−0.92	–
O1–C2	1.328	1.335	1.345(6), 1.329(8)
C2–C3	1.517	1.515	1.486(7), 1.510(9)
C2–O7	1.183	1.182	1.218(6), 1.210(7)
C3–N4	1.459	1.458	1.473(6), 1.471(7)
N4–C8	1.366	1.373	1.365(6), 1.360(7)
N4–C5	1.455	1.460	1.472(6), 1.441(7)
C8–O12	1.203	1.201	1.242(6), 1.230(7)
O1–C2–C3–N4	−28.8	38.4	−38.6(6), −38.0(5)
C2–C3–N4–C5	14.1	−48.5	30.5(6), 18.7(6)
C3–N4–C5–C6	27.1	6.6	15.6(5), 28.3(6)
N4–C5–C6–O1	−59.4	46.6	−59.0(5), −63.3(5)
C5–C6–O1–C2	49.4	−59.9	55.2(5), 47.7(6)
C6–O1–C2–C3	−3.8	14.5	−4.0(6), 3.5(6)
C8–N4–C5–C9	85.4	73.7	81.2(5), 85.1(6)
N4–C5–C9–C10	19.9	30.7	19.2(6), 15.5(7)
C3–N4–C8–O12	0.1	9.2	0.6(7), 2.3(6)
Nd–(C3–C5–C8)[a]	0.02	−0.06	0.06(1), 0.01(1)

[a] Nd, distance (Å) of nitrogen atom from C3–C5–C8 plane.

from the HF/6-31G* basis set showed an equivalent difference although results from the HF/3-21G basis set showed **2a** to be more stable by 6.61 kJ mol^{-1}. The phenyl group at C(5) adopts an axial position in order to reduce the steric interactions between it and the *N*-acyl group which will more strongly interact with equatorial substituents at C(3) and C(5). This is because the acyl group is almost coplanar with the ring structure and the equatorial substituents are closer to the plane of the ring.

The differences between bond lengths in the experimental structure and the theoretical calculations are, in most cases, less than 0.03 Å, although one exception is for the C2–O7 bond (1.183 Å for HF/6-31+G*) which is shorter than the X-ray values (1.218(6), 1.210(7) Å). We compared the structures obtained from different basis sets with the experimental data and concluded that lower basis sets than HF/6-31+G* did not produce sufficient accuracy for our calculations and were particularly inaccurate in regard of torsion angles. Of course it is possible that some variations in crystal geometry are caused by packing effects, but these are not likely to significantly affect the ring conformation. It is interesting that the conformation (**2a**) found in the crystal structure has a slightly higher energy (0.84 kJ mol^{-1}) than conformation (**2b**), but this difference is insignificant compared to possible differences in packing energies.

2.2. Conformational studies of azomethine ylide 1 from 5-phenyl morpholin-2-one and paraformaldehyde

A model structure for the azomethine ylide was built with CERIUS2 software and energy-minimized. The resulting structure was then used as the starting model for conformational analysis with molecular dynamics in the manner described below. After energy minimization with molecular mechanics, four different conformers were obtained, but when these were further fully optimized at the HF/6-31+G* level, only two distinct conformers remained. In these two structures the conformations of the morpholin-2-one ring are very similar (values of torsion angles differ by less than 5°) and can be described as half-chairs. However, the positions of the *C*(5)-phenyl group are different being *pseudo-axial* (torsion angle C(8)–N(4)–C(5)–C(9), 80.8°) for ylide **1a** and *equatorial* (torsion angle C(8)–N(4)–C(5)–C(9), −30.6°) for ylide **1b**. The difference in energy between **1a** and **1b** is small and basis set dependent with values ranging from −0.96 to 0.92 kJ mol^{-1} (see Table 2), but the higher basis sets predict **1b** to be the more stable. We

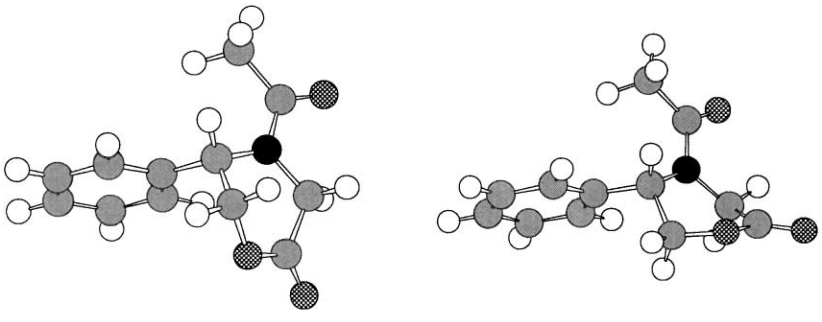

2a 2b

Figure 2. The two low energy conformers of *N*-acetyl morpholin-2-one, **2a** and **2b**, as optimized at the HF/6-31G* level of theory. Hydrogen atoms are represented by open circles, carbons by solid grey circles, nitrogens are black and oxygens are dotted.

Table 2. Calculated energies (hartree) for ylide **1a** and **1b**

Methods	**1a**	**1b**
HF/3-21G//HF/3-21G	−623.559651 (0.00)[a]	−623.559277 (0.96)[a]
HF/6-31G*//HF/6-31G*	−627.054612 (0.17)	−627.054681 (0.00)
HF/6-31+G*//HF/6-31+G*	−627.072382 (0.70)	−627.072741 (0.00)
B3LYP/6-31G*//HF/6-31G*	−630.929657 (0.00)	−630.929538 (0.29)
B3LYP/6-31+G*//HF/6-31+G*	−630.930104 (0.00)	−630.929930 (0.46)
B3LYP/6-31+G*//B3LYP/6-31+G*	−630.961029 (0.92)	−630.961388 (0.00)

[a] Relative energies (kJ mol^{-1}) for each level of theory are given in parentheses.

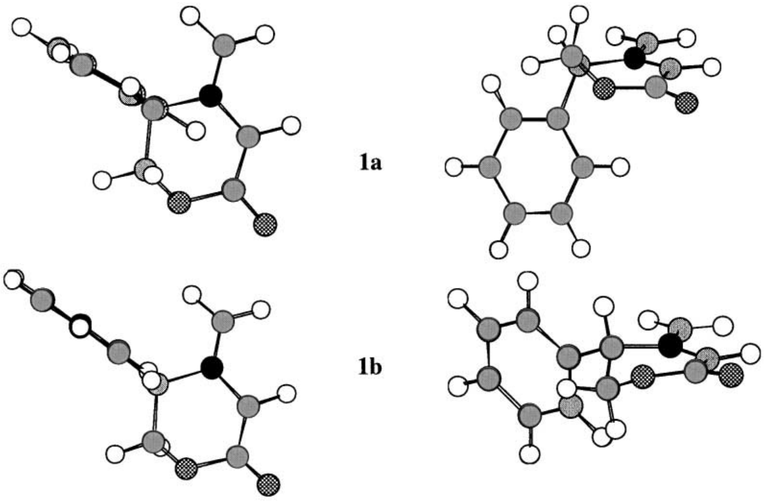


Figure 3. Two views of each of the two ylides, **1a** and **1b**, calculated at HF/6-31+G*.

conclude that the energies of the two conformers are almost equal, and that they could be easily interconverted as the energy barrier for this process is not very high. The resulting conformations **1a** and **1b** are depicted in Fig. 3, with the *C*(5)-phenyl situated in pseudo-axial and equatorial sites respectively. Dimensions are given in Table 3.

It can be seen that in both conformations the N(4)–C(8) bond lengths at 1.286 and 1.285 Å are representative of a double bond, while N(4)–C(5) at 1.491 and 1.498 Å represents a single bond. By comparison the N(4)–C(3) lengths are intermediate between these lengths at 1.363 and 1.369 Å, which are indicative of significant double bond character. As expected and illustrated by the C(2)–C(3)–N(4)–C(5) and O(1)–C(2)–C(3)–N(4) torsion angles (−7.6, 0.1° in ylide **1a**; 11.1, −4.1° in ylide **1b**), both N(4) and C(3) have approximately coplanar trigonal environments.

Table 3. Selected geometric parameters (Å, °) obtained from geometry optimisation at the HF/6-31+G* level for ylide **1a** and **1b**

	1a	**1b**
O1–C2	1.358	1.359
C2–C3	1.425	1.424
C2–O7	1.197	1.197
C3–N4	1.363	1.369
N4–C8	1.286	1.285
N4–C3	1.363	1.369
O1–C2–C3–N4	−7.6	−11.1
C2–C3–N4–C5	0.1	4.1
C3–N4–C5–C6	30.0	28.5
N4–C5–C6–O1	−56.4	−57.5
C5–C6–O1–C2	53.2	54.4
C6–O1–C2–C3	−20.3	−19.7
C8–N4–C5–C9	80.8	−30.6
N4–C5–C9–C10	51.2	−62.1
C3–N4–C8–H12	0.7	0.5
Nd–(C3–C5–C8)[a]	0.01	0.03

[a] Nd, distance(Å) of nitrogen atom from the C3–C5–C8 plane.

We also have investigated the ChelpG[13] charge value of each atom. Results are shown in Fig. 4. As expected in both ylide conformations, the C(3) atom is negatively charged (−0.81e in **1a**, −0.84e in **1b**), and N(4) positively charged (0.47e in **1a**, 0.49e in **1b**). The CHelpG atomic charges (C(3) and N(4)) as well as the bond length (N(4)–C(8) and N(4)–C(5)) describe accurately the nature of the

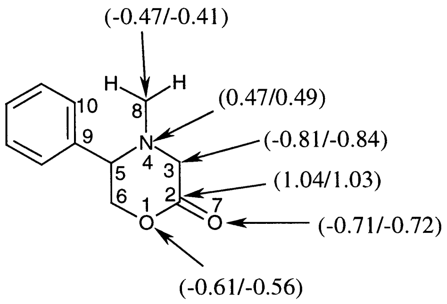
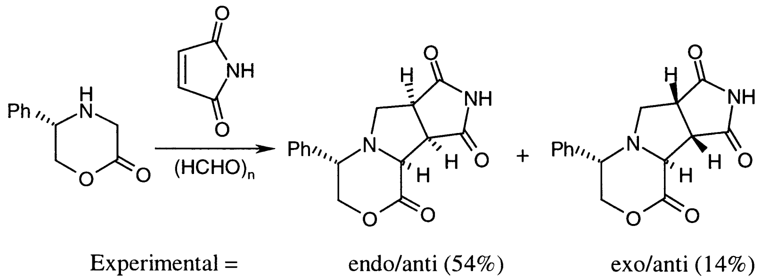


Figure 4. The partial charges on selected atoms in the ylide **1** (**1a**/**1b**) at the HF/6-31+G* level calculated via ChelpG.



Scheme 3.

ylide **1**. In addition, **1** is stabilised by the alternation between positive and negative charges in positions 1–8.

2.3. Study of intermolecular 1,3-dipolar cycloaddition of ylide 1 and maleimide

We are interested in the stereospecific outcome obtained from the reaction between ylide **1** and maleimide. Four different stereochemical approaches are possible; *exo*/*anti*, *endo*/*anti*, *exo*/*syn* and *endo*/*syn* additions. As illustrated in Scheme 3, paraformaldehyde and maleimide react with 5-phenyl-morpholin-2-one to yield the *endo*/*anti* and *exo*/*anti* cycloadduct in 54 and 14%, respectively.[3a]

In attempt to explain the experimental data we have investigated the potential energy surfaces of 1,3-dipolar cycloaddition of the ylide **1** with maleimide. For each conformer, four transition states were investigated and results for each reaction pathway (*endo*/*anti*, *exo*/*anti*, *endo*/*syn*, *exo*/*syn*) are summarised in Table 4. The relative energies of the transition states range from 0.00 to 28.53 kJ mol^{-1} at the HF/6-31+G* level. The most preferable reaction pathways are expected to be via the transition states **TS**-*endo*/*anti*-**1a** and **TS**-*endo*/*anti*-**1b** to afford the *endo*/*anti* cycloadduct as a major product. Indeed we find that the pathways to the *exo*/*anti* cycloadducts (via **TS**-*exo*/*anti*-**1a** and **TS**-*exo*/*anti*-**1b**) are shown to be of slightly higher energy than the *endo*/*anti* pathway (1.09–6.28 kJ mol^{-1}). An *anti* attack by the dipolarophile is favored over *syn* in both the ylides, **1a** and **1b**, since in **1a** the *syn* face is shielded to a large extent by the pseudo-axial phenyl at C(5), while in **1b** the *syn* face is shielded by the axial proton at C(6). This rationale is consistent with the results of the calculation as the optimized pathway of *endo*/*anti* is favored over the *endo*/*syn* and *exo*/*syn* pathways by 10.17–28.53 and 12.22–13.93 kJ mol^{-1}, respectively. These results are also in good agreement with the stereoselectivity observed in the cycloaddition of ylide **1** to maleimide and predict a product mixture containing 69% *endo*/*anti* adduct and 29% *exo*/*anti* adduct at the HF/6-31+G* level. Fig. 5 shows the optimized transition state structures of *endo*/*anti* and *exo*/*anti* pathways. Based on the optimized transition state geometries, it can be concluded that the reaction is likely to occur by the synchronous process often found in 1,3-cycloadditions. For an example, the distances in **TS**-*endo*/*anti*-**1a** for C8–C3″ and C3–C3′ are 2.361 and 2.347 Å, respectively indicative of bond formation.

The activation energies are very basis set dependent and values from the HF/3-21G level were found to be very inaccurate, e.g. values for the *endo*/*anti* addition are only 6.99–7.82 kJ mol^{-1}; far too small for 1,3-dipolar cycloaddition. Values in Table 4 are reported from HF/6-31+G* level calculations and the activation energy for *endo*/*anti* addition is calculated at 50.84–51.71 kJ mol^{-1}.

3. Conclusions

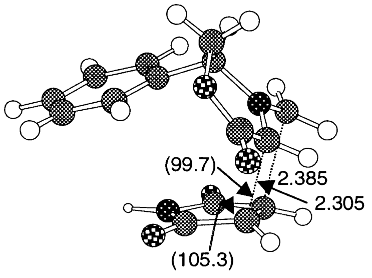
We have obtained two low energy conformations (**2a** and **2b**) of *N*-acetyl morpholin-2-one using molecular dynamics and molecular mechanics and then final geometry optimisation using the 6-31+G* basis set at Hartree–Fock level of theory. It was found that **2a** has a boat conformation with an axial *C*(5)-phenyl group, while **2b** adopts the boat form with a *pseudo-equatorial* *C*(5)-phenyl group. The boat form **2b** is predicted to be slightly more stable by 0.84 kJ mol^{-1}, although the boat conformation of **2a** is that found in the crystal structure of **2**.

The favoured conformations of ylide **1** were examined by

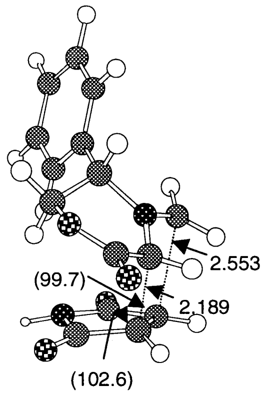
Table 4. The calculation results of possible transition states for 1,3-cycloaddition of ylide **1** with maleimide at the HF/6-31+G* level

	E_{total} (hartree)	$E_{\text{activation}}{}^{a}$ (kJ mol^{-1})	E_{relative} (kJ mol^{-1})
Maleimide	−357.418347	–	–
TS-*endo*/*anti*-**1a**	−984.471722	50.84	0.00
TS-*endo*/*anti*-**1b**	−984.471391	51.71	0.84
TS-*endo*/*anti*-**1a**	−984.469325	57.11	6.28
TS-*endo*/*anti*-**1b**	−984.471313	51.92	1.09
TS-*endo*/*syn*-**1a**	−984.460840	79.41	28.53
TS-*endo*/*syn*-**1b**	−984.467850	61.00	10.17
TS-*exo*/*syn*-**1a**	−984.466414	64.77	13.93
TS-*exo*/*syn*-**1b**	−984.467070	63.05	12.22

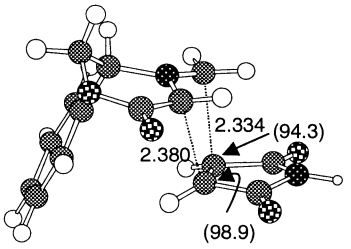
[a] $E_{\text{activation}}=E(\text{TS})-E(\text{reactant})$; $E(\text{reactant})=E(\mathbf{1b})+E(\text{maleimide})$.



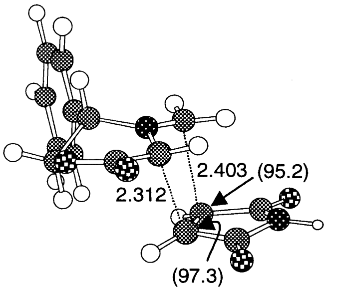
TS-endo/syn-1a



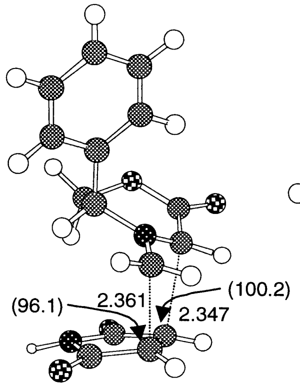
TS-endo/syn-1b



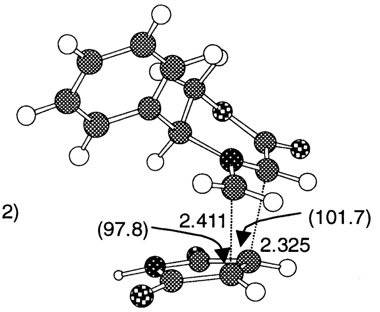
TS-exo/syn-1a



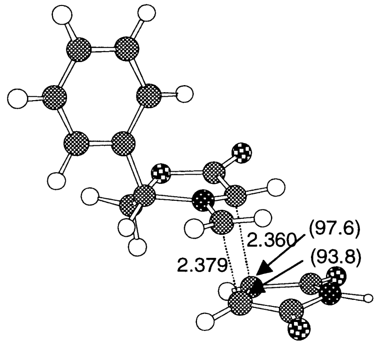
TS-exo/syn-1b



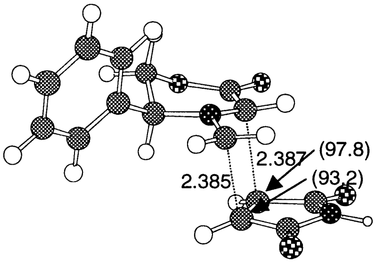
TS-endo/anti-1a



TS-endo/anti-1b



TS-exo/anti-1a



TS-exo/anti-1b

Figure 5. The optimized **TS** structures for 8 possible reaction pathways at HF/6-31+G* with latent C–C bond distances (Å) and the angles between the latent bond and dipolarphile carbon–carbon double bond, indicated at the central carbon atom. Hydrogen atoms are represented by open circles, carbons are solid grey, nitrogens are black, and oxygens are dotted.

Hartree–Fock methods (HF/6-31+G*) and a DFT method (B3LYP/6-31+G*). The results show two low energy conformations, one with the *C*(5)-phenyl group in pseudo-axial disposition (torsion angle C(8)–N(4)–C(5)–C(9), 80.8°) and the other with the group in an pseudo-equatorial orientation (torsion angle C(8)–N(4)–C(5)–C(9), −30.6°) The torsion angles N(4)–C(5)–C(9)–C(10) were shown to be 51.2° in **1a**, −62.1° in **1b** at the HF/6-31+G* level. The **1b** conformation is predicted to be more stable than **1a** by 0.22 kcal mol^{-1} at both HF/6-31+G*//HF/6-31+G* and B3LYP/6-31G*//B3LYP/6-31G* levels. We conclude that the energies of both conformers are almost equal, and could be converted easily if the energy barrier for interconversion is not very high, and both lead to approximately the same percentages of products.

Our results show that in contrast with the *N*-acetyl morpholin-2-one (**2**) in which the phenyl substituent of C(5) is found to be most stable in the axial position, the ylide (**1**) derived from morpholin-2-one and paraformaldehyde adopts one of two main conformations with the most stable having the *C*(5)-phenyl substituent in an equatorial position. These differences between the conformations of **1** and **2** show that the observed axial disposition of the phenyl substituent of C(5) in the *N*-acetyl derivative does *not* indicate an axial disposition in the related ylides. Therefore, any conclusion ascribing the stereofacial discrimination of the 1,3-dipolar cycloaddition of such ylides on the axial disposition of a C(5) substituent is unwarranted. These results also show that a second substituent, at C(6), is unnecessary in order to control the stereoselectivity of 1,3-polar cycloadditions of the 5-phenyl-morpholin-2-one derived ylides. These results concur totally with our successful predictive model in which we invoke a quasi-chair conformation of the morpholinone ring with the *C*(5)-phenyl group in an equatorial disposition.

The present work has rationalized the stereochemical issues associated with the 1,3-dipolar cycloaddition of azomethine ylide derived from 5-phenyl mopholin-2-one. The activation energy of the *endo*/*anti* pathway as the most preferable route is predicted to be 50.84–51.71 kJ mol^{-1}, while the activation energy of the *exo*/*anti* route is predicted to be 51.92–57.11 kJ mol^{-1}. These values are consistent with the experimental results observed. The energy difference of 1.08 kJ mol^{-1} between the two low energy pathways for the *endo*/*anti* and *exo*/*anti* additions corresponds to a ratio of 1.5 to 1 at 350 K in the products, compared to a recovered ratio of 3.9 to 1 experimentally. From the transition state geometry of *endo*/*anti* pathways to major product, a pseudo-axial position for *C*(5)-phenyl is predicted to be slightly more favorable than an equatorial position by 0.84 kJ mol^{-1}, though this value is insignificant compared to thermal energies and is basis set dependent.

4. Experimental

4.1. Computational methods

Conformational analysis was carried out using the QUANTA/CHARMm software[14] using the default force field. Both the grid search and molecular dynamics methods were used initially, but gave equivalent results and so the molecular dynamics method was used subsequently for all compounds. A step size of 1 fs and a temperature of 1000 K was used. 1000 conformations of the molecule were saved at 1 ps intervals and were later refined by molecular mechanics and analysed. There were less than five unique low energy conformations for both molecules. The unique minimised conformations were then used as input models to ab initio quantum mechanics calculations carried out with the GAUSSIAN-94 package.[13] Transition state structures were constructed using the CERIUS2 software[15] by carefully positioning the two relevant molecules. All geometries of the compounds and transition structures have been fully optimized at the restricted Hartree–Fock (RHF) level with the 3-21G, 6-31G(d) and 6-31+G(d) basis sets.[16] Transition state structures all displayed one imaginary frequency which corresponded to motion along the reaction coordinate.

4.2. X-Ray crystallography

Crystal data for **2**, C13 H13 N O3, M=219.23, orthorhombic, $P2_12_12_1$, Z=8, a=8.114(9) Å, b=10.473(12) Å, c=26.74(3) Å, U=2272 Å^3, dm=1.282 mg m^{-3}, F(000)=928. 6001 data were measured on a Marresearch Image Plate system and 3785 unique data (R(int)=0.0289) were used in all calculations. The structure was determined by direct methods using SHELX86[17]. There were two molecules in the asymmetric unit with similar conformations. All non-hydrogen atoms were refined anisotropically and hydrogen atoms bonded to carbon were included in calculated positions. The final refinement on F^2 using the SHELXL program[17] gave $R1$=0.0574, $wR2$=0.1676. Crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (deposition number 159802).

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