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An AM1 And PM3 Molecular Orbital Study Of The Pericyclic Reactivity Of Aryl Carbodiimides.

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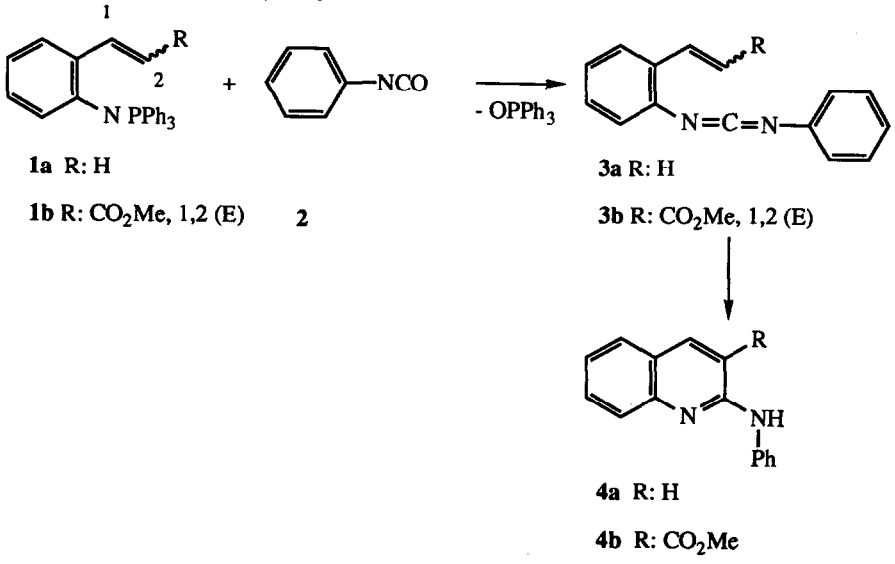
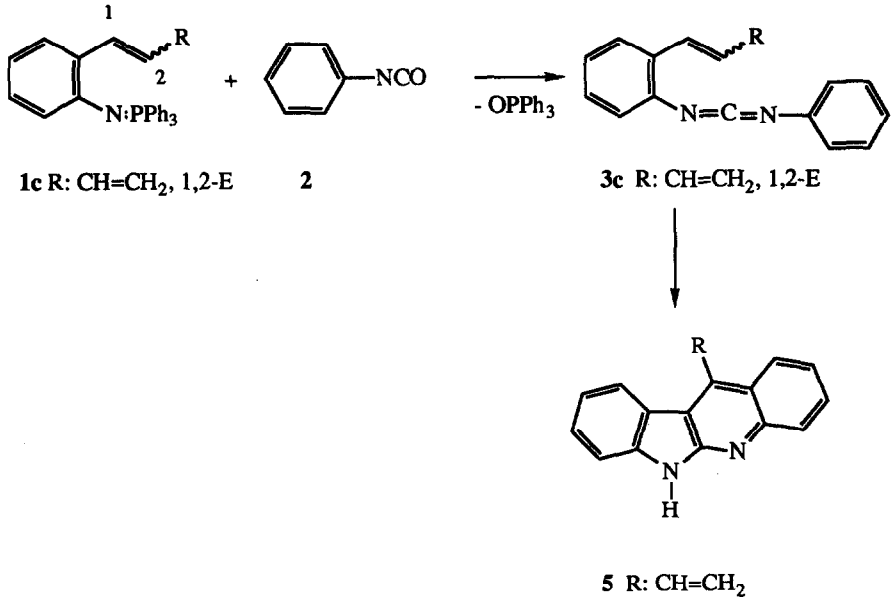
ABSTRACT: AM1 and PM3 SCF-MO calculated transition states for electrocyclisation and cycloadditions of a variety of carbodiimide intermediates (**3** or **7**) in the Aza-Wittig reaction between iminophosphoranes and isocyanates (**2** or **6**) reveal that the observed specificity of these reactions is due to a subtle combination of substituent, stereoelectronic, entropic and steric factors. The previously concluded bias of these semi-empirical methods for one-bond over two-bond reactions is supported by these calculations.

The Aza-Wittig reaction of iminophosphoranes (**1**) with phenyl isocyanate (**2**) has been observed[1] to give the carbodiimides (**3**) in good yields. These species have proved valuable precursors to a variety of heterocyclic systems when heated to 150°C in toluene, but the final product is particularly sensitive to the initial substituents.[2] Quinolines (**4a**) and (**4b**) (Scheme 1) or the quinindoline derivative (**5c**) (Scheme 2) can be obtained from reaction of (**1a**) or (**1b**) with (**2**). In contrast (**1c**) and the styryl isocyanate (**6**) gives specifically the pyrido[2,3-b]indole (**8c**), presumably *via* the carbodiimide (**7c**) (Scheme 3). The reaction is much less sensitive to substitution on the phenyl ring of **2** or **6**.[1,2]



Scheme 1

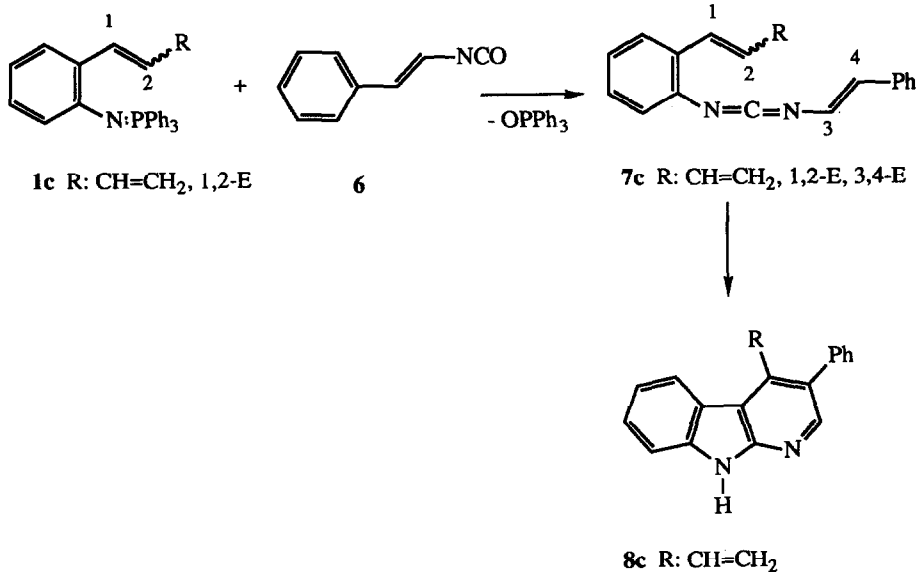
Dedicated to Professor Charles W. Rees



1c R: $CH{=}CH_2$, 1,2-E **2** **3c** R: $CH{=}CH_2$, 1,2-E

5 R: $CH{=}CH_2$

Scheme 2



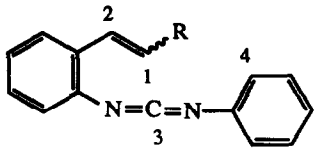
1c R: $CH{=}CH_2$, 1,2-E **6** **7c** R: $CH{=}CH_2$, 1,2-E, 3,4-E

8c R: $CH{=}CH_2$

Scheme 3

The crucial mechanistic step in these reactions is thought to involve either an electrocyclic ring closure or a $\pi^2{}_S + \pi^4{}_S$ cycloaddition reaction of the carbodiimide, followed by hydrogen shifts and aromatisation to give the final products. The observed[1,2] specificity in these reactions can be summarised as follows; *i*) Whereas **3c** reacts *via* a cycloaddition transition state **9**, species **3a** or **3b** react *via* the electrocyclic transition state **10.** Both processes involve loss of aromaticity in one phenyl ring. *ii*) The styryl analogue **7c** reacts regiospecifically *via* cycloaddition **11** rather than the alternative regioisomers **14** or **15**, The electrocyclic ring

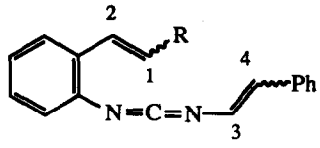
closures **12** or **13** are not observed. We wished to provide a quantitative theoretical framework for rationalising these observed specificities, and to use this framework to predict the outcome of hitherto untested variations such as the reaction of **7a** or **7b** or the reactions of the (Z) isomers **7d** and **7e**.



3a R: H

3b R: CO_2Me, 1,2-E

3c R: $CH{=}CH_2$, 1,2-E



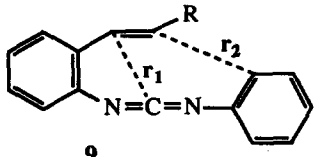
7a R: H, 3,4-E

7b R: CO_2Me, 1,2-E, 3,4-E

7c R: $CH{=}CH_2$, 1,2-E, 3,4-E

7d R: $CH{=}CH_2$, 1,2-Z, 3,4-E

7e R: $CH{=}CH_2$, 1,2-E, 3,4-Z



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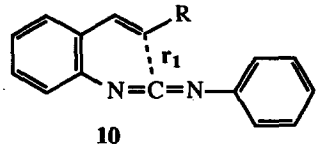

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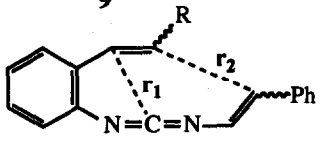

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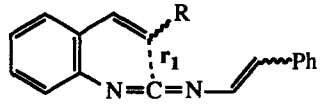

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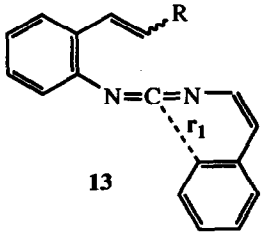

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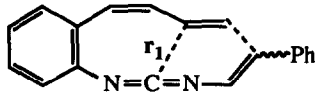

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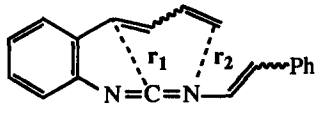

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The conventional application of frontier orbital analysis[3] to pericyclic reactivity has a number of limitations with regard to these specific reactions. The complex π orbital functionality of these systems can make it difficult to identify the appropriate occupied or unoccupied orbitals to be considered, particularly since the π orbitals of the N=C=N system are no longer orthogonal at the transition state. For example, interaction between the carbonyl group in a ketene and alkene substituents in their $\pi 2 + \pi 2$ cycloaddition can dominate the resultant stereochemistry of the product cycloalkanone[4]. Furthermore, the presence of lone pairs in the

N=C=N component introduces the possibility of stereoelectronic assistance at the transition state.[5] Frontier orbital analysis is also not well suited for quantitative comparison between electrocyclic and cycloaddition reactions, or for ring strain and steric effects resulting from differences in stereochemistry in the transition states. For these reasons, we considered a quantitative SCF-MO study involving explicit location of the transition states **9-15** to be essential. The size of these systems, and the importance of including all the functional groups[4] means a computational study is currently practicable only at the semi-empirical SCF-MO level.

A number of reports[6,7] of transition state calculations for cycloaddition reactions using the AM1 or PM3 semi-empirical Hamiltonians have demonstrated that these methods do give transition state geometries in reasonable agreement with SCF or MCSCF level *ab initio* calculations where two C-C bonds are formed. However, for reactions involving C-N bond formation, the AM1 method is known[8] to erroneously predict highly asymmetrical transition state geometries due to excessive core-core repulsion involving the nitrogen atom. PM3 transition structures involving C-N bond formation remain synchronous and the nitrogen core-core repulsion appears more correctly treated at this level.[8,9] For this reason, we have chosen to focus on the use of this method, although selected comparisons with the AM1 method have been made.

Computational Procedure.— Initial geometries for reactants were generated using the MM2(85) molecular mechanics force field, as implemented in the MacroModel (Version 3.0) program system[10]. Approximate geometries for transition states were obtained by constraining individual transition state bond lengths to ca 2.1Å using large force constants. These geometries served as the starting point for re-optimisation of all 3N-6 geometrical variables at the AM1[11] or the PM3[12] levels using the MOPAC program (Version 5.2),[13] and an eigenvector following (EF)[14] implementation for transition state location. Gradient norms of <0.03 kcal $Å^{-1}$ were routinely achievable using this procedure. Computations took typically between 8-60 minutes per transition state on either an IBM RS-6000/530 or a Tektronix CAChe workstation. Stationary points so located had one negative eigenvalue in the Hessian matrix as required of a transition state, with the correct displacement coordinates. Molecular entropies were calculated from the normal vibrational frequencies obtained from the mass-weighted Hessian matrix.

Results and Discussion.— Uncatalysed pericyclic reactions generally proceed under kinetic control and are hence a function of the transition state rather than the product stability. The gas phase calculated enthalpies of formation for reactants **3** or **7** are given in Table 1, whilst the transition state enthalpies are quoted as activation barriers relative to these reactants. Activation entropies and energies are given for selected systems. The corresponding transition bond lengths are given in Table 2.

1) The reaction of 3. We considered first the reaction of **3**, *via* transition states **9** or **10**. The calculated activation enthalpies are higher than would be expected for a reaction occurring at *ca* 150°C, but the PM3 method does predict lower barriers than AM1. The reaction of **3a** (R=H) has a lower barrier than either of the substituted systems **3b** and **3c**, consistent with the higher reactivity of a localised compared with a delocalised alkene. Both AM1 and PM3 predict a lower enthalpic barrier for electrocyclisation **10a-c** rather than for cycloaddition **9a-c** by 10.8, 12.0 and 10.1 (PM3) or 8.1, 10.1 and 7.8 (AM1) kcal mol^{-1} respectively. This is in accord with the observed reactions of **3a** and **3b**, but not so for **3c**. To understand how the these calculations relate to experiment, two effects must be taken into account. Semi-empirical methods such as AM1 and PM3 appear[7] to disfavour a two-bond mechanism (ie **9**) compared to an alternative one-bond pathway (ie **10**) by ≈ 10 kcal mol^{-1}. Secondly, the activation entropy for a two-bond reaction is likely to be more negative than for a one bond reaction, suggesting that $\Delta G^{\ddagger}$ is greater than $\Delta H^{\ddagger}$ particularly for the former (see below). If these

corrections are taken into account, then **10b** remains likely to be favoured over **9b**, but **9c** in particular might now be lower in energy than **10c**. These calculations do reveal a very fine balance between the various alternative pathways dependent on several factors, but they also serve to re-enforce the conclusions previously deduced for semi-empirical methods regarding the relative energetics of one and two-bond mechanisms.

Table 1. Calculated Activation Parameters for Pericyclic Transition States

	AM1	PM3		
	$\Delta H^{\ddagger a}$	$\Delta H^{\ddagger a}$	$\Delta G^{\ddagger b}$	$\Delta S^{\ddagger c}$
3a	124.55	118.69	-	-
9a	39.75	38.26	-	-
10a	31.68	27.47	-	-
3b	39.18	32.65	-	-
9b	47.70	46.74	-	-
10b	37.60	34.79	-	-
3c	137.68	132.83	-	-
9c	46.39	42.10	-	-
10c	38.60	32.00	-	-
7a	136.89	132.65	-	-
11a	28.07	29.67	36.58	- 17.28
12a	30.53	27.50	31.69	- 10.47
7b	50.47	48.91	-	-
11b	36.85	36.55	42.12	- 13.93
12b	35.34	31.81	33.85	- 5.10
7c	148.98	146.80	-	-
11c	35.94	33.79	41.29	- 18.75
12c	38.61	31.27	35.44	- 10.42
15c	-	37.21	43.26	- 15.11
7d	-	146.66	-	-
11d	-	34.33	37.68	- 8.37
12d	-	34.25	36.35	- 5.25
14d	-	32.31	37.18	- 11.58
15d	-	50.67	52.70	- 5.07
7e	-	149.31	-	-
11e	-	37.68	43.59	- 14.78
12e	-	31.44	33.51	- 5.18
13e	-	29.71	31.71	- 5.00
15e	-	37.62	43.13	- 13.79

[a] Calculated enthalpy of formation for reactants, calculated enthalpy of activation for transition states, in kcal mol^{-1}. [b] Calculated free energy of activation, in kcal mol^{-1} at 400K. [c] Calculated entropy of activation, in cal K^{-1} mol^{-1} at 400K.

The result favouring electrocyclisation over cycloaddition for R=CO_2Me is also readily rationalised in terms of both frontier orbital and charge control. For reactant **3a**, the π-type $HOMO_{ene}$-$LUMO_{diene}$ energy gap (in eV) corresponding to C_2-C_3/C_1-C_4 cyclo-addition (9.07/PM3, 8.95/AM1) is significantly more favourable

than the alternative $HOMO_{diene}$-$LUMO_{ene}$ (9.81/PM3, 9.81/AM1) combination. Considering therefore the coefficients of the former combination only, Σc^2 on C_2 is 0.072 and on C_3 is 0.193 (AM1). For reactant **3b**, the analogous energy gap is larger (9.30/PM3, 9.23 eV/AM1) and the coefficients smaller (0.041 on C_2 and 0.198 on C_3), hence significantly disfavouring cycloaddition for this substituent. The alternative π-type orbital combination of $HOMO_{diene}$-$LUMO_{ene}$ for **3b** is actually lower in energy, but in this case, Σc^2 for C_3 is essentially zero which also disfavours cycloaddition. A similar preference can be seen with the calculated AM1 atomic charges (C_2, -0.131, C_3 +0.147 for **3a**; C_2, -0.034, C_3 +0.146 for **3b**) which suggests there is no electrostatic promotion of cycloaddition in the presence of the ester group.

Table 2. Calculated Transition State Bond Lengths r_1 and r_2 (in Å).

	AM1		PM3	
	r1	r2	r1	r2
9a	2.127	1.946	2.018	2.125
10a	1.924		1.961	
9b	2.064	2.028	1.984	2.198
10b	1.956		1.999	
9c	1.920	2.165	1.934	2.254
10c	1.993		1.982	
11a	2.142	2.050	2.099	2.175
12a	1.914		1.956	
11b	2.107	2.100	2.077	2.233
12b	1.974		2.001	
11c	2.044	2.155	2.042	2.272
12c	1.955		1.993	
15c	-	-	2.165	2.032
11d	-	-	2.016	2.279
12d	-		1.996	
14d	-	-	2.165	2.127
15d	-	-	2.671	1.610
11e	-	-	2.075	2.270
12e	-		1.996	
13e	-		1.998	
15e	-	-	2.179	2.012

One final noteworthy aspect concerns the structure of the transition states **9** and **10** (Figure 1). Both *endo* and *exo* isomers are possible for **9**, but we found that the *exo* form was 13.5 kcal mol^{-1} higher than the *endo*, and was not considered further in this study. In principle, two isomers relating to the configuration about the C=N-Ph double bond are possible in **10**. Only one could be located, corresponding to a stereochemistry in which the nitrogen lone pair was located specifically *antiperiplanar* to the forming/cleaving C-C bond. Such stereoelectronic effects have been previously noted in hydride transfer reactions[5] and in this instance, the effect induces a transition state geometry that is sterically more hindered than the alternative configuration in which the nitrogen lone pair would have been *syn* to the forming C-C bond. Such a result again emphasises how explicit consideration of the transition state can reveal effects that a frontier orbital treatment of the reactant cannot.

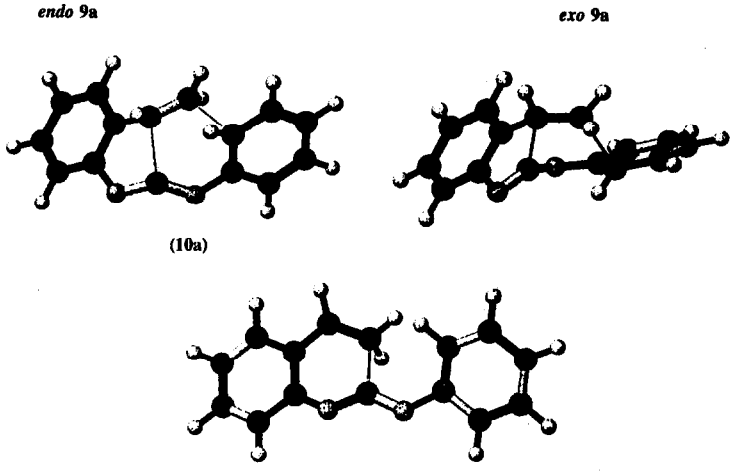

Figure 1 Calculated PM3 structures for transition states *endo* **9a**, *exo* **9a** and **10a**. Bonds with *ca* single bond character are shown in red, *ca* double bond character in yellow and transition state bonds in green. The radii of the bond cylinders are proportional to the calculated bond orders.

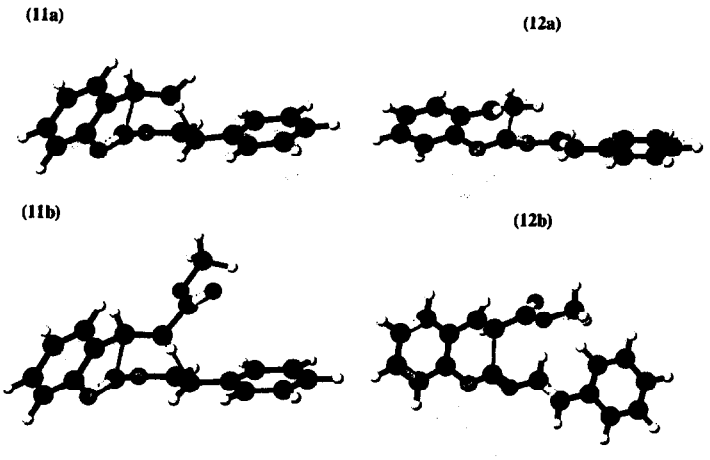

Figure 2. Calculated PM3 structures for transition states **11a**, **12a** , **11b** and **12b**.

ii) The Reaction of 7. The transformation of 7 is more complex than 3, since the addition alkene bond can participate in the reaction. Furthermore both (E) and (Z) isomers for two of the three double bonds are possible. In the original experimental study[1,2], only the (Z) isomers were employed. Our calculations reveal several interesting trends. Firstly, the enthalpic preference for electrocyclisation **12** over cycloaddition **11** is much reduced compared with **3** as a reactant, since unlike **12**, no aromaticity is destroyed in **11**. For the reaction of **7a**, AM1 predicts **11** to be actually more stable than **12** by 2.5 whilst at the PM3 level **12** is the more stable by 2.1 kcal mol^{-1} (Table 1). For both Hamiltonians, the approximate correction discussed above of 10 kcal mol^{-1} in favour of the two-bond transition state **11** would clearly now favour this mode. The

introduction of an ester group (**7b**) disfavours **11** for much the same reasons as discussed previously for **3b**, as does the entropic contribution to $\Delta G^{\ddagger}$ (Table 1). but neither effect is sufficient to inhibit cycloaddition as the preferred mode once the two-bond correction is applied. In both cases, the stereoelectronic effect incurred from the nitrogen lone pair is apparent in the transition state **12** (Figure 2).

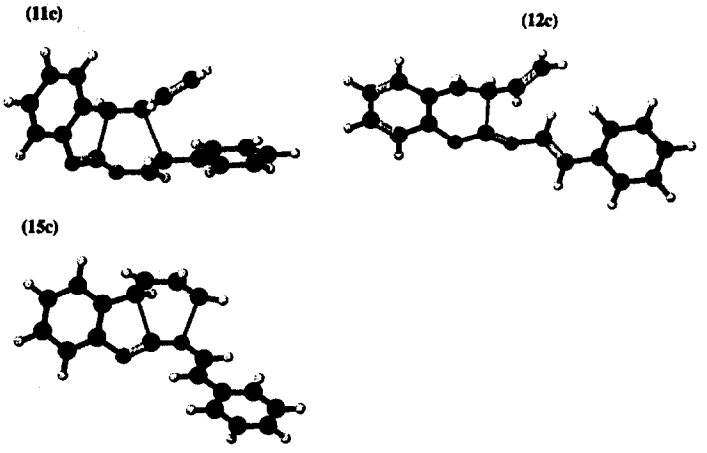

Figure 3. Calculated PM3 structures for transition states **11c**, **12c** and **15c**.

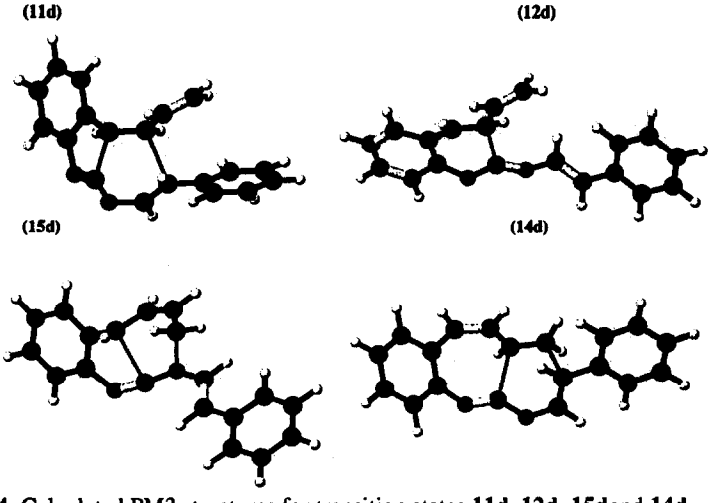

Figure 4. Calculated PM3 structures for transition states **11d**, **12d**, **15d**and **14d**.

The introduction of a double bond (**7c**, Figure 3) makes possible an alternative cycloaddition reaction (**15c**) involving the butadiene component and the C=N group, which is nevertheless not observed experimentally. The PM3 activation enthalpy for this mode is indeed higher (Table 1), but interestingly, its entropy is less negative than for **11c** which means that the discrimination in $\Delta G^{\ddagger}$ is smaller than in $\Delta H^{\ddagger}$. The AM1 transition state **15c** reveals the typical asynchronous behaviour associated with the formation of C-N bonds[8].

The isomer **7d** represents an interesting example of the application of theory to predicting a novel experiment.

Whilst this isomer was isolated during purification of **7c**, no reactions on it were performed in the original experimental study.[1,2] The change in stereochemistry allows a new cycloaddition mode **14d** and indeed this mode is the lowest according to activation enthalpy. Again, a significant difference in entropy means that from the point of view of free energy barriers, **11d** and **14d** are virtually isoenergetic. This prediction remains to be verified experimentally. In contrast, **15d** becomes prohibitively high in energy due to the considerable amount of strain introduced. This strain energy has one unique consequence, rendering the PM3 transition state highly unsymmetrical (Figure 4, Table 2). Whilst high level *ab initio* calculations appear to have clearly established that unstrained $\pi^2_s + \pi^4_s$ cycloadditions are normally symmetrical and hence synchronous reactions, this does not preclude asymmetry in cases where steric strain might favour such a geometry. One such example of strain induced asymmetry is of $\pi^2_s + \pi^2_a$ cycloaddition reactions involving an antarafacial component[7] and **15d** may represent a rare example of a strain induced asymmetric $\pi^2_s + \pi^4_s$ cycloaddition. However, a contrary interpretation[7] is that **15d** represents a failure of the PM3 carbon parametrisation; in particular of the subtle details in the core-core repulsion functions. Clearly high level *ab initio* calculations are needed to resolve this point.

The final predictive example involves changing the stereochemistry of the other isolated double bond (**7e**). Here yet another transition state alternative (**13e**) becomes possible. The calculations show **11e** to be clearly higher in energy than the isomeric **11c**, and this in turn can be attributed to less conjugation between the phenyl group and the adjacent reacting system as a result of steric effects. The lowest energy transition does in fact correspond to the electrocyclic reaction **13e**,.by a margin in free energy of 11.4 kcal mol^{-1} over the lowest cycloaddition **15e** (Table 1). This difference is close to the ≈ 10 kcal mol^{-1} two-bond correction discussed above, and suggests that these two pathways are finely balanced. Ultimately, computational accuracy of < 1 kcal mol^{-1} would be required to ensure reliable predictions of the outcome of these reactions!

Conclusions. A comprehensive wealth of experimental detail is available for the periselectivity of a range of carbodiimides **3** and **7**. Semi-empirical modelling of these reactions without compromising on the nature of the substituents is shown to be quite successful in rationalising this selectivity, provided known errors of the methods are taken into account. The selectivity arises from a complex interaction between electronic (orbital and electrostatic) effects, steric effects resulting from specific stereochemistry, stereoelectronic effects arising from nitrogen lone-pairs and entropic effects from the different degrees of freedom in the various transition states. Modelling of hitherto unobserved substituent schemes results in several specific predictions which are in principal amenable to further experimental study.

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