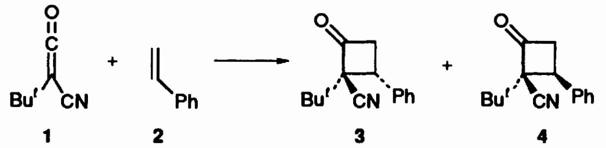
An MCSCF Study of the Effect of Substituents and Solvent on the [2 + 2]Cycloaddition of *tert*-Butylcyanoketene to Phenylethene

Mar Reguero,[a] Rafael R. Pappalardo,[a] Michael A. Robb[a] and Henry S. Rzepa†,[b]
[a] *Department of Chemistry, King's College London, Strand, London, UK WC2R 2LS*
[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*

The effect of solvent and substituents on the [2 + 2]cycloaddition of *tert*-butylcyanoketene to phenylethene (styrene) was studied using a CAS-MCSCF method with a four orbital four electron active space in an STO-3G basis. The most favoured reaction path proceeds *via* a biradical intermediate in which the steric interactions between the three substituents are minimised, an arrangement which nevertheless results in a final cyclobutanone product in which the Bu^t and the Ph groups adopt the less stable *cis* rather than the more stable *trans* stereochemistry. A continuum solvation model based on a multipolar expansion within an ellipsoidal cavity suggests that benzene solvent enhances this preference. The results agree quantitatively with previous semi-empirical results, although the interpretation differs.

The mechanism of organic cycloadditions has been the subject of many experimental and theoretical studies for many years.[1] Arguments have been presented defending concerted mechanisms, synchronous and asynchronous but a strong case has also been made supporting step-wise mechanisms *via* biradical-like intermediates.[2] Indeed several mechanisms can be competitive for a single reaction depending on substituents, ring size or solvation conditions. Accurate treatment of substituents and solvent is increasingly recognised as essential, since interactions between even quite remote groups can be either repulsive or attractive. Each group may also play a critical electronic role and the various interactions may be modified by solvent. While *ab initio* procedures constitute suitable theoretical methods for investigating model systems, realistically substituted systems have been more conventionally treated by semi-empirical methods because of computational cost. The purpose of this paper is to examine the validity of this strategy, with *ab initio* computations including solvent corrections for the cycloaddition of *tert*-butylcyanoketene to phenylethene (Scheme 1). In particular the subtle interplay between the electronic roles of the phenyl, carbonyl and cyano groups, and the possibility of longer range repulsion or attraction between these groups and also the Bu^t group needs to be investigated.



Scheme 1

It has been long known that [2 + 2]cycloadditions of ketenes produce predominantly the more hindered product.[3] For example, experimental evidence[3b] indicates that the only product of the cycloaddition of *tert*-butylcyanoketene **1** to styrene **2** in benzene as solvent is the cyclobutanone **3**, with the Ph and the Bu^t groups vicinal and *cis*, although conventional conformational analysis would suggest that the *trans* stereoisomer **4** should be more stable on steric grounds. Nevertheless, it is possible that if appropriately orientated and spaced, Ph and Bu^t groups can adopt a less expected *cis* orientation,[4] due it is thought to weak electrostatic interactions which might be described as π-facial hydrogen bonding onto the face of the phenyl ring. Such a possibility emphasises the need to explicitly include all substituents in modelling such reactions within the framework of full geometry optimisation. For the examples of **3** and **4**, a previous such AM1 semi-empirical SCF-MO investigation[5] found the latter to be energetically favoured by about 4 kcal mol^{-1} ‡ suggesting that **3** is truly the less favourable product thermodynamically, with in this instance no apparent π-facial electrostatic stabilisation.

Detailed *ab initio* MC-SCF computations on the model system ethene + ketene have been carried out previously[6,7] and the reaction between **1** and **2** has been investigated semi-empirically including solvent effects.[5] For the model [2 + 2]cycloaddition reactions between ethene + ethene and ethene + ketene, MCSCF computations[6,7] show that the *supra-antara* ($\pi^2s + \pi^2a$) transition structure is a critical point of order two and the actual transition state is highly asymmetrical and biradical-like. For the ethene + ketene cycloaddition, both concerted and non-concerted paths have been explored.[7] The energetically favourable mechanism corresponds to a highly asynchronous attachment of the alkene into the plane of the ketene to form a biradical intermediate, in the process preserving the π-conjugation of the ketene component. The AM1 computations on **1** + **2** yielded a similar surface topology. It is one objective of this paper to use MCSCF methodology to show the influence of more realistic substituents on the mechanism of such cycloaddition reactions.

A second objective of estimating the influence of solvent on the relative energies of stationary points is a more difficult target, as the different available approaches for the theoretical calculation of solvation energies still suffer from diverse technical or intrinsic difficulties.[8] The use of discrete models to represent the solvent make the calculations computationally expensive and the global minima for the supermolecule can be very difficult to locate with confidence. Continuum models for the solvent by-pass this problem and enable the use of more accurate approximations for the solute, but the requirement for the calculation of gradients during geometry optimisation imposes current restrictions on the models that can be used. The best developed of these in terms of *ab initio* gradient techniques are models based on a multipolar expansion of the dielectric screening energy, centred within a regular spherical or ellipsoidal cavity. This is the model that will be used here, but as

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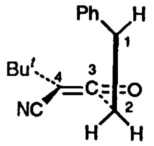
† E-mail: rzepa@ic.ac.uk.

‡ 1 cal = 4.184 J.



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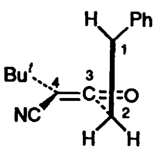

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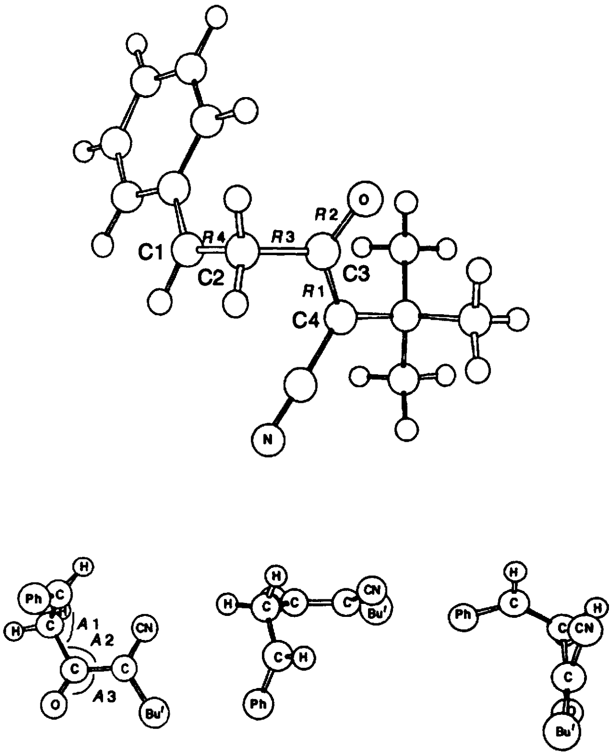

Fig. 1 MCSCF optimised geometry for **6**; internal parameters are given in Table 1

it will be seen, the application to our complex system gives only qualitative results. Models in which solvent accessible areas of irregular shape are defined using finite element constructions and a distributed multipolar analysis of the charge distribution is used are intrinsically more satisfactory. Recent progress in evaluation of the gradients required for optimisation of stationary points[9] using such methods suggests that reliably predicting the effect of solvent on the geometries of stationary points may soon also become possible.

Computation

The calculations have been carried out at the CAS-MCSCF level using the GAUSSIAN-92 package of programs,[10] employing the direct MCSCF[11] method and a STO-3G basis set. The use of such a minimal basis set is dictated by the size of the system. The active space contains four orbitals and four electrons corresponding to the p_π systems of the reactants that will form the new bonds in the product. The optimisation of the geometries was performed in the complete set of internal coordinates with an MCSCF gradient procedure.[12] For the inclusion of the solvent effects the continuum model used is that of Rivail *et al.*[13] as implemented in the SCRFPAC program[14] and modified for the MCSCF wavefunction. The gas phase geometries were used without further optimisation. The cavities used were ellipsoidal, being derived from the gas phase optimised geometries, and the multipole expansion was developed up to the 6th order. Some calculations were done to 15th order to test for convergence.

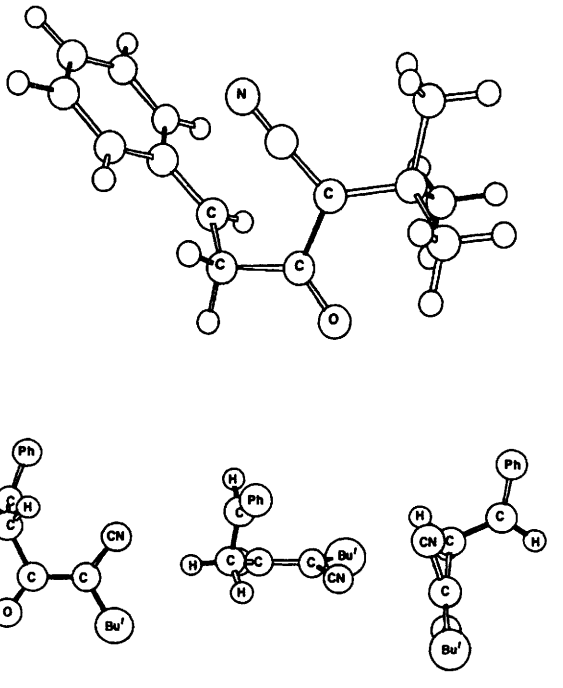

Fig. 2 MCSCF optimised geometry for **5**; definition of internal parameters as in Fig. 1

Results and Discussion

The key point in understanding the stereochemistry of this reaction is the comparison of the transition states of the reaction paths leading to the two possible products **3** and **4**, and the role of solvent effects on their relative stabilities. Guided by the results for the model system and previous semi-empirical investigations of the substituted system, the search was confined to the region of the surface corresponding to bond formation between C(2) and C(3). The trajectory of the forming C(2)–C(3) bond occurs approximately in the plane of the Bu^t and CN substituents and lies *anti* to the Bu^t group to minimise repulsion with this group. This direction of approach makes the π-oxygen orbital rotate to maintain the double bond with C(3), breaking the C(3)–C(4) double bond, but allowing the five p_π orbitals of the O=C–C–C=N fragment to be parallel and hence conjugated. Furthermore, an approximately orthogonal rather than a parallel orientation of the C(1)–C(2) and C(3)–C(4) bonds should minimise any non-bonded repulsion between C(1) and the ketene. Such an orientation can also be thought of as constituting part of any antarafacial component enforced by considerations of orbital symmetry in a purely concerted reaction pathway, rather than of steric requirements in a biradical like structure. Within these constraints, two configurations **5** and **6** can be envisaged, the former resulting in eventual formation of the *trans* product **4** and the latter resulting in formation of the observed *cis* product **3**.

Isolated Molecule Models.—While the transition state C(2)–C(3) distance for the model ketene + ethene system was ≈ 1.9 Å, we could not find such a transition state in this region for either **5** or **6**. Rather, the optimisation procedure converged to a different region where this bond was already formed [C(2)–C(3) = 1.58 Å]. A search for a minimum converged to essentially the same geometry as this transition state, indicating a very flat region in the potential energy surface where the geometries of the transition state and the nearby minimum are essentially indistinguishable, and for which therefore the distinction between a concerted and a stepwise reaction is difficult to make. The geometries of the minima correspond to a biradical intermediate in which the ring is open (Figs. 1 and 2)

Table 1 Main geometrical parameters (Å or °) and energy differences (kcal mol^{-1}) between **5** and **6**

	AM1[5]		MCSCF		MCSCF	
	6	**5**	Ketene + ethene[6]		**6**	**5**
E_{tot}[a]					−698.482 27	−698.480 60
*R*1	1.45	1.45	1.34[b]	1.35[c]	1.52[c]	1.52[c]
*R*2	1.24	1.24	1.30	1.40	1.22	1.22
*R*3	1.57	1.56	1.97	1.58	1.58	1.58
*R*4	1.41	1.41	1.40	1.50	1.52	1.52
*A*1	100.4	101.6	114.0	124.4	111.4	109.7
*A*2	112.6	113.7	107.7	112.2	116.3	116.6
*A*3	129.7	128.9	138.6	122.1	122.0	121.9
Dihed[d]	59.8	−69.0	67.9	95.9	61.5	−66.4
ΔE_{6-5}		3.2				1.1
E_{tot}(PhH)[e]					−698.486 15	−698.482 71
ΔE_{6-5}(PhH)[e]						2.16

[a] In Hartree (1 $E_h \approx 4.359\,75 \times 10^{-18}$ J). [b] Transition state. [c] Minimum. [d] Dihedral angle C(1)–C(2)–C(3)–C(4). Labelling of parameters referring to Fig. 1. [e] MC Self-consistent-reaction-field model, using a relative permittivity of 2.28 corresponding to benzene. Calculated volume for **5**, 416.88 Å^3; **6**, 416.90 Å^3. Dimensions of principal ellipsoidal axes, *a,b,c* 3.52, 3.77, 7.51 Å (**5**), *a,b,c* 3.56, 4.03, 6.94 Å (**6**).

with the most important geometrical parameters listed in Table 1. The reaction path to form products corresponds to the C(1)–C(4) closure of the ring without a significant barrier. The Hessian was calculated numerically for the most important internal variables in the reaction coordinate, *i.e.* the C(2)–C(3) distance and the C(1)–C(2)–C(3)–C(4) dihedral angle (Figs. 1 and 2). The lowest eigenvalue was found to be very small for both the transition state and the intermediate minimum, being <0 for the former and >0 for the latter. The optimised geometries are similar to those obtained previously using the semi-empirical AM1 method, whilst the small calculated AM1 value of the transition state imaginary mode corresponding to C(2)–C(3) formation (52 cm^{-1}) is supported by the present finding that the surface is very flat. Comparison of the reaction paths for both conformers reveals that **6** is energetically favoured at the *ab initio* level, but the difference in energy of 1.05 kcal mol^{-1} between the minima may not be entirely large enough to explain the experimental predominance of the *cis* product. This experimental result is obtained in benzene, and we shall discuss the results of including solvent effects in the calculation of the potential energy surfaces and location of reaction paths below.

From the geometries of intermediates it is clear that the higher energy of **5** in this region is not due to any interaction between any atoms of the Ph and Bu^t groups, since in both cases the shortest distance is large enough to ensure that these two groups will not interact either attractively or repulsively (5.14 Å for **6**, 5.47 Å for **5**). However, for the phenyl and cyano groups, the distances are small enough and sufficiently different (4.38 Å for **6**, 3.69 Å for **5**) to produce a differentiation in favour of **6** due to mutual non-bonded repulsion between the electrons in the two π systems when these groups are close. It is possible that appropriate substitution on the phenyl ring (*e.g. p*-nitro) might reduce such repulsion, and hence the selectivity of this reaction! The most significant effect of the substituents is on the geometry of the biradical intermediates. In the unsubstituted system, the C=C double bond (*R*1) in the ketene fragment is maintained, whilst the C=O double bond (*R*2) becomes single with the oxygen bearing the radical site. The reverse is true for **6**, the carbonyl double bond being retained and the C=C bond is converted to a radical site on C(4) stabilised by both the CN and Bu^t groups. The differences in the dihedral angle between **6** and the unsubstituted systems are easily understandable due to steric effects of the bulky substituents.

Solvation Models.—The most significant difference between the AM1 and *ab initio* results is found in the value of the dipole moment for **6** [6.4 D(AM1), 1.5 D(MCSCF)]. We attribute this to the single determinantal nature of the AM1 wavefunction which overemphasises the gas phase ionic contributions. However it is also true that neglect of solvent dipole stabilisation might over emphasise the importance of biradical contributions. To assess these effects and to reproduce the experimental conditions, dielectric screening effects corresponding to benzene were introduced for the gas-phase geometry of the minima, on the assumption that such solvation will not induce major changes in the geometry.[15] The screening energy is computed using a continuum model in which the electrostatic solute–solvent interaction is represented using a multipole expansion of the solute charge distribution. Unfortunately, despite many attempts satisfactory convergence could not be obtained and the present results provide only a semi-quantitative indication. Multipole expansion of up to 6th order has been used successfully for other systems,[16] but did not converge here even using 15 terms. In order to check if the divergence was due to an inappropriate definition of the cavity, the accessible molecular surface value[17] was computed using the GEPOL program[18] and the cavity was scaled to give the same volume. The same divergent behaviour was observed. The distances between the atoms and the wall of the ellipsoids were computed using the program Ellipsoid,[19] which revealed that no atom was close enough to the wall to justify the divergence. In order to test if the source of the problem was the limitation of the small basis set used, some calculations were performed at the UHF level using a 3-21G basis set, also with similar lack of convergence. These results suggest that the multipolar expansion about the centre of the cavity must be suspect. An ellipsoidal cavity does not adequately reproduce the shape of the molecule and the charge distribution in such a complex system must be poorly represented by a monocentric expansion. This might occur for example when the dipole or higher moment of the molecule does not coincide with the centre of the ellipsoidal cavity.

In spite of these problems, the results using a 6th order expansion give a qualitative measure of the influence of the solvent on the two competitive reaction paths. The dielectric screening stabilisation for the minima in benzene was 2.43 kcal mol^{-1} for **6** and 1.32 kcal mol^{-1} for **5** with the result that the *cis* reaction path is now favoured by 2.16 kcal mol^{-1}. We note that this model does not take into account other contributions to the solvation enthalpy such as dispersion terms. These MCSCF results are more in accordance with experiment, and indicate a slightly larger dipolar character for **6** than for **5**. This result also serves to emphasise the importance of including solvation corrections for such asynchronous pericyclic reactions, where a significant measure of observed selectivity may originate from differential solvation effects.

Conclusions

In spite of the fact that semi-empirical methods such as AM1 introduce non-dynamic electron correlation in an ambiguous way, the agreement between semi-empirical and MCSCF treatment of substituent effects in the reaction between **1** and **2** is remarkably good. The use of an STO-3G basis in the present case is justified by the fact that STO-3G and 4-31G computations on the model system give rise to the same surface topology. The present results not only clearly indicate that the observed stereochemistry of the product of reaction can be explained at least in part by considering the steric interactions in the biradical like intermediate, and need not involve any explicitly antarafacial components in a concerted transition state, but also highlight that solvation effects may play a major role. The problems associated with the solvent model used in this work based on a monocentric multipolar expansion of the charge distribution within an ellipsoidal cavity must serve as a warning to the potential users of this method for large molecules, and serves to encourage development of alternative methodologies based on more realistic cavity models and charge distributions.

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