

The Reactions of 1,2,3-Triazolium-1-imides with Dipolarophiles: Kinetics and Mechanism. Azolium 1,3-Dipoles

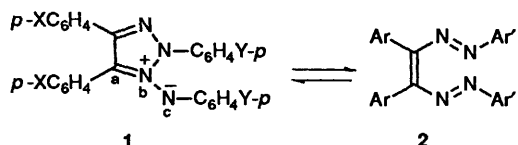
Richard N. Butler,^{a,*} Fiona A. Lysaght^a and Luke A. Burke^b

^a Chemistry Department, University College Galway, Ireland

^b Chemistry Department, Rutgers University, Camden, New Jersey 08102, USA

The reactions of substituted 1,2,3-triazolium-1-imides with dipolarophiles are dipole-HOMO controlled concerted cycloadditions. The second-order rate constants are insensitive to solvent polarity and the reaction shows a high negative entropy of activation. Substituent effects at the triazole carbon terminus of the dipole show a linear Hammett σ_p correlation with $\rho = 1.51$. Substituents at the N-terminus of the dipole show a rare inverted V-type Hammett correlation with the reaction being dramatically inhibited by both MeO and NO₂ groups. Dipolarophile variation suggests that triazolium imides are Type I dipoles. The regioselectivity of the reactions agree with *ab initio* calculated orbital coefficients and HOMO and LUMO energies.

Recently we described a wide synthetic scope for 1,2,3-triazolium-1-imide systems (1) in consecutive multi-step reactions with a range of 2π dipolarophiles which lead to many new ring systems¹ (Scheme 1). The compounds 1 are 1,3-dipoles and



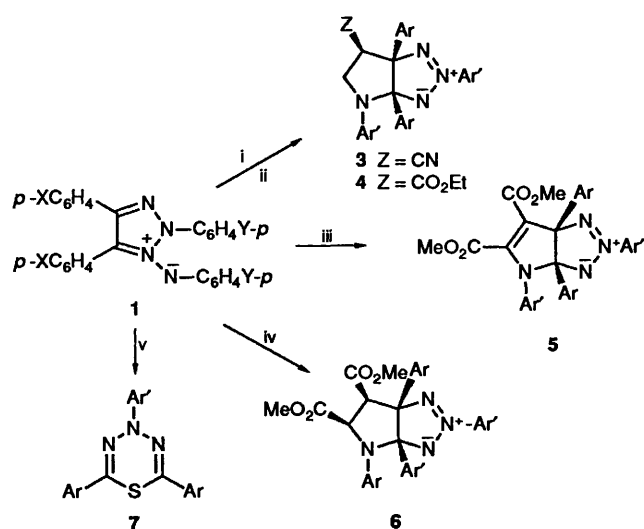
they are in equilibrium with a 1,2-*cis*-bis(arylo)ethene form 2 which is unreactive towards 2π -dipolarophile molecules.^{2,3} From the stereospecificity of the observed reactions and limited preliminary pseudo-first-order kinetic data we favoured a 1,3-dipolar cycloaddition process for the reactions. Herein we report a study of the second-order rate constants for these reactions including (i) the influence of substituent variation at the carbon and nitrogen termini of the dipole, (ii) variation of dipolarophiles, (iii) solvent effects and (iv) thermodynamics of activation. These measurements are complemented by *ab initio* calculations on the dipole and determinations of Sustmann⁴

ΔE values [eqn. (1), Scheme 2] for reactions with a range of dipolarophiles. The results show the reactions to be concerted 1,3-dipolar cycloadditions with the compounds 1 behaving as type I dipoles.^{4,5a} These, however, show a rare^{5b} and remarkable inverted V-shaped Hammett correlation for substituents at the N-terminus of the dipole.

Results and Discussion

(i) Kinetics.—(a) *Substituents and solvent.* The kinetics of the series of reactions in Scheme 1 have been measured by following the disappearance of the dipole 1 at an appropriate UV wavelength (Table 1). In each case the first part of the reaction involves an interaction of the 2π -molecule at atoms a and c of the molecules 1. The final products 3–7 arise from subsequent reactions of the initial adduct.¹ The first reaction could be a Michael-type addition giving a dipolar intermediate *i.e.* a two-step cycloaddition or it could be a concerted one-step cycloaddition. The response of the second-order rate constant for the reactions of 1a with acrylonitrile (AN) in four solvents is shown in Table 1. The rates are independent of solvent E_T values[†] and similar to values reported^{5c} for concerted cycloadditions of 1,3-dipoles such as diphenyldiazomethane. Hammett plots for the influence of substituents at the carbon terminus a and the nitrogen terminus c of the dipoles 1 with AN in acetone at 37 °C are shown in Fig. 1. The rates for the substituents X at the carbon terminus show a good linear correlation with Hammett σ_p values giving $\rho = 1.51$ ($r = 0.999$) [Fig. 1(a)]. This behaviour is indicative of a dipole HOMO controlled reaction *i.e.* a Type I dipole.⁶

Substituents Y (Scheme 1) at the nitrogen terminus of the dipole surprisingly gave an inverted V-shaped Hammett plot [Fig. 1(b)]. Bent Hammett plots are a common feature of concerted 1,3-dipolar cycloadditions but they are usually V or U shaped and they arise when dipoles show Type II behaviour, *i.e.* when the respective HOMO–LUMO energy separations of both pairs of reactants are approximately equal. In these situations all substituents enhance the reaction relative to hydrogen. The dipoles 1 show the reverse in a rare phenomenon where all substituents inhibit the reaction [Fig. 1(b)]. The data suggest correlations with σ^+ and σ^- values for substituents



Scheme 1 Reagents: i, acrylonitrile (AN); ii, ethyl acrylate (EA); iii, dimethyl acetylenedicarboxylate (DMAD); iv, dimethyl maleate (DMM); v, methyl cyanodithioformate (MCDTF). Ar = *p*-X-C₆H₄; Ar' = *p*-Y-C₆H₄. For Y = H, X = H (a); Me (b); MeO (c); Cl (d); NO₂ (e). For X = H, Y = H (a); Me (f); MeO (g); Br (h); NO₂ (i).

[†] The solvent polarity parameter E_T is used as defined in N. A. Issacs, *Physical Organic Chemistry*, Longman Scientific and Technical, Harlow, Essex, 1987, p. 194; the Hammett σ values used herein are from the same source, p. 134.

Table 1 Second-order rate constants measured at 37 °C in acetone

Reaction no.	Dipole ^a	Dipolarophile ^a (solvent)	λ^c/nm	$k_2/10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
1	1a ^b	AN ^b	400	1.47 ^b
2	1b	AN	410	2.07
3	1c	AN	440	2.21
4	1d	AN	400	0.455
5	1e	AN	430	0.081
6	1f	AN	400	0.615
7	1h	AN	460	0.055
8	1b	AN	410	0.41
9	1i	AN	500	0.0061
10	1a	MCDTF	400	1630
11	1a	DMAD	400	800
12	1a	EA	400	0.57
13	1a	DMM ^a	400	0.108
14	1a	AN (MeCN)	400	1.53
15	1a	AN (C ₆ H ₆)	400	1.265
16	1a	AN (EtOAc)	400	0.86

^a See Scheme 1. ^b Arrhenius data: at 30 °C, $k_2 = 0.815 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$; at 25 °C, $k_2 = 0.60 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, $\Delta E^{\text{act}} = 57.5 \text{ kJ mol}^{-1}$ at 25 °C, $\Delta H^{\text{act}} = 55.1 \text{ kJ mol}^{-1}$, $\Delta S^{\text{act}} = -122 \text{ J mol}^{-1} \text{ K}^{-1}$.

^c Wavelength λ at which rates were measured.

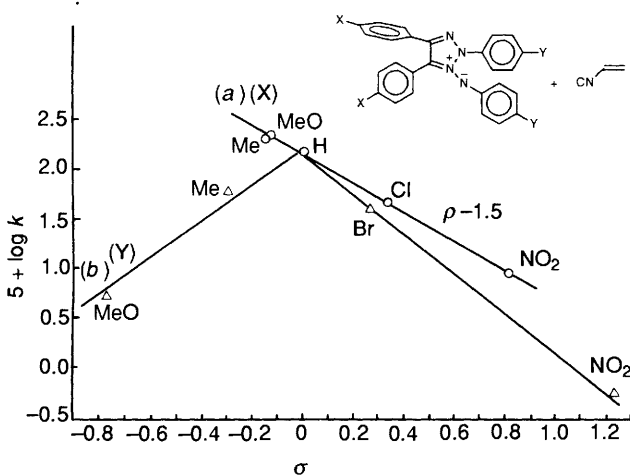
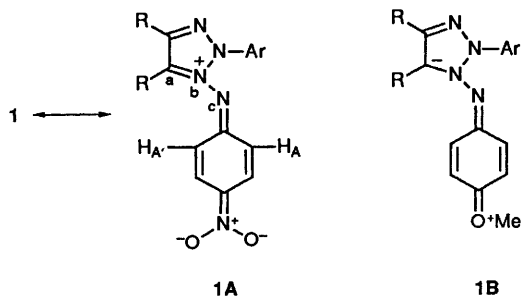


Fig. 1 Plots of $\log k$ vs. Hammett σ values for the reaction of compounds **1** with AN: (a) for substituents X, Y = H; (b) for substituents Y, X = H (Scheme 1)

indicating strong resonance interactions and we suggest that the rate inhibition arises from resonance destruction of 1,3-dipole character in the substrates **1** as shown in structures **1A** and **1B** rather than a change in mechanism.



In both of these forms the orthogonal π -electrons on the nitrogen terminus of the dipole are replaced by a π -bond to the aryl substituent and 1,3-dipole character is lost. In a study of the structure of these dipoles we have previously² obtained direct evidence for a strong contribution from form **1A** when, at -87°C , the 270 MHz proton NMR spectrum showed severely restricted rotation of the N–C bond at the nitrogen

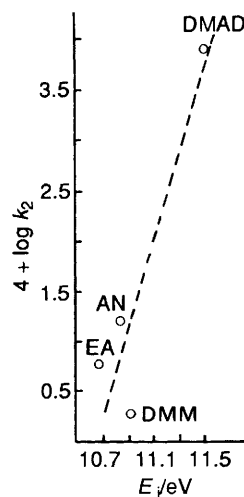


Fig. 2 Plot of $\log k$ vs. dipolarophile ionisation potential (E_i) for the reaction of **1a** with dipolarophiles

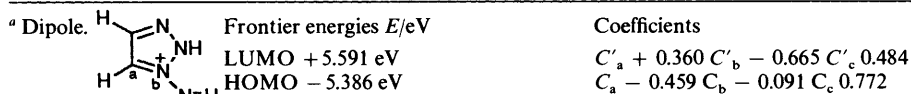
terminus and gave two separate doublet signals from the protons H_A and $H_{A'}$ in **1A** [$R, R' = (\text{CH}_2)_4$] thereby confirming the double bond character in the N–C aryl bond.² Thus, the capacity of the 1,2,3-triazole ring to behave as a source of electrons and an electron sink allows for strong interactions with both electron-donating and -withdrawing substituents, thereby increasing the activation energy by stabilising the ground state and reducing the reactive 1,3-dipole character giving rise to Fig. 1(b). These rate inhibitions did not affect the synthetic nature of the reaction and in all of the reactions of the substrates **1a–i** with AN the products **3** were formed in high yields. A possible alternative explanation for the effect of the Y-substituent on the kinetics could be interference by the dipole cyclic–acyclic equilibrium, $1 \rightleftharpoons 2$. If the substituents acted in opposite directions on the equilibrium and the cycloaddition reaction it could give rise to a Hammett plot like the one observed. However, we do not favour such an explanation because it implies that at one or other end of the sequence the reaction should be changing to first order *i.e.* where the dipole formation becomes the rate-controlling step. This was checked carefully and pure second-order rates were observed in all cases. We believe the cyclic–acyclic equilibrium in the dipole is much more rapid than the cycloaddition reaction.

(b) *Dipolarophiles and thermodynamics of activation.* The second-order rate constants for the reaction of the dipole **1a** with five dipolarophiles at 37 °C in acetone are shown in Table 1 (no. 1, 10–13). A plot of $\log k$ vs. the ionization potential of the dipolarophile (Fig. 2) places these reactions on the upper right-hand limb of the Sustmann⁶ and Huisgen⁷ U-shaped curves. Kinetic measurements were also attempted on cyclohexene and the enamine 1-*N*-pyrrolidinocyclohexene but these were so slow as to be unmeasurable. These latter two dipolarophiles would be on the left-hand limb of a U-shaped curve and hence U-shaped behaviour is not observed with the dipoles **1** confirming their Type I dipole HOMO-controlled behaviour. The C=S bond of methylcyanodithioformate (MCDTF) shows 'super-dipolarophile'⁸ character and its reactions with the dipole **1a** are over 1000 times faster than those of AN. This feature was strikingly evident in the synthetic reactions which could be carried out at ambient temperatures.⁹ Arrhenius data (Table 1, footnote b) gave a high negative entropy for the reactions which is consistent with a concerted cycloaddition process.

(c) *Regioselectivity.* Using HMO perturbation theory, Sustmann^{4,6} has provided eqn. (1) (Scheme 2) as a measure of the transition state energy gain for bond formation between the dipole termini a and c with the dipolarophile atom d and e.

Table 2 STO-3G calculations^{a,b}

Reaction no. (from Table 1)	Dipolarophile	Frontier energies, E/eV		Coefficients		TS 1 vs. TS 2	
		HOMO	LUMO	C _d	C _e	ΔE ($\Delta E'$) ^d	ΔE ($\Delta E'$) ^d
				C' _d	C' _e		
				C'' _d	C'' _e		
12	EA	-8.873	0.452	0.477	-1.214	-1.097	
		6.405	0.489	-0.681	(-1.812)	(-1.778)	
		11.248	0.676	-0.477			
1	AN	-9.091	0.514	0.548	-1.579	-1.457	
		6.033	0.576	-0.747	(-1.961)	(-1.916)	
		12.258	0.598	-0.364			
13	DMM	-9.555	0.414	0.414	0.712	-0.712	
		5.160	0.422	-0.422	(-1.697)	(-1.697)	
		8.180	0.162	+0.162			
		13.459	0.761	-0.761			
11	DMAD	-8.873	0.441	+0.441	-1.086	-1.086	
		+4.996	0.535	-0.535	(-1.837)	(-1.837)	
		8.681	0.166	+0.166			
		11.548	0.628	-0.628			
10	MCDTF	-6.907	0.266	-0.619 ^c	-1.270	1.335	
		4.204	0.674	-0.710	(-1.439)	(-1.582)	
		11.712	0.497	-0.209			

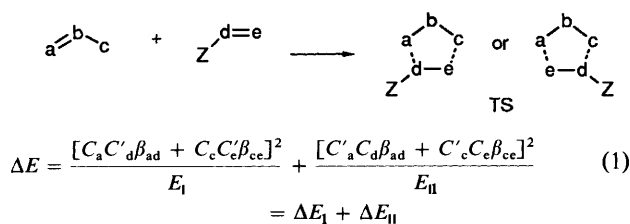


^b STO-3G calculated orbital energies, coefficients and ΔE values [Scheme 2, eqn. (1)] for some reactions in Table 1. An early TS with 2 Å distance between the connecting atoms was chosen and calculations were performed using optimised geometries for dipole and dipolarophile. ^c The HOMO coefficients have a negative sign as it is part of a branched 6 π -electron system. ^d $\Delta E'$ values incorporate the interaction of the dipole HOMO with all of the unoccupied orbitals (UMOs) of the dipolarophile.

Bond formations which give the highest ΔE values are the most favoured. STO-3G calculated ΔE values (Scheme 2) for the reactions are shown in Table 2. The values for the dipole **1** were necessarily calculated for the parent structure with hydrogen atoms in place of the aryl substituents and values for the dipolarophiles were calculated using hydrogen atoms in place of methyl groups of ester moieties (Table 2). For nos. 12 and 1 (Table 1) the ΔE values agree with the observed regioselectivity of the reactions where the bond connections giving the higher ΔE values were exclusively observed with AN and ethyl acrylate (EA). In the case of MCDTF one would expect a matching of the largest HOMO-LUMO coefficients on the S and N atoms, giving a-d, c-e (Table 2), based on Frontier Molecular Orbital Theory. This is not the case experimentally⁹ or from the ΔE

values which gave greater absolute values for the a-e and c-d matching. This result can also be expected from Hard-Soft Acid-Base Theory wherein the softer S in the C-S pair would bond with the softer C atom of the 1,3 dipole.

(ii) *Mechanism*.—The previous synthetic studies¹⁰ had shown the reaction to be a stereospecific *endo* addition. The results herein support our preliminary suggestions of a concerted dipole-HOMO controlled cycloaddition with orbital-controlled regioselectivity giving a transition state B (Scheme 3) where the dipolarophile approaches over the plane of the triazolium imide dipole to give an initial unstable adduct **9**. The *endo*-orientation could be due to favourable secondary orbital interactions (which are possible in all of the dipolarophiles used) or to favourable alignment of dipoles (**8**, see arrows) in the transition state. A rapid 1,4-sigmatropic rearrangement in the adduct **9** gives rise to the main products **3-6** which are represented by the general structure **10** (Scheme 3). In some cases this structure may progress through further steps⁹ to give products such as **7**, which could also be formed *via* decomposition of the initial cycloadduct as in Scheme 4.

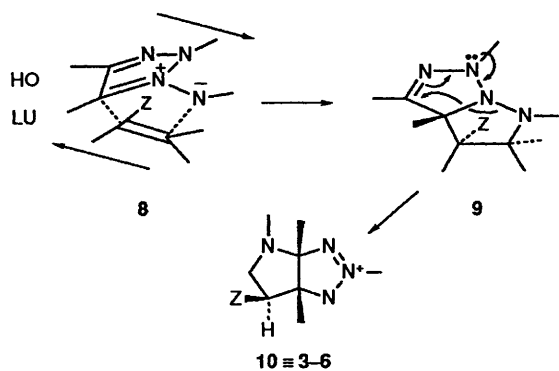


E_I = HOMO (1,3-Dipole) - LUMO (Dipolarophile)
 E_{II} = HOMO (Dipolarophile) - LUMO (1,3-Dipole)
 C_a, C_c, C_d, C_e : atomic orbital coefficients of HOMO
 C'_a, C'_c, C'_d, C'_e : atomic orbital coefficients of LUMO
 β_{ad} and β_{ce} = resonance integrals of new σ bonds

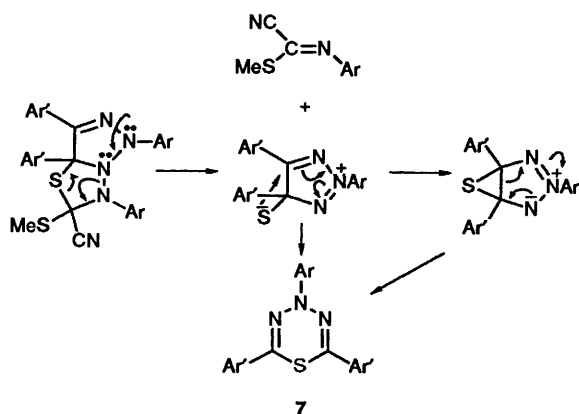
Scheme 2 STO-3G calculated ΔE values

Experimental

The substituted 1,2,3-triazolium-1-imide 1,3-dipoles/1,2-bis-(arylo)ethenes **1** were prepared by oxidation of the corresponding bis(aryl hydrazones) of substituted benzils using procedures previously described.^{2,10} Synthetic reactions giving high yields of the substituted products **3-7** were carried out by methods similar to those previously reported.¹⁰ Details of the



Scheme 3



Scheme 4

parent compounds and some derivatives have already been described¹⁰ and the remainder will be reported elsewhere. The rate constants (Table 1) were measured by following the disappearance of the dipole **1** at the wavelengths shown (Table 1) using a Philips PU8740 UV-VIS scanning spectrophotometer equipped with an internal timer and a constant-temperature cell compartment. Temperatures were accurate to ± 0.5 °C. The accuracy of reproduction on the rate constants was $\pm 2.5\%$. Rates were measured under pseudo-first-order conditions with the dipolarophiles present in a molar excess of at least 2500. The pseudo-first-order rate constants k_1 were obtained from straight line plots of $\ln(A_t - A_\infty)$ vs. t , the slopes of which were $-k_1$. These k_1 values gave linear plots with the initial concentration of the dipolarophile (as expected for normal second-order reactions) and the second-order rate constants k_2 (Table 1) were the slopes of these lines. The rate constants quoted are the mean values of at least three runs. Because of interference by product and dipolarophile absorptions a different method was used for rates with MCDTF (reagent **v**, Scheme 1). A published procedure^{11,12} for obtaining rate constants when initial and final absorption readings are uncertain which involves the use of identical concentrations of the reactants was found to be successful and gave a reproducible rate constant (no. 10, Table 1).

In the theoretical calculations the geometries of the molecules studied were optimized using the standard force constant methods for *ab initio* SCF-MO calculations as found in the GAUSSIAN88 series of programs.¹³ The split-valence 3-21G basis set¹⁴ was employed throughout, except for MDCTF where the 3-21G* basis set¹⁴ was used. This latter set provides the same basic functions as does the 3-21G set but also an

extra set of d orbital functions are included on second row atoms such as sulfur.

The use of these two closely-related basis sets leads to accurate geometries.* However, being of a double-zeta type they lead to two coefficients for every pair of s and p atomic orbitals that are combined to form molecular orbitals. In order to fit the Sustmann E formula there should be a minimum basis set calculation performed, which provides one atomic orbital coefficient with its s and p type functions. Therefore, calculations using the STO-3G minimum basis set were performed using geometries optimized with the larger basis sets.

The values of the resonance integrals β in eqn. (1) were taken from the work of Houk¹⁵ where the internuclear distance was chosen to be 2.0 Å. This distance is close to that found in the Diels-Alder transition-state structures.¹⁶ The resonance integrals involving the S atom in MDCTF were estimated to be 20% less than those involving the C atom,¹⁷ viz.; $\beta_{CC} = 5.00$, $\beta_{CN} = 4.35$, $\beta_{CS} = 4.00$, $\beta_{NS} = 3.48$ (at 2.0 Å), in accord with usual practice.¹⁵

* Optimised geometries will be supplied upon request to L.A.B., e-mail address: Burke@Zodiac.rutgers.edu.

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