The kinetic profile of phthalazinium-2-dicyanomethanide 1,3-dipole with 2π-dipolarophiles: U-shaped dipolarophilic activity and classic type II dipole behaviour. Reaction rates and DFT calculations

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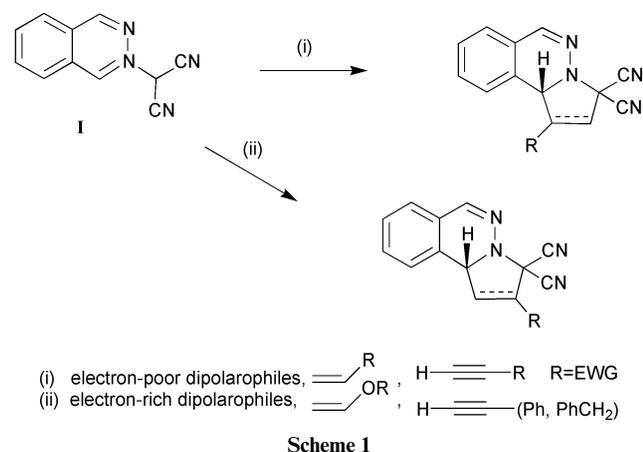[a] Chemistry Department, National University of Ireland, Galway, Ireland
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Kinetic data measured for the reactions of phthalazinium-2-dicyanomethanide 1,3-dipole with 26 dipolarophiles ranging from electron-poor to electron-rich place this dipole firmly in the class II category where reactions may be dipole-HOMO or -LUMO controlled depending on the nature of the dipolarophile. Minimal solvent polarity effects, small Hammett ρ values, and highly negative entropies of activation and DFT calculations support concerted non-synchronous cycloadditions and the observed regiochemistry for the full range of dipolarophiles.

There has been wide interest in the synthetic reactions of exocyclic azinium ylide 1,3-dipoles, systems where two of the four π electrons of the 1,3-dipole are part of an azine π-system.[1–5] However, kinetic studies of such systems are rare. Herein we report a full kinetic profile of the phthalazinium-2-dicyanomethanide dipole **I** in its reactions with a significant range of dipolarophiles. While our work was in progress Sauer *et al.*[6] reported a kinetic study of some substituted pyridazinium dicyanomethanides without the fused benzo moiety with a number of dipolarophiles. The reactions of their systems were mainly dipole-LUMO controlled.[6] We have previously reported on the synthetic reactions (stereospecific) of the dipole **I** with symmetrical alkenes and alkynes,[7] and on the reaction of the unstabilised dipole **I** (H for CN) with thioketones.[8] Recently, we have reported[9] a detailed synthetic study on the regiochemistry of the reaction of **I** with unsymmetrical alkenes and alkyne dipolarophiles (Scheme 1). The observed reversals of

Fig. 1 Experimental rates *versus* DFT ionization potential.

420 nm, the disappearance of which could be readily followed to infinity values in a range of solvents. Second order rate constants for a series of dipolarophiles, ranging from electron-poor to electron-rich, are listed in Table 1. These are plotted against the ionization potential of the dipolarophile, representing the HOMO energy, in Fig. 1. The plot is a classic "U-shaped" curve showing the dipole to be a "Type II"[10,11] system where the HOMO–LUMO and LUMO–HOMO gaps are similar for either mixing in the transition state. For a single dipole the preferred frontier orbital interaction then varies with the dipolarophile. On the right hand side of the curve the reactions are dominated by the HOMO dipole–LUMO dipolarophile interaction in the transition state. A small part of this limb of the curve represents *p*-substituted *N*-phenylmaleimide dipolarophiles (**19**–**26**, Table 1). The rate constants for a series of these are in Table 1 (Section C) and they give a Hammett ρ value of +0.15 in agreement with a dipole-HOMO controlled reaction,[11] the rates being slightly enhanced by electron-withdrawing groups which lower the LUMO energy. On the left hand side of Fig. 1 the reactions are LUMO dipole–HOMO dipolarophile controlled and this change accounts for unexpected reversals of regiochemistry which we have

(i) electron-poor dipolarophiles,
(ii) electron-rich dipolarophiles,

Scheme 1

regiochemistry and unexpected product mixtures merited a kinetic study as did the paucity of detailed kinetic data on azinium ylide 1,3-dipoles in general and the absence of kinetic data on the dipole **I**.

Results and discussion

The dipole **I** is particularly suitable for kinetic studies. It is a stable compound with a strong UV–VIS absorption band at
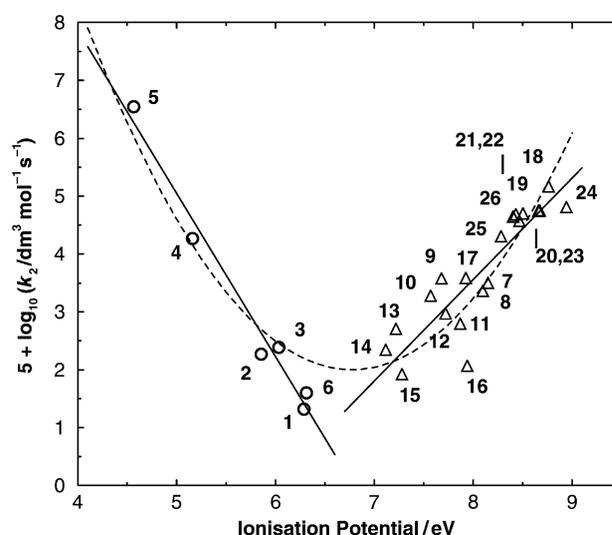
observed[9] with some electron-rich dipolarophiles (Scheme 1)]. The effects of solvent polarity on the rates for a series of selected dipolarophiles from both sides of the curve in Fig. 1 are given in Table 2. Solvent variations of 2 to 3 orders of magnitude are expected for reactions involving two steps with dipolar intermediates. In all cases the reactions are insensitive to solvent polarity (Fig. 2) as expected for concerted cyclo-additions. The reaction does not change to a two-step process for electron-rich dipolarophiles as is the case[13] with the other non-aromatic azomethinium dicyanomethanide dipoles. Throughout the data in Table 1 there are indications of some steric slowing of the rates, e.g. the pairs **9**, **10**, and **13**, **14**. Measured Arrhenius data for the reactions with selected dipolarophiles from both sides of Fig. 1 (measured in the range 300–340 K) are listed in Table 3. The thermodynamics of

activation are similar throughout. Low activation energies reflect easy reactions and the high negative entropies fit in the normal range[11] for concerted cycloadditions. DFT calculated activation energies are in reasonable agreement with the measured values (Tables 3, 4). The calculations also give high negative activation entropies from -170 to -190 J mol^{-1} K^{-1}.

In conclusion the dipole **I** is shown experimentally to be a classic example of a Sustmann "Type II" 1,3-dipole which may react by either HOMO-dipole or LUMO-dipole control depending on the type of dipolarophile employed. This has significant implications for reactivity and regiochemistry and needs to be recognized in planning synthetic reactions.

Theoretical calculations

The results of DFT calculations on the dipolarophiles and dipole are summarized in Table 4 including the ionization potentials used in Fig. 1 (for experimental IP values, see ref. 14). The frontier orbital gaps, LUd-HOp (dipole$_{LUMO}$–dipolarophile$_{HOMO}$) and LUp-HOd clearly show the changeover in the dominant frontier orbital interactions in the cycloaddition transition state throughout the series of dipolarophiles. The calculations confirmed concerted but non-synchronous bond formations for the full series of reactions and there is no changeover to a stepwise mechanism. A number of computational methods incorporated into the Gaussian98 A7 series of programs were used in this study.[15] All geometry optimisations were carried out with the RB3LYP[16] DFT method. The standard split valence plus polarisation 6-31G(d) basis set was used in all cases. Normal mode analysis was performed to ascertain the nature of all structures identified as stationary points. All dipolarophiles were optimised and their lowest energy conformations were used in this study. The geometries of all carbonyl groups were optimised to a cis or quasi cis configuration to the C=C bond in the transition states as these configurations give lower energies than the trans configurations in the separated dipolarophiles. Transition state structures were calculated for all four stereo-(endo/exo) and regio-isomeric products from CC double bond dipolarophiles and for both regioisomeric stereoproducts from CC triple bond dipolarophiles.

Table 1 Rate constants for reaction of **I** with dipolarophiles in MeCN at 37 °C, $k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}

Section A: electron-rich

Compound	Dipolarophile	k_2
1	H–C≡C–Ph	0.21
2	n-Butyl vinyl ether	1.85
3	Styrene	2.45
4	1-Morpholinocyclohexene	186
5	1-Pyrrolidinocyclopentene	35000
6	Cyclopentene	0.40

Section B: electron-poor

Compound	Dipolarophile	k_2
7	H–C≡CCO$_2$Me	31.8
8	H–C≡CCO$_2$Et	23.1
9	Methyl acrylate	37.7
10	tert-Butyl acrylate	19.1
11	Acrylonitrile	6.28
12	2-Chloroacrylonitrile	9.42
13	Methyl methacrylate	5.12
14	tert-Butyl methacrylate	2.24
15	Methyl crotonate	0.838
16	Dimethyl maleate	1.17
17	Dimethyl fumarate	38.8
18	MeO$_2$–C≡C–CO$_2$Me	1470

Section C: N-substituted maleimides

Compound	N-Substituent	k_2
19	Ph	506[a]
20	p-BrC$_6$H$_4$	561[a]
21	p-EtC$_6$H$_4$	488[a]
22	p-MeOC$_6$H$_4$	449[a]
23	p-ClC$_6$H$_4$	568[a]
24	p-NO$_2$C$_6$H$_4$	650[a]
25	t-Bu	202
26	PhCH$_2$	376

[a] Hammett ρ, +0.15, r, 0.982.

Fig. 2 Plot of log k_2 versus solvent E_T values for dipole **I**.

Table 2 Solvent effects for reactions of **I** with dipolarophiles at 37 °C, $k_2/10^{-3}$ dm^3 mol^{-1} s^{-1}

| Dipolarophile (Table 1) | Solvent (E_T)[a] | | | |
	MeCN (46)	Acetone (42.2)	EtOAc (38.1)	1,4-Dioxane (36)
13	5.12	6.03	10.9	13.8
18	1470	1690	2150	2530
2	1.85	1.75	3.36	5.60
4	186	73	28	33
19	506	450	854	948

[a] E_T(30) values from ref. 12.

Table 3 Arrhenius data for reactions of **I** in acetonitrile

Dipolarophile (Table 1)	$k_2/10^{-3}$ dm^3 mol^{-1} s^{-1} (T/K)	ΔE^{act}/kJ mol^{-1}	ΔH^{act}/kJ mol^{-1}	ΔS^{act}/J mol^{-1} K^{-1}
7	12.4 (299), 31.8 (310), 145 (338)	51.5 (46.6)[a]	48.5	−118
13	4.5 (307), 8.7 (316), 11.7 (321), 26.9 (338)	48 (60.6)	46	−139
19	314 (302), 506 (310), 1820 (338)	40 (40.0)	37	−131
2	0.88 (300), 1.85 (310), 10.3 (338)	53.5 (68.2)	51	−134
4	117 (300), 186 (310), 430 (338)	28.5	25.5	−177

[a] Parentheses contain DFT calculated values, *cf.* Table 4.

Table 4 DFT calculations (orbital energies and gaps/E_h)

Dipolarophile (Table 1)	π-HOMO	HOMO	LUMO	LUd-HOp	LUp-HOd	IP/eV[a]	H/N[b]	ΔE^{act} DFT[c]
1	−0.2311	−0.2311	−0.0284	0.1295	0.1784	6.289	N	55.1
2	−0.2151	−0.2151	0.0412	0.1135	0.2480	5.853	N	68.2[d]
3	−0.2217	−0.2217	−0.0305	0.1201	0.1763	6.033	N	62.6
4	−0.1896	−0.1896	0.0426	0.0880	0.2494	5.159	—	
5	−0.1678	−0.1678	0.0842	0.0662	0.2910	4.567	N	21.0
6	−0.2320	−0.2320	0.0357	0.1304	0.2425	6.313	N	61.0
7	−0.2995	−0.2806	−0.0443	0.1979	0.1625	8.150	H	46.6
8	−0.2976	−0.2781	−0.0421	0.1960	0.1647	8.098	—	
9	−0.2822	−0.2728	−0.0440	0.1806	0.1628	7.679	H	48.1
10	−0.2781	−0.2627	−0.0403	0.1765	0.1665	7.568	—	
11	−0.2892	−0.2892	−0.0563	0.1876	0.1505	7.870	H	52.2
12	−0.2837	−0.2837	−0.0694	0.1821	0.1374	7.720	H	71.5
13	−0.2652	−0.2652	−0.0368	0.1636	0.1700	7.217	N	60.6
14	−0.2615	−0.2601	−0.0333	0.1599	0.1735	7.116	—	
15	−0.2676	−0.2659	−0.0363	0.1660	0.1705	7.282	—	
16	−0.2918	−0.2652	−0.0651	0.1902	0.1417	7.940	S	
17	−0.2913	−0.2805	−0.0814	0.1897	0.1254	7.927	S	
18	−0.3220	−0.2833	−0.0540	0.2204	0.1528	8.762	S	
19	−0.3125	−0.2382	−0.1003	0.2109	0.1065	8.504	S	40.0
20	−0.3183	−0.2363	−0.1071	0.2167	0.0997	8.661	S	
21	−0.3099	−0.2290	−0.0981	0.2083	0.1087	8.433	S	
22	−0.3088	−0.2946	−0.0971	0.2072	−0.0878	8.403	S	
23	−0.3187	−0.2391	−0.1071	0.2171	0.0997	8.672	S	
24	−0.3287	−0.2645	−0.1180	0.2271	0.0888	8.944	S	
25	−0.3044	−0.2644	−0.0930	0.2028	0.1138	8.283	S	49.2[d]
26	−0.3112	−0.2287	−0.0994	0.2096	0.1074	8.468	S	
1,3-Dipole	−0.2087	−0.2087	−0.1016					

[a] Calculated from the π-HOMO energies; values are used in Fig. 1. [b] Point of attachment for substituted C atom of dipolarophile to the dipole, N = dicyanomethanide terminus, H = CH terminus, S = symmetric dipolarophile, — not calculated. [c] In kJ mol^{-1}. [d] Me substituent used in DFT rather than the Bu employed in experiment.

In many of the dipolarophiles used in this study there is a possibility for one or more lone pair orbitals to be the HOMO(s). As we are dealing with cycloaddition reactions the highest π C=C MO should be considered for frontier orbital interactions. All dipolarophile LUMOs in this study are π C=C MOs. Table 4 reports the HOMO, π-HOMO and LUMO energies for the dipole and dipolarophiles as well as the energy gaps (E_h) between the LUMOd–πHOMOp and LUMOp–HOMOd (p = dipolarophile, d = dipole) combinations. It was verified that the HOMO and LUMO of the 1,3-dipole are composed mainly of the AO coefficients from the three dipole atoms and not a lone pair or another part of the benzo system.

The activation energies for twelve dipolarophiles are given in Table 4. The recorded values are for the lowest energy transition state configurations. In the ten cases where there was a possibility for regioisomeric products it was observed that the lower E^{act} followed the case where the frontier orbital gap was lower. Thus, with electron-rich dipolarophiles, the LUMOd–HOMOp energy gaps were smaller than the LUMOp–HOMOd gaps and *vice versa* for the electron-poor dipolarophiles. In conclusion, the kinetic results combined with the DFT calculations provide insight into the nature of the dipole **I** and they explain the observed regiochemistry of its cycloaddition reactions (Scheme 1).

Experimental

The kinetics were measured by recording the disappearance of the dipole **I** using its UV–VIS spectrum. Spectra were measured using a Cary1/Cary 3 UV–VIS spectrophotometer featuring an automatic changer for up to six glass cuvettes of pathlength 1 cm with thermostated water circulating around the cell holder, The temperature was maintained at 37 °C (±0.1 °C) The reaction was monitored under pseudo-first order conditions. The phthalazinium-2-dicyanomethanide **I**, prepared as previously described,[7] was recrystallised twice before use. Liquid dipolarophiles were distilled before use. The solid substituted maleimides were recrystallised from cyclohexane and the dimethyl fumarate was recrystallised from acetonitrile. The substituted phenylmaleimides were synthesised according to the literature procedure.[17] Other dipolarophiles **1**–**14**, **18**, **25**, and **26** were purchased from Aldrich and dipolarophiles **15** and **16** were purchased from Lancaster. These were all checked by NMR analysis prior to use. The solvents used were HPLC grade and were purified further by standard procedures.

The initial concentration of the dipole was 3.2×10^{-5} M and the dipolarophiles were used in large excess ranging from 50 to 60000 times according to their reactivity. The reactions were monitored using the π–π* transition of the dipole at 420 nm and were followed to infinity values. Kinetic runs were per-

formed with four different concentrations of the dipolarophiles and repeated a minimum of three times. The rate constants reported in the Tables 1–3 were reproducible to ±2%.

Acknowledgements

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