Steric Reversal of the *endo*-Selectivity Effect in 1,3-Dipolar Cycloadditions of Phthalazinium-2-ylides with *N*-Substituted Maleimides: *endo*- and *exo*-1,2-(Dicarboxy-*N*-substituted imido)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazines†

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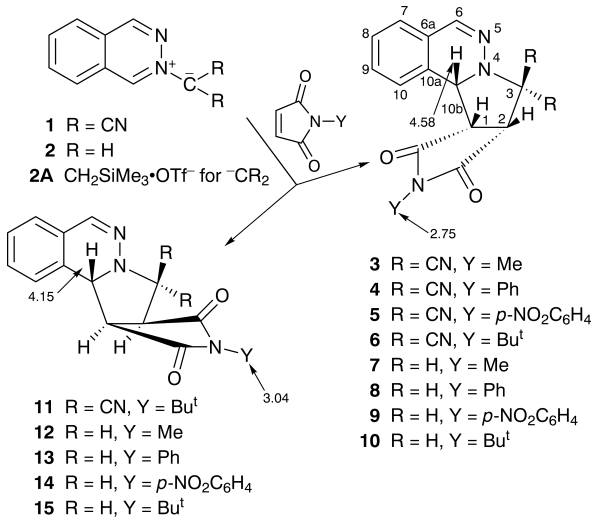
Richard N. Butler* and Derval M. Farrell

Chemistry Department, University College Galway, Ireland

N-Methyl- and *N*-aryl-maleimides undergo cycloadditions with phthalazinium-2-dicyanomethanide and -2-unsubstituted methanide 1,3-dipoles to give exclusive or predominant *endo*-cycloadducts but with *N*-*tert*-butylmaleimide this *endo* effect is reversed to favour the *exo*-cycloadducts *exo*-1,2-(dicarboxy-*N*-*tert*-butylimido)-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]phthalazines **11** and **15**.

The transition state factors which direct the stereocourse of many Diels–Alder and 1,3-dipolar cycloadditions to favour *endo*-cycloadducts, such as bonding secondary orbital interactions, favourable alignments of dipole moments and others, have aroused considerable interest.[1–3] Anti-bonding secondary orbital interactions may alter the reaction to *exo*-selective[4] and in cases where the *endo*-selectivity is delicately balanced a variety of secondary factors can lead to mediocre *endo*- and *exo*-selectivities.[3,5–10] Catalysts may also reverse the *endo* effect.[11,12] Recently[13] we have examined the cycloadditions of the phthalazinium-2-methanide 1,3-dipoles **1** and **2** with a range of alkyne and alkene dipolarophiles and a preference for *endo*-cycloadditions was noted. Herein we explore this effect with a series of *N*-substituted maleimide dipolarophiles. For these systems the *endo* effect required the absence of steric hindrance in the cycloaddition and it depended also on the stability and hence selectivity of the dipole. A large steric effect in the dipolarophile reversed the *endo* effect and gave an exclusive *exo*-cycloaddition.

The 1,3-dipole **1** is a stable solid while species **2** is highly unstable and decomposes rapidly even at −30 °C and can only be generated and trapped *in situ*.[13] When dipole **1** was separately treated with *N*-methyl-, *N*-phenyl- and *N*-(*p*-nitrophenyl)-maleimide in acetonitrile at ambient temperatures the exclusive *endo*-cycloadducts **3**, **4** and **5** respectively were formed (Scheme 1; Table 1, entries 1–3). In these reactions steric hindrance did not overcome the secondary factors which favour the *endo*-cycloaddition and the electronic substituent influence of varying from NMe to



Scheme 1 Some ^{1}H NMR shifts shown for Y = Me, R = H

$NC_6H_4NO_2$-*p* did not affect the *endo*-selectivity. However with *N*-*tert*-butylmaleimide as dipolarophile to the dipole **1** steric inhibition swamped the *endo* effect and the reaction was exclusively switched over to the *exo* product **11** (Table 1, entry 4). A similar trend was observed with the unstable dipole **2** but in this case *endo*/*exo* mixtures were encountered in each case with the balance being turned from predominantly *endo* to predominantly *exo* by the *N*-*tert*-butyl substituent (Table 1, entries 5–8). These results illustrate the importance of steric effects and the stability/selectivity of the dipole in the *endo* effect. The more unstable and less selective dipoles **2** gave *endo*/*exo* mixtures rather than exclusive *endo*- or *exo*-cycloaddition. With the stable dipole **1** the

Table 1 Cycloadducts

Entry[a]	Compd.	Mp/°C	Yield (%)	Compd.	Mp/°C	Yield (%)
	endo			*exo*		
1	**3**	233–235[b]	94[d]	—	—	<1
2	**4**	252–254[b]	87[d]	—	—	<1
3	**5**	148–150[c]	89[d]	—	—	<1
4	**6**	—	<1	**11**	157–159[c]	80[d]
5	**7**	164–165[b]	48	**12**	124–126[b]	25
6	**8**	208–210[b]	46	**13**	105–107[b]	25
7	**9**	190–192[b]	52	**14**	162–164[b]	25
8	**10**	202–204[b]	25(8)[e]	**15**	218–220[b]	49(16)[e]

[a]Entries 1–4 from dipole **1**; entries 5–8 from dipole **2**. [b]From ethanol. [c]From acetonitrile. [d]Exclusive products; remainder was recovered **1**. [e]Parentheses contain conversion yields. Reaction yields are corrected for recovery of starting material.

*To receive any correspondence (*e-mail:* r.debuitleir@ucg.ie).

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endo effect required minimum steric constraints from the dipolarophile.

The stereoisomeric products were not interconvertible and their structures were established from microanalyses, IR, ^1H and ^{13}C NMR spectra which showed all of the expected signals and splitting patterns. The *endo*-isomers **3**–**10** were readily distinguished by (a) NOE difference spectra which showed NOE enhancements of 12–25% between the *cis* protons at C-10b and C-1 and (b) *J* values of 8–10 Hz between these same protons confirming the *cis* alignment with a small dihedral angle. The *exo*-isomers **11**–**15** did not show NOE enhancements between the *trans* H atoms at C-10b and C-1 and they showed reduced *J* values of 5–7.5 Hz confirming the *trans* alignment with a larger dihedral angle. The H-10b proton in structures **11**–**15** also showed a shielding effect from the *cis*-imido unit (Scheme 1). Also, H atoms or Me groups lying *endo* to the plane of the phthalazine ring current showed more upfield (shielded) signals than those in the *exo* positions (Scheme 1).

Experimental

Mps were measured on an Electrothermal apparatus. IR spectra were measured with a Perkin Elmer 983G spectrophotometer and microanalyses on a Perkin Elmer model 240 CHN analyser. NMR spectra were measured on a JEOL GXFT 400 instrument using $CDCl_3$ or $(CD_3)_2SO_2$ as solvent. Dipole **1** was prepared and dipole **2** generated in solution from salt **2A** as previously described.[13] The following are typical examples of cycloaddition reactions.

endo-1,2(*Dicarboxy*-N-*methylimido*)-3,3-*dicyano*-1,2,3,10*b*-*tetrahydropyrrolo*[2,1-a]*phthalazine* **3** (*Table* 1, *entry* 1).—A suspension of compound **1** (0.35 g, 1.8 mmol) in acetonitrile (15 ml) was treated with *N*-methylmaleimide (0.2 g, 1.8 mmol) and the mixture stirred at ambient temperature for 12 h. Removal of solvent under reduced pressure yielded compound **3** (94%); mp 233–235 °C (from ethanol) (Found: C, 68.4; H, 3.6; N, 19.7. $C_{16}H_{11}N_5O_2$ requires C, 68.7; H, 3.5; N, 19.9%); ν_{max}(mull)/cm^{-1}, 2305 (C≡N), 1785, 1716 (C=O); δ_H ([$^2H_5$]DMSO), 2.89 (3 H, s, CH_3), 4.31 (1 H, m, H-1), 4.57 (1 H, d, *J* = 8.1 Hz, H-2), 5.00 (1 H, d, *J* = 7.3 Hz, H-10b), 7.55–7.70 (3 H, m, H-7 to H-9), 7.85 (1 H, d, H-10), 8.01 (1 H, s, H-6); δ_C [$^2H_6$]DMSO), 25.3 (CH_3), 43.4 (C-2), 50.1 (C-1), 58.4 (C-3), 58.7 (C-10b), 110.9 and 112.1 (C≡N), 124.0 (C-10a), 130.2 (C-6a), 127.0, 127.7 and 129.1 (C-8 to C-10), 131.6 (C-7), 147.6 (C-6), 171.1 and 173.2 (C=O).

exo-1,2-(*Dicarboxy*-N-*tert-butylimido*)-3,3-*dicyano*-1,2,3,10*b*-*tetrahydropyrrolo*[2,1-a]*phthalazine* **11** (*Table* 1, *entry* 4).—A suspension of compound **1** (0.35 g, 1.8 mmol) in acetonitrile (15 ml) was treated with *N*-*tert*-butylmaleimide (0.28 g, 1.8 mmol), and the mixture stirred at ambient temperature for 12 h. Removal of the solvent under reduced pressure yielded compound **11** (80%); mp 157–159 °C (from acetonitrile) (Found: C, 65.4; H, 4.7; N, 20.0. $C_{19}H_{17}N_5O_2$ requires C, 65.7; H, 4.9; 20.2%); ν_{max}(mull)/cm^{-1}, 2290 (C≡N), 1696, 1718 (C=O); δ_H ([$^2H_5$]DMSO): 2.17 (9 H, s, Bu^t protons), 3.93–3.96 (1 H, dd, H-1), 4.56 (1 H, d, *J* = 8.1 Hz, H-2), 4.82 (1 H, d, *J* = 5.1 Hz, H-10b), 7.43–7.58 (3 H, m, H-7 to H-9), 7.73 (1 H, d, *J* = 15.8 Hz, H-10), 8.12 (1 H, s, H-6); δ_C ([$^2H_6$]DMSO): 38.9–40.1 (Bu^t CH_3 overlapping with solvent peaks), 43.9 (C-2), 53.4 (C-1), 54.3 [Bu^t *C*$(CH_3)_3$], 58.9 (C-3), 69.4 (C-10b), 118.8 (C≡N), 125.2 (C-10a), 124.5, 126.3, 128.8 (C-8 to C-10), 131.1 (C-6a), 134.1 (C-7), 142.9 (C-6), 168.4 and 173.9 (C=O).

exo-1,2-(*Dicarboxy*-N-p-*nitrophenylimido*)-1,2,3,10*b*-*tetrahydropyrrolo*[2,1-a]*phthalazines* **14** *and the* endo *isomer* **9** (*Table* 1, *entry* 7).—A solution of triflate salt **2A** (0.35 g, 0.96 mmol) and *N*-(*p*-nitrophenyl)maleimide (0.42 g, 1.91 mmol) in dry dichloromethane (20 ml) under anhydrous conditions was treated with an excess of caesium fluoride (0.40 g, 2.63 mmol) and stirred at ambient temperature for 24 h. The resulting mixture was filtered and the filtrate (together with CH_2Cl_2, filter-cake washings) evaporated under reduced pressure to 4 cm^3, placed on a flash column of silica gel (230–400 mesh ASTM) packed with dichloromethane and eluted with mixtures of dichloromethane–diethyl ether having gradient variations of 5% from 100:0 to 50:50 v/v. The first product eluted from the column was compound **14** (25%); mp 162–164 °C (from ethanol) (Found: C, 62.8; H, 3.7; N, 15.2. $C_{19}H_{14}N_4O_4$ requires C, 63.0; H, 3.9; N, 15.5%); ν_{max}(mull)/cm^{-1}: 1715 (C=O), δ_H ($CDCl_3$): 3.55–3.67 (3 H, m, H-3$_{endo}$, H-2, H-1), 4.35–4.42 (2 H, m, H-10b, H-3$_{exo}$), 7.27–7.64 (7 H, m, H_o of *N*-$C_6H_4NO_2$ and H-6 to H-10), 8.34 (2 H, d, H_m of *N*-$C_6H_4NO_2$), δ_C ($CDCl_3$): 44.2 (C-2), 50.6 (C-1), 57.7 (C-3), 61.5 (C-10b), 123.5 (C-10a), 131.1 (C-6a), 131.5 (C-7), 140.8 (C-6), 125.8, 126.4, 129.2 (C-8 to C-10), 136.9, 124.4, 126.9, 147.0 (*N*-$C_6H_4NO_2$, C-1′, C-2′, C-3′, C-4′ resp.), 174.7 and 175.2 (C=O).

Compound **9** was subsequently eluted from the column (52%); mp 190–192 °C (from ethanol) (Found: C, 62.8; H, 3.7; N, 15.2. $C_{19}H_{14}N_4O_4$ requires C, 63.0; H, 3.9; N, 15.5%); ν_{max}(mull)/cm^{-1}: 1715 (C=O); δ_H ($CDCl_3$): 3.54–3.70 (3 H, m, H-3$_{endo}$, H-2, H-1), 4.53 (1 H, d, *J* = 12.4 Hz, H-3$_{exo}$), 4.75 (1 H, d, *J* = 7.6 Hz, H-10b), 7.19–7.69 (7 H, m, H-6 to H-10 and H_o of *N*-$C_6H_4NO_2$), 8.25 (2 H, d, J_m of $C_6H_4NO_2$); δ_C ($CDCl_3$): 43.8 (C-2), 48.5 (C-1), 58.9 (C-3), 60.4 (C-10b), 121.9 (C-10a), 126.9 (C-6a), 127.8 (C-7), 138.7 (C-6), 124.4, 124.7, 129.6 (C-8 to C-10), 135.9, 122.7, 125.5, 145.1 (*N*-$C_6H_4NO_2$, C-1′, C-2′, C-3′, C-4′ resp.), 171.9 and 174.7 (C=O).

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