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Selectivities in the 1,3-dipolar cycloaddition of nitrile oxides to dicyclopentadiene and its derivatives

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Dedicated to Professor S. N. Balasubrahmanyam on the occasion of his 72nd birthday

Abstract—The 1,3-dipolar cycloaddition of nitrile oxides, generated from aldoximes and nitroalkanes, to dicyclopentadiene proceeds with complete chemo- and stereoselectivity. The approach of the dipole takes place exclusively from the *exo*-face of the bicycloheptane moiety providing a mixture of regioisomers in approximately 55:45 ratio. On the other hand, nitrile oxide cycloaddition to dimethyldicyclopentadiene dicarboxylate (Thiele's ester), besides exhibiting chemo- and stereoselectivity as in the case of dicyclopentadiene, exhibits complete regioselectivity as well providing a single isomer in good yield. The Influence of remote substituents, including sterically 'sterile' ones, on the regioselectivity has also been investigated using 8-hydroxy and 1-keto derivatives of dicyclopentadiene. These experimental observations have been investigated through gas phase and solvent model MO calculations on the transition state geometries at semiempirical (PM3) and hybrid ab initio-DFT levels of theory. The Computational methods employed in this study were rigorously tested by performing model calculations on well-established experimental observations.

1. Introduction

1,3-Dipolar cycloadditions offer convenient one-step routes for the construction of a variety of five-membered heterocycles.[1,2] In particular, cycloaddition of nitrile oxides to olefins are of considerable interest as the resulting isoxazolines are versatile intermediates in the synthesis of a variety of natural products.[3,4] Recently, isoxazolines fused to bicyclic frameworks have been subjected to molybdenum mediated N–O bond cleavage to afford stereoselectively substituted cyclopentane rings.[5] Achievement of a high degree of selectivity is, therefore, of paramount importance for further expanding the scope and exploiting the potential of this elegant synthetic strategy.

Regioselectivity in the addition of nitrile oxides **1** to unsymmetrical acyclic[6,7] and simple cyclic[8] dipolarophiles **2** has been investigated experimentally[6,8] and theoretically.[7,8] For instance, addition of nitrile oxide **1** to methyl acrylate **2** (X=CO_2Me) provides 5-isoxazoline **3a** in overwhelming predominance, compared to its regioisomer, 4-isoxazoline **3b** (ratio ~95:5).[6,7] As for stereochemistry, π face selection[9,10] in the addition of nitrile oxides to various dipolarophiles such as norbornene,[11] 2,3-dioxabicyclo[2.2.2]octane,[12] *cis*-3,4-dichlorocyclobutene,[13] α-chiral alkenes[14] etc. has been investigated.[15] In the case of norbornene **4** (X=H), the approach of the dipole preferentially takes place from the *exo* face.[11] Further, in the case of unsymmetrically substituted norbornenes **4** (X=hexyl, $SiMe_3$, CO_2Et) formation of single stereo- and regioisomers has been observed, i.e. the *exo* isomer **5** in which oxygen of the dipole is attached to the more substituted center of the dipolarophile.[16] A handful of other reports on the inter-[13] and intramolecular[14] cycloadditions of nitrile oxides to bicyclic systems, viz. norbornenes[17,18] and norbornadienes[18,19,20] also reflected this feature. However, in the intermolecular reactions of norbornadienes[18,19] and in presence of sterically demanding groups on the *exo* face of norbornenes,[17,18] formation of considerable amount of *endo* isomers is observed.

Keywords: Nitrile oxide; 1,3-Dipolar cycloaddition; Dicyclopentadiene; Thiele's ester.
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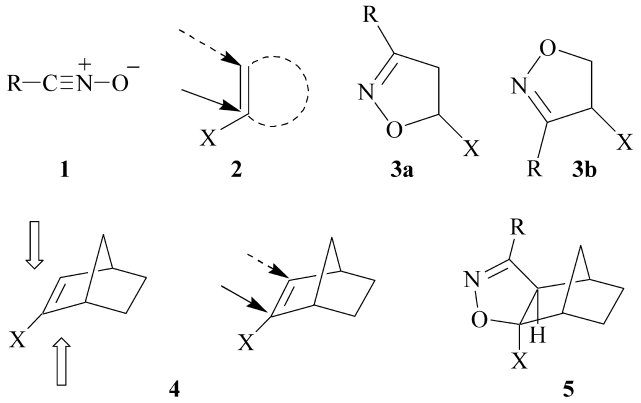


Although nitrile oxide cycloadditions to dienes (e.g., norbornadienes, vide supra) and polyenes (e.g., fulvene)[21] have been reported in the literature, to our knowledge, selectivities in the cycloaddition of nitrile oxides to systems possessing multiple π-faces has not been investigated.[22,23] Herein, we report the remarkable selectivities observed in the cycloaddition of nitrile oxides to representative tricyclic systems.

2. Results and discussion

Dicyclopentadiene **6a** and its derivatives, viz. dicarboxylate, Thiele's ester, **6b**,[24] alcohol **6c**[25] and enone **6d**[25,26] were chosen as the dipolarophiles as three degrees of differentiation, viz. chemo, stereo and regio, in their cycloaddition with suitable dipoles such as nitrile oxides would be possible (Fig. 1). Although norbornene has been shown to be much more reactive than cyclopentene in the cycloaddition with nitrile oxides (vide infra),[27] the dipole could, in principle, react with the C2–C3 double bond or C5–C6 double bond exhibiting chemoselectivity. The approach of the dipole could take place from the ββ-face, βα-face, αβ-face or αα-face. Furthermore, formation of two regioisomers in which the dipole oxygen is bonded to C2 or C3/C5 or C6 is also a possibility for every cycloaddition. Therefore, there is a statistical possibility of formation of 8 monocycloadducts and 16 biscycloadducts taking the total number of products expected to 24.

The dipoles, acetonitrile oxide **1a** and benzonitrile oxide **1b**, were generated from two different precursors, viz. aldoximes[28] (Scheme 1, path A) and nitroalkanes (Scheme 1, path B),[29,30] in order to probe whether or not the selectivities are influenced by the method by which the dipole is generated (Tables 1 and 2). The ^{1}H and ^{13}C NMR spectra of the products formed from dicyclopentadiene **6a** indicated the formation of mixtures of two monocycloadducts **7a/8a** and **7b/8b**, respectively, in ~55:45 ratio (Table 1).[31]

In contrast to the behavior of dicyclopentadiene **6a**, the reaction of its dicarboxylate, Thiele's ester, **6b** with acetonitrile oxide **1a** and benzonitrile oxide **1b** provided single monocycloadducts **7c** and **7d**, respectively (Table 2).[32]

Further examination of Tables 1 and 2 indicates that the isomer ratios of the cycloadducts formed in the nitrile oxide cycloaddition to dicyclopentadiene **6a** and its dicarboxylate **6b** are independent of the method of generation of nitrile oxide **1**[33] However, it has been observed that in our hands path B (nitroalkane, BOC_2O, DMAP, THF; Scheme 1, see Section 5)[30] is superior for the generation of acetonitrile oxide **1a** (Table 1, entry 2 and Table 2, entry 2) over path A, method A (aldoxime, NCS, Et_3N, CH_2Cl_2; see also Table 1, entry 1 and Table 2, entry 1) and path A, method B (aldoxime, NaOCl, Et_3N, CH_2Cl_2). On the other hand, path A, method B (aldoxime, NaOCl, Et_3N, CH_2Cl_2) turned out to be better for the generation of benzonitrile oxide **1b** (Table 1, entry 3 and Table 2, entry 3) as compared to path B (Table 1, entry 4 and Table 2, entry 4).

In view of the above, only **1b**, generated via path A, method B, has been employed for the subsequent cycloaddition with alcohol **6c** and enone **6d**. A mixture of isomers **7e/8e**, similar to that observed in the case of dicyclopentadiene **6a**, has been isolated when *syn*-alcohol **6c** was reacted with benzonitrile oxide **1b** (Table 3, entry 1). Finally, the enone **6d**, when treated with benzonitrile oxide **1b**, provided a mixture of isomers **7f** and **8f** in 34:66 ratio (Table 3, entry 2).

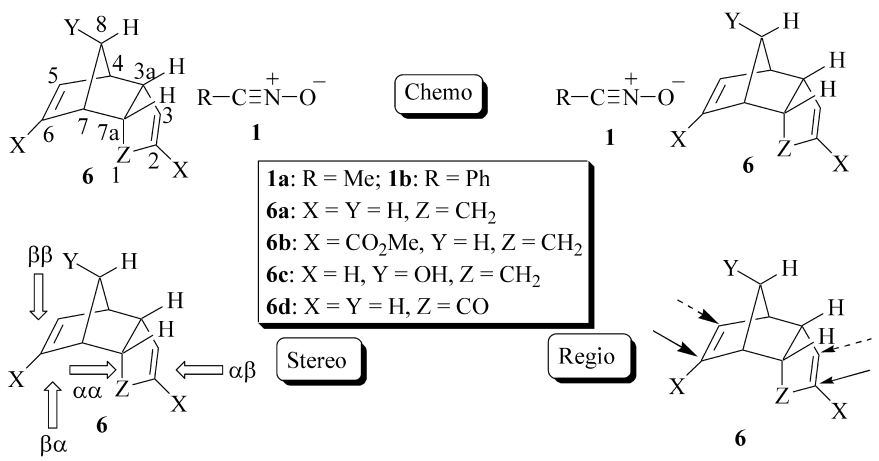
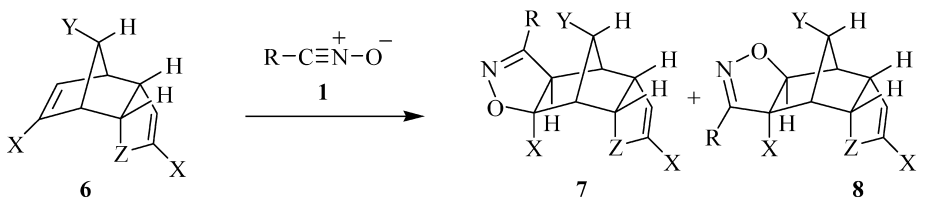


Figure 1. Chemo-, stereo- and regioselectivity in the cycloaddition of nitrile oxides **1** to dicyclopentadiene moiety **6**.



Path A, Method A: Aldoxime, NCS, Et_3N, CH_2Cl_2
Path A, Method B: Aldoxime, NaOCl, Et_3N, CH_2Cl_2
Path B: Nitroalkane, BOC_2O, DMAP, THF

7, 8a: R = Me, X = Y = H, Z = CH_2;
b: R = Ph, X = Y = H, Z = CH_2;
c: R = Me, X = CO_2Me, Y = H, Z = CH_2
d: R = Ph, X = CO_2Me, Y = H, Z = CH_2;
e: R = Ph, X = H, Y = OH, Z = CH_2;
f: R = Ph, X = Y = H, Z = CO

Scheme 1. 1,3-Dipolar cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a** and its derivatives **6b**–**d**.

The ^1H and ^{13}C NMR spectra of all the products revealed the preferential reactivity of the bicycloheptenyl (C5–C6) double bond in **6a**–**d** vis-à-vis the cyclopentenyl (C2–C3) double bond. There is no evidence for the formation of the cycloadduct arising from reaction of the cyclopentenyl (C2–C3) double bond with the nitrile oxides. This is broadly consistent with the reactivity of dicyclopentadiene **6a**[18] and Thiele's ester **6b**[34] although evidence to the contrary also exists in the literature.[35,36] In any event, the lower reactivity amounting to inertness of the *endo*-oriented cyclopentenyl (C2–C3) double bond in the dipolar cycloaddition is attributable to the preferential entry of the approaching dipole from the *exo* face of the bicycloheptane skeleton.

Having confirmed the chemoselectivity in the dipolar cycloaddition, the stereo and regio preferences observed in the cycloaddition had to be ascertained. It is evident from ^1H NMR spectra that all the cycloadditions follow the '*exo* rule'[37] of Alder and Stein providing exclusively the *exo*-cycloadducts. This is also in accord with the formation of *exo*-cycloadducts as the exclusive or predominant products in the cycloaddition of nitrile oxides to norbornenes[11,17,18,38] and norbornadienes.[18,19,20]

Reaction of dicyclopentadiene **6a** with nitrile oxides **1a** and **1b** proceeds with high stereoselectivity providing exclusively the *exo* cycloadducts (Table 1). The protons H^a (X^a=H^a) and H^b in the cycloadducts appear as doublets (J=8.25 Hz) coupled only with each other, but not with H^c or H^d) indicating their *endo* orientation (Fig. 2). However, unlike the case of Thiele's ester **6b** where single regioisomer **7c** or **7d** is formed (vide infra), regioselectivity in the case of **6a** is low, as expected, providing a mixture of regioisomers **7a/8a** and **7b/8b** in ~55:45 ratio (Table 1). In the major isomer **7a** of **7a/8a** pair, the ^1H NMR chemical shift values for the key resonances viz. the two *endo* hydrogens and the Me are δ 4.36, 2.97 and 1.80, respectively. The corresponding values for the minor isomer **8a** are δ 4.28, 2.92 and 1.83, respectively. In the **7b/8b** pair, the *endo* hydrogens appear at δ 4.66 and 3.63 for the major isomer **7b** and at δ 4.58 and 3.58 for the minor isomer **8b**. This was confirmed by NOESY experiment in that, in **7b**, besides the positive NOE between H^b and the aromatic protons, the key positive NOE between H^a and the *endo*-methylene protons as well as between H^b and the olefinic proton H-3 were discernible.

Quite remarkably, a single stereo- and regioisomer **7c** or **7d** is formed from Thiele's ester **6b** in its reaction with nitrile oxide **1a** or **1b** (Table 2). That H^b in **7c** (δ 3.43) and in **7d** (δ 4.00) is *endo* oriented (Fig. 2) is evident from the fact that it appears either as a singlet (in **7c** no coupling with H^c) or shows only very weak coupling (~2 Hz) with H^c (dihedral angle of close to 90° between H^b and H^c). As for the regiochemistry, the regioisomer **7c** or **7d** in which the oxygen of the nitrile oxide bonded to the more substituted (ester-bearing) olefinic carbon C6 is preferentially formed. This is consistent with the reactivity of aceto- and benzonitrile oxides with methyl acrylate[6,7] as well as with unsymmetrically substituted norbornenes.[16] The ^{13}C-SEFT (APT) spectra show that the carbons attached to the oxygen in the isoxazoline rings of **7c** and **7d** appearing at δ 93.1 and 94.7, respectively, are quaternary carbons. The above assignment is further confirmed by NOESY experiment. For instance, H^b in **7d** has a positive NOE with H^c, the olefinic proton H-3 and the aromatic protons (presumably the *ortho* protons). This, taken together with the absence of any NOE between H^b and H^d, confirms structure **7d** and, therefore, by analogy, structure **7c** for the cycloadducts.

Table 1. 1,3-Dipolar cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a**

Entry	1	Path	Yield[a] (%)	7:8[b]
1	**1a**	A (A)[c]	57	53:47
2	**1a**	B	84	53:47
3	**1b**	A (B)[c]	86	54:46
4	**1b**	B	52	53:47

[a] Isolated yield after column chromatography.
[b] Obtained by ^1H NMR (400 MHz) integration of the crude product.
[c] Method in parenthesis.

Table 2. 1,3-Dipolar cycloaddition of nitrile oxides **1** to Thiele's ester **6b**

Entry	1	Path	Yield[a] (%)	7:8[b]
1	**1a**	A (A)[c]	52	>99:1
2	**1a**	B	72	>99:1
3	**1b**	A (B)[c]	73	>99:1
4	**1b**	B	50	>99:1

[a] Isolated yield after column chromatography.
[b] Obtained by ^1H NMR (400 MHz) integration of the crude product.
[c] Method in parenthesis.

Table 3. 1,3-Dipolar cycloaddition of nitrile oxides **1** to alcohol **6c** and enone **6d**

Entry	1	6	Path	Yield[a] (%)	7:8[b]
1	**1b**	**6c**	A (B)[c]	70	55:45
2	**1b**	**6d**	A (B)[c]	68	34:66

[a] Isolated yield after column chromatography.
[b] Obtained by ^{1}H NMR (400 MHz) integration of the crude product.
[c] Method in parenthesis.

Subsequently, the influence of remote substituents on the reactivity of the bicycloheptenyl double bond has been investigated using *syn*-alcohol **6c** and enone **6d** (Table 3, entries 1 and 2). Interestingly enough, despite the presence of a hydroxy group syn to the bicycloheptenyl (C5–C6) double bond, the behavior of alcohol **6c** is analogous to that of **6a**. A mixture of regioisomers **7e** and **8e** (**7e/8e**=55:45) is formed when **6c** reacts with benzonitrile oxide **1b** (Table 3, entry 1). When the *endo*-methylene group in dicyclopentadiene **6a** is replaced by a carbonyl group (as in **6d**), substantial alteration in the ratio of the regioisomers (**7f/8f**=34:66) arising from the reaction of the bicycloheptenyl double bond (in **6d**) is observed (Table 3, entry 2). Comparison of the reactivity of **6a** and **6d** indicates that the reversal in the regioselectivity is attributable to electronic effects (vide infra) as the *exo* face of the bicycloheptenyl double bond in both **6a** and **6d** experiences similar steric environment.

The structure and stereochemistry of the pairs of cycloadducts **7e/8e** and **7f/8f** were confirmed as described in the case of the cycloadducts arising from dicyclopentadiene **6a** and Thiele's ester **6b**. The structure of **8f** has been further established by single crystal X-ray crystallography (Fig. 3).[39]

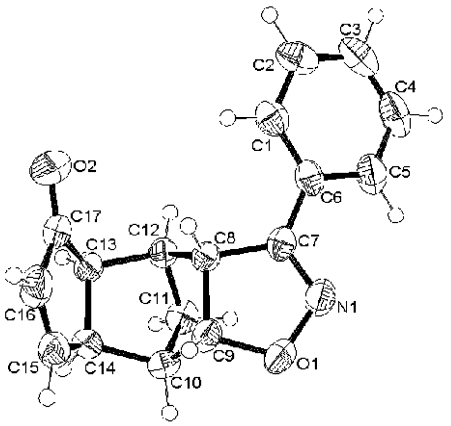


Figure 3. X-ray crystal structure of **8f**.[39]

3. Theoretical calculations

In order to probe the selectivities observed during the 1,3-dipolar cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a** and Thiele's ester **6b** and other derivatives **6c–d**, TS energy calculations were carried out at semiempirical (PM3) and hybrid ab initio-DFT levels of theory. All the TS geometries were optimized at PM3 level and characterized with one imaginary frequency.[40] Single point calculations were performed using B3LYP/6-31G* level of theory at PM3 TS geometries.[41] Solvent corrections[42] were modeled with aqueous model[43] and organic solvent (THF).[44] It may be noted that THF was used in the generation of nitrile oxides **1** from nitroalkanes and its subsequent cycloaddition with **6a** and **6b**. Solvent continuum model, IPCM was employed to calculate the energies in presence of THF.[42,43]

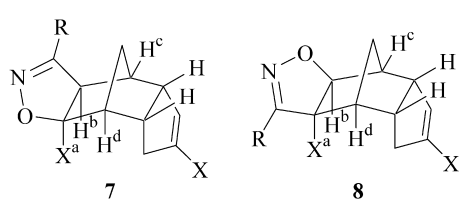


Figure 2.

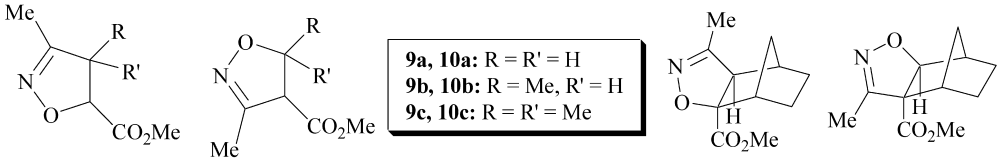
Though aqueous model has been used to examine the selectivity in all the cases at both the levels of theory, THF has been employed only with B3LYP/6-31G*//PM3 basis set. The reliability of these calculations for predicting the selectivities observed in the 1,3-dipolar cycloaddition were first examined by performing model calculations as described below.

The relative reactivities of cyclopentene and norbornene with acetonitrile oxide **1a** were first examined. As mentioned earlier, norbornene has been shown to be much more reactive than cyclopentene in their cycloaddition with nitrile oxides by Huisgen and co-workers (vide infra).[27] In addition, we have examined the regioselectivity in the cycloaddition of nitrile oxide **1a** to methylacrylate, β-methyl methylacrylate and β,β-dimethyl methylacrylate that has earlier been investigated by Huisgen and Houk.[6,7]

Our calculated results on the relative reactivities of ethylene, cyclopentadiene and norbornene with acetonitrile oxide **1a** showed good qualitative agreement with Huisgen's results. Transition states were located for the cycloaddition of acetonitrile oxide **1a** with ethylene, cyclopentene and norbornene, at PM3 level and the relative activation barriers calculated at B3LYP/6-31G*//RHF/PM3 level were 12.2, 17.1 and 11.1 kcal mol^{-1}, respectively. The corresponding rate constants k (sec^{-1}) calculated using Arrhenius equation are 0.00224, 0.000193 and 0.00388, respectively. The relative rate constants for the cycloaddition of cyclopentene and norbornene with respect to ethylene (0.086 and 1.73, respectively) clearly indicate the preferential reactivity of norbornene towards nitrile oxide **1a** visà-vis cyclopentene. The fact that the cyclopentene moiety in **6** is *endo* fused to the norbornene moiety further diminishes the reactivity of the former and, therefore, points to the observed chemoselectivity.

As far as our model calculations on the regioselectivity are concerned, results obtained at semi-empirical (PM3) and hybrid ab initio-DFT levels of theory, for the cycloaddition of nitrile oxide **1a** to methylacrylate, β-methyl methylacrylate and β,β-dimethyl methylacrylate, by locating the transition states (TS's) of cycloadducts, viz. 5-isoxazoline **9** and 4-isoxazoline **10**, concurred well with the observed experimental results[6,7] (see Table 4).

Table 4. Semi-empirical (PM3) and hybrid ab initio/DFT (B3LYP/6-31G*) level calculated relative TS energy differences in kcal/mol for the cycloaddition of acetonitrile oxide **1a** with substituted acrylates



9 **10** **11** **12**

Row/col	1	2	3	4	5	6	7	8	9
	Method	**9a**	**10a**	**9b**	**10b**	**9c**	**10c**	**11**	**12**
1	RHF/PM3 (A)	0.0	0.3	0.9	0.0	1.4	0.0	0.2	0.0
2	PM3 SM5.4 (B)[a]	0.0	1.6	0.0	0.1	0.1	0.0	0.0	1.8
3	B3LYP/6-31G*//PM3 (C)	0.0	2.0	2.7	0.0	8.6	0.0	0.0	2.5
4	B3LYP/6-31G*//PM3 SM5.4 (D)[a]	0.0	3.4	1.8	0.0	6.9	0.0	0.0	4.2
5	B3LYP/6-31G*//PM3 (E)[b]	0.0	2.2	2.7	0.0	8.2	0.0	0.0	2.6

[a] Aqueous model.
[b] THF model.

The gas phase and solvent model calculations at semi-empirical (PM3) and hybrid ab initio/DFT levels of theory predicted the predominant formation of 5-isoxazoline **9a** over 4-isoxazoline **10a** (Table 4, cols 2 and 3) in the cycloaddition of methylacrylate with acetonitrile oxide **1a** (experimental ratio[6] **9a**:**10a**=95:5). The selectivity is reversed in the cycloaddition of acetonitrile oxide **1a** with β-methyl methylacrylate in that the 4-isoxazoline **10b** is the major isomer (cols 4 and 5, experimental ratio[6] **9b**:**10b**=36:64). Further methyl substitution at the β-position of acrylate, i.e. β,β-dimethyl methylacrylate, leads to exclusive formation of 4-isoxazoline **10c** (cols 6 and 7, experimental ratio[6] **9c**:**10c**=0:100). The regio and stereoselectivity observed in the cycloaddition of acetonitrile oxide **1a** to norbornene carboxylate **4** (X=CO_2Me)[16] is also qualitatively supported by our calculations at various levels of theory (cols 8 and 9, experimental ratio, X=CO_2Et,[16] **11**:**12**=100:0).

Having established the efficacy of our approach to satisfactorily predict the selectivities observed in the previous experimental studies,[6,16] we turned to the chemo-, stereo- and regioselectivities observed in our laboratories in the cycloaddition of nitrile oxides **1** to dicyclopentadiene **6a**, its dicarboxylate, Thiele's ester, **6b**, and other derivatives **6c–d** and the results are summarized in Table 5. Since the experimental results provided no evidence for the formation of any bis-cycloadducts, they were excluded from calculations. Further, the relative TS energies corresponding to βα- and αα-approach of the dipole **1a** towards both **6a** and **6b** and the corresponding approaches of the dipole **1b** towards dipolarophile **6d** were found to be prohibitively high and, therefore, were omitted from Table 5 for simplicity. The analysis of PM3 TS geometries suggested that the computed TS's for addition of dipole **1a** to dipolarophiles **6a** and **6b** and those for the addition of dipole **1b** to dipolarophile **6d** are concerted and slightly asynchronous in nature.[45]

The gas phase and aqueous model calculations at semi-empirical level for the cycloaddition of **1a** to dicyclopentadiene **6a** (Table 5, entry 1), though favor the ββ-approach of the dipole **1a** over the αβ and other approaches, make no distinction between the TS's leading to two regioisomers **7** and **8**. However, calculations at higher level, i.e. B3LYP/6-31G* (including gas phase, aqueous and THF model, Table 5, entry 2), predicted the marginal preference for the formation of isomer **7** over isomer **8**, as observed experimentally (**7a**:**8a**=53:47).

As for the cycloaddition of nitrile oxide **1a** to Thiele's ester **6b**, calculations at semi-empirical level (PM3, gas phase and aqueous model, Table 5, entry 3) showed the marginal preference for the approach of nitrile oxide **1a** towards the C2–C3 double bond (αβ-approach) of Thiele's ester **6b**. However, the ββ-approach of the dipole **1a** in which the dipole oxygen is bonded to the ester-bearing carbon C6 of **6b** is preferred over the ββ-approach in which the dipole C is bonded to C6 by 0.6 and 1.4 kcal mol^{-1}, respectively. Higher level (B3LYP/6-31G*) calculated results very

Table 5. Semi-empirical (PM3) and B3LYP/6-31G* calculated relative transition state energy differences for the cycloaddition of **1a** with **6a** and **6b** and **1b** with **6d** in kcal/mol[a]

Entry	Computational level	6	ββ(XC,O)[b] **7**	ββ(XC,C)[c] **8**	αβ(XC,O)	αβ(XC,C)
1	RHF/PM3	**6a**	0.0 (0.0)	0.0 (0.0)	0.7 (0.7)	0.7 (0.8)
2	B3LYP/6-31G*//PM3	**6a**	0.0 (0.0, 0.0)	0.1 (0.05, 0.1)	6.1 (6.0, 5.9)	6.0 (5.9, 6.0)
3	RHF/PM3	**6b**	0.4 (0.2)	1.0 (1.6)	0.9 (0.0)	0.0 (1.7)
4	B3LYP/6-31G*//PM3	**6b**	0.0 (0.0, 0.0)	3.0 (4.0, 3.4)	3.9 (3.2, 3.6)	6.7 (8.8, 7.1)
5	RHF/PM3	**6d**	0.4 (0.0)	0.0 (0.9)	1.1 (0.5)	0.4 (2.3)
6	B3LYP/6-31G*//PM3	**6d**	0.5 (0.0, 0.3)	0.0 (0.5, 0.0)	6.9 (6.0, 6.4)	2.3 (3.6, 2.8)

[a] Solvent calculated (aqueous model, THF model) energy differences in parentheses.
[b] (XC,O): dipole oxygen forms bond with C–X.
[c] (XC,C): dipole carbon forms bond with C–X.

clearly predicted the formation of the experimentally observed product **7c** over **8c** and the products arising from αβ-approach of the dipole **1a** (Table 5, entry 4). Furthermore, upon incorporating the solvent model (aqueous and THF) at B3LYP/6-31G* level, the calculated results show even larger preference for the formation of experimentally observed product **7c** (**7c**:**8c**=>99:1).

In the case of **6d**, PM3 and B3LYP/6-31G* calculated results predicted the preferential approach of nitrile oxide **1b** towards the ββ-face of C5–C6 double bond over the αβ-face of C2–C3 double bond. The regioselectivity obtained from our calculations is in agreement with our experimental results. Aqueous model, however, altered the preference in favor of ββ(XC,O) approach, and can be understood on the basis of the dipole moment of the transition states. The calculated dipole moment of the TS corresponding to ββ(XC,O) approach is relatively higher and gets more stabilized in the polar solvent. However, the calculations performed in THF are in accordance with gas phase results. The overall calculated results suggest that the hybrid ab initio/DFT (B3LYP) levels predict more accurately the experimental observations. It has been found that for 1,3-dipolar cycloadditions, B3LYP calculations often give comparable or slightly better results than other high level MP2, CASSCF or CCSD(T) calculations.[46] The perturbation MO treatment of cycloaddition reactivity pioneered by Sustmann[47] has generally been applied to explain the regioselectivity qualitatively of 1,3-dipolar cycloadditions.[48] Such frontier molecular orbital analysis performed for **6a**, **6b** and **6d** does not provide any clear picture towards the origin of regioselectivity in these cases. However, turning to the Mulliken population analysis, the charges calculated for **6b** and **6d** at B3LYP/6-31G* shows that the C6 carbon of **6b** bears a positive charge (0.100), while C5 has a negative charge of (−0.118) and in the case of **6d**, C6 carries slightly more negative charge (−0.111) in comparison to C5 (−0.106). This result explains the regioselectivity observed for **6b** qualitatively, where the negative end of the dipole **1a** (oxygen) is attached to the C6 carbon of **6b** and the positive end of the dipole **1a** (carbon) is attached to C5 of **6b**. The difference in the charge between C5 and C6 is smaller in the case of **6d**, and leads to a mixture of regioisomers. Mayo et al. have performed similar charge analysis to rationalize the regioselectivity observed for the 1,3-dipolar cycloaddition of nitrile oxides with unsymmetrically substituted norbornenes.[16]

The above calculated results for the cycloaddition of nitrile oxide **1** to dicyclopentadiene **6a** and its derivatives **6b–d** have shown that the norbornene units of **6a–d** are comparatively more reactive than cyclopentene units as predicted and observed in the case of isolated norbornenes and cyclopentenes.[27] Regioselectivities predicted and observed for the addition of nitrile oxide **1a** to Thiele's ester **6b** are in accordance with the norbornene esters.[16] Overall, it appears that the reactivity of norbornene units in **6a–d** are not perturbed in presence of cyclopentene units.

4. Summary and conclusions

The 1,3-dipolar cycloaddition of nitrile oxides to representative systems possessing multiple π-faces, viz. dicyclopentadiene and its derivatives, has been investigated. The greater reactivity of bicycloheptenyl double bond vis-à-vis cyclopentenyl double bond in the dicyclopentadienyl moiety towards the nitrile oxide dipole is amply evident from the exclusive formation of the *exo*-cycloadduct arising from approach of the dipole from the *exo* face of the bicycloheptenyl double bond. Furthermore, in the case of substituted dicyclopentadienes, viz. the dicarboxylate (Thiele's ester), the exclusive regioisomer is the one in which the dipole oxygen is attached to the carbon bearing the substituent. Influence of remote substituents, including sterically 'sterile' ones, on the regioselectivity has also been demonstrated. The combination of semi-empirical (PM3) and hybrid ab initio/DFT (B3LYP) methods was used to predict the chemo-, stereo- and regioselectivity of dicyclopentadienes and its derivatives. These more economical methods have successfully predicted the selectivity in the 1,3-dipolar cycloadditions of nitrile oxide to model systems as well as complex real systems. Regioselectivities observed in these cases were rationalized on the basis of Mulliken population analysis. The commonly used frontier molecular orbital analysis failed to predict the regio-selectivity in these cases at the levels of theory employed.

5. Experimental

5.1. General

The melting points are uncorrected. IR spectra were recorded on an Impact 400/Nicolet FT spectrometer. NMR spectra (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY) were recorded on a JEOL-400, AMX-400 or VXR-300S spectrometer with TMS as the internal standard. High resolution mass spectra (CI in methane or *i*-butane) were recorded at 60–70 eV on a VG-Fisons 'Autospec' spectrometer. X-ray data were collected on a MACH3S-CAAD4/NONIUS diffractometer.

5.2. Procedure for the generation of acetonitrile oxide 1a from acetaldoxime and its reaction with 6 (path A, method A)

To a stirred solution of **6** (0.5 mmol) and *N*-chlorosuccinimide (134 mg, 1 mmol, 2 equiv.) in CH_2Cl_2 (10 ml) at 0 °C under N_2 was added acetaldoxime (59 mg, 1 mmol, 2 equiv.) followed by Et_3N (22 mg, 0.22 mmol, 0.44 equiv.). The reaction mixture was stirred at rt overnight (12 h). The reaction mixture was then diluted with CH_2Cl_2 (20 ml), washed with 5% HCl (20 ml), brine (20 ml), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to ^{1}H NMR (400 MHz) analysis in order to determine the isomeric purity/composition and then purified by silica gel column chromatography by eluting with ethylacetate/pet. ether.

5.3. Procedure for the generation of benzonitrile oxide 1b from benzaldoxime and its reaction with 6 (path A, method B)

To a stirred solution of **6** (0.5 mmol), oxime (1 mmol, 2 equiv.) and few drops of Et_3N in CH_2Cl_2 (10 ml) at 0 °C

was added dropwise 4% NaOCl solution (10 ml, excess). The cooling bath was removed and the reaction mixture, while stirring continued, was allowed to warm to rt overnight (12 h). The layers were separated, the organic layer was washed with 5% HCl (20 ml), brine (20 ml), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to ^1H NMR (400 MHz) analysis as before and then purified by silica gel column chromatography by eluting with ethylacetate/pet. ether.

5.4. Procedure for the generation of nitrile oxide 1 from nitroalkane (nitroethane or nitrophenylmethane) and its reaction with 6 (path B)

To a stirred solution of **6** (0.5 mmol) and nitroalkane (1 mmol, 2 equiv.) in THF (10 ml) under N_2 was added DMAP (12 mg, 0.1 mmol, 20 mol%) followed by BOC_2O (327 mg, 1.5 mmol, 3 equiv.). The reaction mixture was stirred at rt overnight (12 h). The reaction mixture was then diluted with water (20 ml) and extracted with ether (3×15 ml). The combined organic layer was washed with 5% HCl (20 ml), brine (20 ml), dried over anh. Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to ^1H NMR (400 MHz) analysis as before and then purified by silica gel column chromatography by eluting with ethylacetate/pet. ether.

5.4.1. Cycloaddition of acetonitrile oxide 1a with dicyclopentadiene 6a. Total yield of cycloadducts 3-methyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno [5,6-*d*]isoxazole **7a** +3-methyl-4,4a,5,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **8a** (inseparable mixture; **7a**:**8a**=53:47): path A, method A: 57%, path B: 84% (see also Table 1, entries 1 and 2); colorless crystalline solid; mp 60–62 °C; IR (KBr) cm^{-1} 2960 (s), 1453 (s), 1262 (s); ^1H NMR ($CDCl_3$) δ 1.30 (d, J=9.2 Hz, 1H), 1.45 (d, J=9.2 Hz, 1H), 1.80, 1.83 (d, J=0.8 Hz, 3H), 2.05–2.32 (m, 3H), 2.38 (m, 1H), 2.45–2.60 (m, 1H), 2.92, 2.97 (d, J=8.3 Hz, 1H), 3.08 (m, 1H), 4.28, 4.36 (d, J=8.3 Hz, 1H), 5.45–5.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 10.6, 11.8, 31.5, 32.4, 34.6, 35.0, 39.3, 40.7, 41.3, 42.9, 45.5, 47.3, 50.2, 51.6, 53.4, 56.6, 81.6, 84.0, 130.5, 131.2 (×2), 131.8, 156.2, 156.4; MS (CI, CH_4) *m/e* (rel intensity) 190 (MH^+, 12) 189 (M^+, 42), 169 (80), 168 (100), 141 (96), 131 (62), 115 (78); HRMS calcd for $C_{12}H_{15}NO$ (M^+) 189.1154, found:189.1164.

5.4.2. Cycloaddition of benzonitrile oxide 1b with dicyclopentadiene 6a. Total yield of cycloadducts 3-phenyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno [5,6-*d*]isoxazole **7b** +3-phenyl-4,4a,5,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **8b** (**7b**:**8b**=54:46): path A, method B: 86%, path B: 52% (see also Table 1, entries 3 and 4).

3-Phenyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **7b** (major isomer). Separated from the **7b/8b** mixture by fractional crystallization from ethanol; colorless crystalline solid; mp 85–87 °C; IR (KBr) cm^{-1} 2962 (s), 1600 (m), 1461 (s); ^1H NMR ($CDCl_3$) δ 1.40 (d, J=10.3 Hz, 1H), 1.60 (d, J=10.3 Hz, 1H), 2.30 (m, 2H), 2.60 (m, 3H), 3.20 (m, 1H), 3.63 (d, J=8.4 Hz, 1H), 4.66 (d, J=8.4 Hz, 1H), 5.68 (m, 1H), 5.78 (m, 1H), 7.36 (m, 3H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 31.4, 35.2, 39.3, 42.4, 47.5, 51.8, 52.9, 83.3, 126.6, 128.5, 129.1, 129.5, 131.1, 132.1, 157.6; MS (CI, CH_4) *m/e* (rel intensity) 251 (M^+, 100), 183 (22), 157 (19), 156 (17), 155 (19), 117 (15), 105 (18), 91 (18); HRMS calcd for $C_{17}H_{17}NO$ (M^+): 251.1310, found: 251.1314.

3-Phenyl-4,4a,5,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazole **8b** (minor isomer). Colorless crystalline solid; mp 95–96 °C; IR (KBr) cm^{-1} 2960 (s), 1604 (m), 1459 (s), 1348 (s); ^1H NMR ($CDCl_3$) δ 1.40 (d, J=10.3 Hz, 1H), 1.60 (d, J=10.3 Hz, 1H), 2.40 (m, 2H), 2.60 (m, 2H), 2.75 (d, J=5.6 Hz, 1H), 3.20 (m, 1H), 3.58 (d, J=8.4 Hz, 1H), 4.58 (d, J=8.4 Hz, 1H), 5.70 (m, 2H), 7.36 (m, 3H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 32.6, 34.6, 40.8, 44.0, 45.7, 49.5, 50.2, 85.7, 126.6, 128.5, 129.2, 129.4, 130.6, 131.2, 157.3; MS (CI, CH_4) *m/e* (rel intensity) 251 (M^+, 100), 183 (26), 155 (33), 141 (17), 115 (15), 105 (16); HRMS calcd for $C_{17}H_{17}NO$ (M^+): 251.1310, found: 251.1290.

5.4.3. Cycloaddition of acetonitrile oxide 1a with dimethyldicyclopentadiene dicarboxylate 6b. Yield of cycloadduct dimethyl 3-methyl-3a,4,4a,7,7a,8-hexahydro-8a*H*-4,8-methanoindeno-[5,6-*d*]isoxazole-6,8a-dicarboxylate **7c**: path A, method A: 52%, path B: 72% (see also Table 2, entries 1 and 2); colorless crystalline solid; mp 175–177 °C; IR (KBr) cm^{-1} 2960 (s), 1737 (s), 1716 (s), 1314 (m), 1262 (s); ^1H NMR ($CDCl_3$) δ 1.48 (d, J=11.0 Hz, 1H), 1.79 (d, J=11.0 Hz, 1H), 1.94 (s, 3H), 2.34 (m, 1H), 2.48 (m, 1H), 2.62 (d, J=5.1 Hz, 1H), 2.82 (m, 1H), 2.88 (d, J=4.4 Hz, 1H), 3.37 (m, 1H), 3.43 (s, 1H), 3.73 (s, 3H), 3.75 (s, 3H), 6.60 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.7, 30.3, 37.4, 40.1, 42.9, 49.1, 51.4 (×2), 52.4, 56.7, 93.1, 137.8, 141.5, 156.6, 164.6, 168.5; MS (CI, CH_4) *m/e* (rel intensity) 306 (MH^+, 5), 305 (M^+, 1), 274 (8), 246 (7), 232 (8), 214 (11), 204 (15), 183 (100), 173 (14), 172 (26), 151 (75), 117 (23); HRMS calcd for $C_{16}H_{20}NO_5$ (MH^+): 306.1342, found: 306.1360.

5.4.4. Cycloaddition of benzonitrile oxide 1b with dimethyldicyclopentadiene dicarboxylate 6b. Yield of cycloadduct 3-phenyl-3a,4,4a,7,7a,8-hexahydro-8a*H*-4,8-methanoindeno-[5,6-*d*]isoxazole-6,8a-dicarboxylate **7d**: path A, method B: 73%, path B: 50% (see also Table 2, entries 3 and 4); colorless crystalline solid; mp 160–161 °C; IR (KBr) cm^{-1} 2939 (s), 1738 (s), 1716 (s); ^1H NMR ($CDCl_3$) δ 1.50 (d, J=10.6 Hz, 1H), 1.89 (d, J=10.6 Hz, 1H), 2.40 (m, 1H), 2.52 (m, 1H), 2.78 (dd, J=5.1 and 2.2 Hz, 1H), 2.88 (m, 1H), 2.98 (d, J=4.4 Hz, 1H), 3.39 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 4.0 (d, J=2.2 Hz, 1H), 6.74 (d, J=1.8 Hz, 1H), 7.40 (m, 3H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.3, 37.5, 40.1, 44.1, 49.2, 51.5 (×2), 52.5, 53.2, 94.7, 127.0, 128.3, 128.7, 130.2, 137.9, 141.5, 158.1, 164.7, 168.3; MS (CI, CH_4) *m/e* (rel intensity) 367 (M^+, 23), 331 (24), 308 (10), 280 (24), 232 (12), 183 (100), 151 (49); HRMS calcd for $C_{21}H_{21}NO_5$ (M^+) 367.1420, found: 367.1420.

5.4.5. Cycloaddition of benzonitrile oxide 1b with dicyclopentadien-8-ol 6c. 3-Phenyl-4,4a,7,7a,8,8a-hexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazol-9-ol **7e** (major isomer) +3-phenyl-4,4a,5,7a,8,8ahexahydro-3a*H*-4,8-methanoindeno[5,6-*d*]isoxazol-9-ol **8e** (minor isomer): Total

yield (inseparable mixture, **7e**:**8e**=55:45) 70% (see also Table 3, entry 1); colorless crystalline solid; mp 140–142 °C; IR (KBr) cm^{-1} 3399 (b), 2976 (s), 1658 (s), 1351 (s), 1038 (s); ^1H NMR ($CDCl_3$) δ 1.55 (m, 2H), 2.45 (m, 1H), 2.65 (m, 1H), 2.81 (m, 1H), 3.36 (m, 1H), 3.39, 3.48 (d, J=8.4 Hz, 1H), 4.43, 4.49 (d, J=8.4 Hz, 1H), 4.83 (m, 1H), 5.87–5.95 (m, 1H), 6.02–6.05 (m, 1H), 7.40–7.48 (m, 3H), 7.60–7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 35.2, 35.7, 42.4, 43.0, 45.5, 46.6, 49.5, 50.6, 51.0, 51.1, 52.2, 52.6, 75.6, 76.8, 83.5, 85.0, 126.7, 126.8, 128.72, 128.74, 129.0 (×2), 129.9 (×2), 133.6, 134.9, 137.1, 137.4, 157.3, 157.6; MS (CI, *i*-butane) *m*/*e* (rel intensity) 268 (MH^+, 61), 267 (M^+, 100), 250 (13); HRMS calcd for $C_{17}H_{17}NO_2$ (M^+): 267.1259, found 267.1236.

5.4.6. Cycloaddition of benzonitrile oxide 1b with dicyclopentadien-1-one 6d. Total yield of cycloadducts (**7f**:**8f**=34:66) 68% (see also Table 3, entry 2).

3-Phenyl-3a,4,4a,7a,8,8a-hexahydro-5*H*-4,8-methanoindeno[5,6-*d*]isoxazol-5-one (major isomer) **8f**. Separated from the mixture by fractional crystallization from ethanol, colorless crystalline solid; mp 210–211 °C; IR (KBr) cm^{-1} 2976 (m), 1697 (s), 1351 (w), 1274 (m), 1184 (w), 1076 (w), 890 (m); ^1H NMR ($CDCl_3$) δ 1.70 (ABq, J=11.0 Hz, 2H), 2.77 (t, J=6.1 Hz, 1H), 2.95 (d, J=4.9 Hz, 2H), 3.36 (m, 1H), 3.44 (d, J=8.5 Hz, 1H), 4.44 (d, J=8.5 Hz, 1H), 6.21 (m, 1H), 7.39–7.40 (m, 3H), 7.68 (m, 2H), 7.73 (dd, J=6.1, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 36.5, 43.6, 45.2, 46.5, 50.7, 52.3, 84.2, 126.7, 128.2, 128.69, 129.9, 135.9, 156.9, 164.4, 209.6; MS (CI, *i*-butane) *m*/*e* (rel intensity) 266 (MH^+, 265 (M^+, 100), 172 (79), 144 (12), 143 (15), 128 (8), 117 (9), 93 (54), 76 (14); HRMS calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103, found 265.1106.

3-Phenyl-3a,4,4a,7a,8,8a-hexahydro-7*H*-4,8-methanoindeno[5,6-*d*]isoxazol-7-one (minor isomer) **7f**. Colorless crystalline solid; mp 158–160 °C; IR (KBr) cm^{-1} 2970 (m), 1697 (s), 1345 (w), 1095 (w); ^1H NMR ($CDCl_3$) δ 1.70 (ABq, J=11.0 Hz, 2H), 2.78 (m, 2H), 3.18 (d, J=4.9 Hz, 1H), 3.35 (m, 2H), 4.52 (d, J=8.5 Hz, 1H), 6.25 (m, 1H), 7.41 (m, 3H), 7.67 (m, 2H), 7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 36.3, 42.0, 47.1, 48.3, 48.9, 50.7, 52.0, 52.8, 83.3, 126.6, 128.5, 128.72, 129.9, 136.5, 157.1, 163.5, 208.5; MS (CI, *i*-butane) *m*/*e* (rel intensity) 266 (MH^+, 59), 265 (M^+, 100), 86 (23); HRMS calcd for $C_{17}H_{15}NO_2$ (M^+): 265.1103, found 265.1117.

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33. Presence of excess nitrile oxide precursors (up to 4 equiv. of oxime or nitroalkane) and/or excess reagents did not alter the isomer ratios. In presence of excess dipolarophile, on the other hand, the reaction remained incomplete, but the isomer ratio remained unchanged. However, best yields were obtained when nitrile oxides **1** were generated in presence of the dipolarophile.
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