JOC*Article*

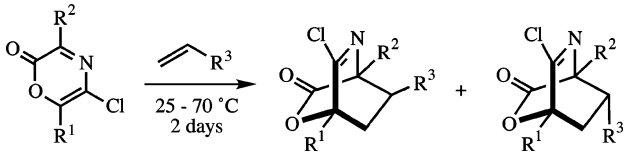
Investigation of the Diels−Alder Cycloadditions of 2(*H*)-1,4-Oxazin-2-ones

Kamyar Afarinkia,*,† Akmal Bahar,† Michael J. Bearpark,‡ Yésica Garcia-Ramos,† Andrea Ruggiero,† Judi Neuss,§ and Maushami Vyas†

Department of Chemistry, King's College, Strand, London WC2R 2LS, U.K., Department of Chemistry, Imperial College, Exhibition Road, London SW7 2AY, U.K., and UCB, 216 Bath Road, Slough, Berkshire, SL1 4EN, U.K.

kamyar.afarinkia@kcl.ac.uk

Received August 5, 2005



A variety of 5-chloro-2(*H*)-1,4-oxazin-2-ones bearing a range of substituents at their 3- and 6-positions undergo Diels−Alder cycloaddition as a 2-azadiene component with electron-rich, electron-deficient, and electron-neutral dienophiles. These reactions proceed with moderate regio- and stereoselectivity to afford relatively stable and readily isolable bridged bicyclic lactone cycloadducts. Chemical manipulation of these cycloadducts affords highly substituted and functionally rich piperidines. The regio- and stereochemical preferences of the cycloadditions of 5-chloro-2(*H*)-1,4-oxazin-2-ones are investigated computationally using density functional theory (B3LYP/6-31G*).

Introduction

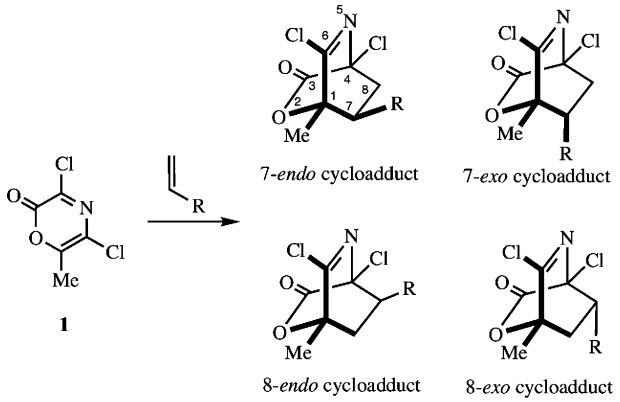
The Diels−Alder reaction of azadienes is a long established and useful method in organic synthesis.[1] In particular, the azadiene components of many aromatic nitrogen-containing heterocycles have been utilized in [4 + 2] cycloadditions.[2] These include 1,2,4-triazines,[3] oxazoles,[4] thiazoles,[5] pyrimidines,[6] 1,3-oxazin-2-ones,[7] and 1,3-oxazin-6-ones.[8] More recently, Hoornaert reported the use of 1(*H*)-pyrazin-2-ones[9] and 1,4-oxazin-2-ones, such as 3,5-dichloro-6-methyl-2(*H*)-1,4-oxazin-2-one **1**, as a 2-azadiene component in Diels−Alder cycloadditions.[9c,d,f,10] An intriguing and highly unusual feature of the cycloadditions of **1** was that it underwent cycloadditions with examples of electron-deficient (methyl acrylate), electron-neutral (styrene), and electron-rich (ethyl vinyl ether) dienophiles (Scheme 1). Although the reac-

† King's College.
‡ Imperial College.
§ UCB.

(1) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
(2) (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
(3) (a) Sauer, J.; Heldmann, D. K. *Tetrahedron Lett.* **1998**, *39*, 2549. (b) Wan, Z. K.; Snyder, J. K. *Tetrahedron Lett.* **1998**, *39*, 2487. (c) Rykowski, A.; Branowska, D.; Kielak, J. *Tetrahedron Lett.* **2000**, *41*, 3657.
(4) (a) Ohba, M.; Izuta, R.; Shimizu, E. *Tetrahedron Lett.* **2000**, *41*, 10251. (b) Ohba, M.; Izuta, R. *Heterocycles* **2001**, *55*, 823.
(5) Kopka, I. E. *Tetrahedron Lett.* **1988**, *29*, 3768.
(6) Brown, D. J.; England, B. T. *Aust. J. Chem.* **1970**, *23*, 625.
(7) For example, see: (a) Baydar, A. E.; Boyd G. V., Lindley P. F., Watson F. *J. Chem. Soc., Chem. Commun.* **1979**, 178.
(8) Boger, D. L.; Wysocki, R. J., Jr. *J. Org. Chem.* **1989**, *54*, 714.
(9) (a) Tutonda, M.; Vanderzande, D.; Vekemans, J.; Toppet, S.; Hoornaert, G. *Tetrahedron Lett.* **1986**, *27*, 2509. (b) Loosen, P. K.; Khorasani, M. F.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron* **1991**, *47*, 9269. (c) Tutonda, M. G.; Vandenberghe, S. M.; Van Aken, K. J.; Hoornaert, G. J. *J. Org. Chem.* **1992**, *57*, 2935. (d) Hoornaert, G. J. *Bull. Soc. Chim. Belg.* **1992**, *101*, 53. (e) Vandenberghe, D. M.; Hoornaert, G. J. *Bull. Soc. Chim. Belg.* **1994**, *103*, 185. (f) Hoornaert, G. J. *Bull. Soc. Chim. Belg.* **1994**, *103*, 583. (g) Buysens, K. J.; Vandenberghe, D. M.; Toppet, S. M.; Hoornaert, G. J. *Tetrahedron* **1995**, *50*, 12463. (h) Vandenberghe, S. M.; Buysens, K. J.; Meerpoel, L.; Loosen, P. K.; Toppet, S. M.; Hoornaert, G. J. *J. Org. Chem.* **1996**, *61*, 304. (i) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211. (j) Tahri, A.; De Borggraeve, W.; Buysens, K.; Van Meervelt, L.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **1999**, *55*, 14675. (k) Rombouts, F. J. R.; Vanraes, D. A. J.; Wynendaele, J.; Loosen, P. K.; Luyten, I.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2001**, *57*, 3209. (l) Rombouts, F. J. R.; De Borggraeve, W.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron Lett.* **2001**, *42*, 7397. (m) De Borggraeve, W. M.; Rombouts, F. J. R.; Verbist, B. M. P.; Van der Eycken, E. V.; Hoornaert, G. J. *Tetrahedron Lett.* **2002**, *43*, 447.
(10) (a) Meerpoel, L.; Deroover, G.; Vanaken, K.; Lux, G.; Hoornaert, G. J. *Synthesis* **1991**, 765. (b) Fannes, C.; Meerpool, L.; Hoornaert, G. J. *Synthesis* **1992**, 705. (c) Fannes, C. C.; Hoornaert, G. J. *Tetrahedron Lett.* **1992**, *33*, 2049. (d) Vanaken, K. J.; Lux, G. M.; Deroover, G. G.; Meerpoel, L.; Hoornaert, G. J. *Tetrahedron* **1994**, *50*, 5211. (e) Vanaken, K. J.; Lux, G. M.; Deroover, G. G.; Meerpoel, L.; Hoornaert, G. J. *Tetrahedron* **1996**, *52*, 2591. (f) Lux, G.; Wu, X. J.; Toppet, S.; Hoornaert, G. J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 623. (g) De Borggraeve, W.; Rombouts, F.; Van der Eycken, E.; Hoornaert, G. J. *Synlett* **2000**, 713. (h) Wu, X. J.; Dubois, K.; Rogiers, J.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2000**, *56*, 3043.

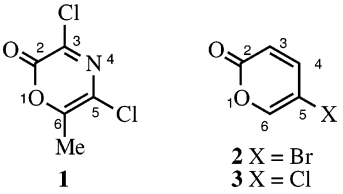
10.1021/jo051646i CCC: $30.25
Published on Web 10/20/2005

SCHEME 1



R = CO_2Me, 8-endo : 7-endo : 8-exo : 7-exo = 35 : 33 : 32 : 0
R = Ph, 8-endo : 7-endo : 8-exo : 7-exo = 53 : 20 : 18 : 9
R = OEt, 8-endo : 7-endo : 8-exo : 7-exo = 73 : 0 : 27 : 0

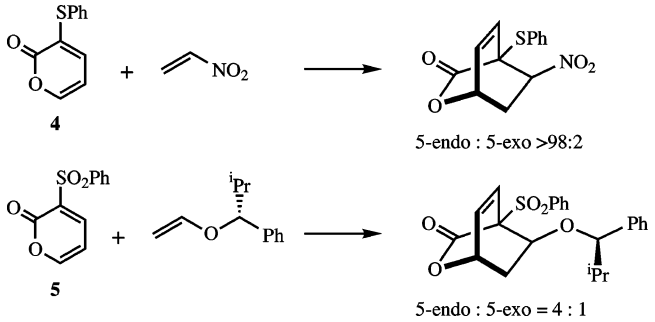
tions were not regio- and stereoselective, affording all four possible stereo- and regioisomeric cycloadducts, this was the only known example of an "ambident" 2-azadiene, i.e., one which is capable of both normal and inverse electron-demand Diels–Alder cycloadditions. Curiously, the only other known ambident dienes are halogenated 2(*H*)-pyran-2-ones, e.g., 3-bromo-2(*H*)-pyran-2-one,[11a] 5-bromo-2(*H*)-pyran-2-one **2**,[11b,c] 5-chloro-2(*H*)-pyran-2-one **3**,[12] and 3,5-dibromo-2(*H*)-pyran-2-one.[13] Therefore, it appears that 2(*H*)-1,4-oxazin-2-ones are 2-azadiene counterparts of the well-investigated 2(*H*)-pyran-2-one dienes. To complement our long-standing interest in the cycloaddition reactions of 2(*H*)-pyran-2-ones[11,12] and their synthetic applications,[14] we decided to evaluate the cycloaddition reactions of several 1,4-oxazin-2-ones with the aim of extending the scope of the reaction and exploring their potential for synthesis of complex molecules.[15]



Results and Discussion

Preparation of 2(*H*)-1,4-Oxazin-2-one. If 2(*H*)-1,4-oxazin-2-ones are to be useful in synthesis, their cycloaddition should be versatile and tolerate a range of substituents both on the azadiene (i.e., the 1,4-oxazin-2-one ring) and dienophile. This requires convenient routes to a wide range of substituted 2(*H*)-1,4-oxazin-2-ones. During his studies, Hoornaert had reported a method for the preparation of 6-substituted 3,5-dichloro-2(*H*)-1,4-oxazin-2-ones.[16] This presented us with an ideal opportunity to prepare a wide range of substituted 1,4-oxazin-2-ones, both through Hoornaert's original synthesis (through variation of the 6-substituent) and also by chemical manipulation of the chloro substituents.

SCHEME 2



Furthermore, to make this an efficient methodology, the Diels–Alder cycloadditions should proceed in good yield and with regio- and stereoselectivity. This can be best achieved by matching the electronic demand of the dienophile with that of the 2(*H*)-1,4-oxazin-2-one by means of appropriate ring substitution. This approach has been successfully used by Posner, who has demonstrated that 3-phenylsulfenyl-2(*H*)-pyran-2-one **4**[17] and 3-phenylsulfonyl-2(*H*)-pyran-2-one **5**[18] react with electron-deficient and electron-rich dienophiles, respectively, and that the reactions proceed to give the isolable cycloadducts with excellent regio- and stereocontrol (Scheme 2).

A telling example from Hoornaert's cycloaddition studies was that the only moderately selective cycloaddition was that between ethyl vinyl ether, an electron-rich dienophile, and 3,5-dichloro-6-methyl-2(*H*)-1,4-oxazin-2-

(11) (a) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Afarinkia, K. *Tetrahedron Lett.* **1991**, *32*, 5295. (b) Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.* **1992**, *33*, 7839. (c) Afarinkia, K.; Daly, N. T.; Gomez-Farnos, S.; Joshi, S. *Tetrahedron Lett.* **1997**, *38*, 2369. (d) Posner, G. H.; Afarinkia, K.; Dai, H. *Organic Synthesis* **1995**, *73*, 231. For reviews, see: (e) Afarinkia, K.; Nelson, T. D.; Vinader, M. V.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. (f) Woodward, B. T.; Posner, G. H. *Adv. Cyloaddition* **1999**, *5*, 47.

(12) (a) Afarinkia, K.; Bearpark, M.; Ndibwami, A. *J. Org. Chem.* **2003**, *68*, 7158. (b) Afarinkia, K.; Bearpark, M.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122.

(13) (a) Cho C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* **2001**, *42*, 1065. (b) Cho C.-G.; Kim, Y.-W.; Lim, Y.-K.; Park, J.-S.; Lee, H.; Koo, S. *J. Org. Chem.* **2002**, *67*, 290. (c) Shin, J.-T.; Shin S.; Cho C.-G. *Tetrahedron Lett.* **2004**, *45*, 5857.

(14) (a) Afarinkia, K.; Mahmood, F. *Tetrahedron* **1999**, *55*, 3129. For further examples of the use of 2-pyrone cycloadditions in the synthesis, see: (b) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, T. J.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (c) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050. (d) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033. (e) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. (f) Ahmed, S. A.; Bardshiri, E.; Simpson, T. J. *J. Chem. Soc., Chem. Commun.* **1987**, 883. (g) Yamaguchi, R.; Otsuji, A.; Utimoto, K.; Kozima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 298. (h) Posner, G. H.; Dai, H.; Afarinkia, K.; Murthy, N. N.; Guyton, K. Z.; Kensler, T. W. *J. Org. Chem.*, **1993**, *58*, 7209. (i) Markó, I. E., Seres, P.; Evans G. R.; Swarbrick T. M. *Tetrahedron Lett.* **1993**, *34*, 7305. (j) Posner, G. H.; Lee, J. K.; White, M. C.; Hutchings, R. H.; Dai, H. Y.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. *J. Org. Chem.* **1997**, *62*, 3299. (k) Kim, W. S.; Lee, J. H.; Kang, J.; Cho C.-G. *Tetrahedron Lett.* **2004**, *45*, 1683. (l) Vijgen, S.; Nauwelaerts, K.; Wang, J.; Van Aeschot, A.; Lagoja, I.; Herdewijn, P. *J. Org. Chem.* **2005**, *70*, 4591.

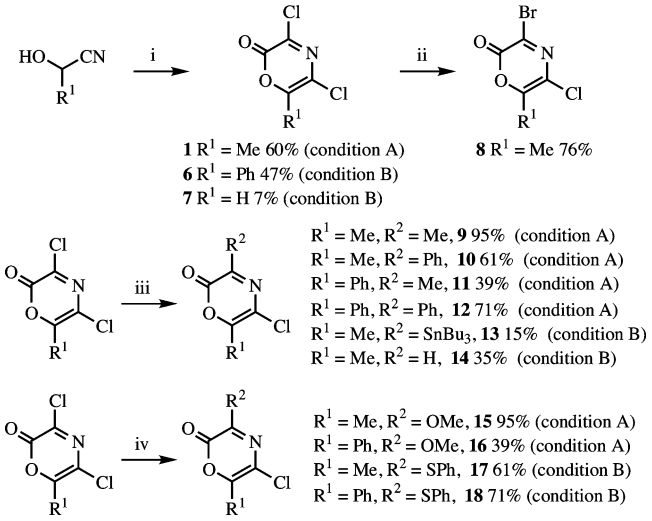
(15) For a preliminary communication, see: (a) Afarinkia, K.; Bahar A.; Neuss, J.; Ruggerio, A. *Tetrahedron Lett.* **2004**, *45*, 3995. (b) Afarinkia, K.; Bahar A.; Neuss, J.; Vyas, M. *Tetrahedron Lett.* **2004**, *45*, 7121.

(16) (a) Meerpool, L.; Hoornaert, G. J. *Tetrahedron Lett.* **1989**, *30*, 3183. (b) Meerpool, L.; Hoornaert, G. J. *Synthesis* **1990**, 905. (c) Vanaken, K. J.; Meerpoel, L.; Hoornaert, G. J. *Tetrahedron Lett.* **1992**, *33*, 2713.

(17) (a) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. (b) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Johnson, N. *J. Org. Chem.* **1992**, *57*, 4083.

(18) (a) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. (b) Posner, G. H.; Haces, A.; Harrison, W.; Kinter, C. M. *J. Org. Chem.* **1987**, *52*, 4836. (c) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967. (d) Posner, G. H.; Nelson, T. D. *Tetrahedron* **1990**, *46*, 4573.

SCHEME 3 [a]



[a] Key: (i) condition A: $(COCl)_2$, $Me_3N{\cdot}HCl$, toluene, reflux, 24 h; condition B: $(COCl)_2$, $Me_3N{\cdot}HCl$, chlorobenzene, 90 °C, 24 h; (ii) HBr, acetic acid, rt, 1 h; (iii) condition A: R^2SnMe_3, $Pd(PPh_3)_4$, toluene, reflux, 24 h; condition B: R^2SnBu_3, $Pd(PPh_3)_4$, toluene, reflux, 24 h; (vi) condition A: methanol, HCl, rt, 2 h; condition B: thiophenol, $AlCl_3$, CH_2Cl_2, rt, 15 h.

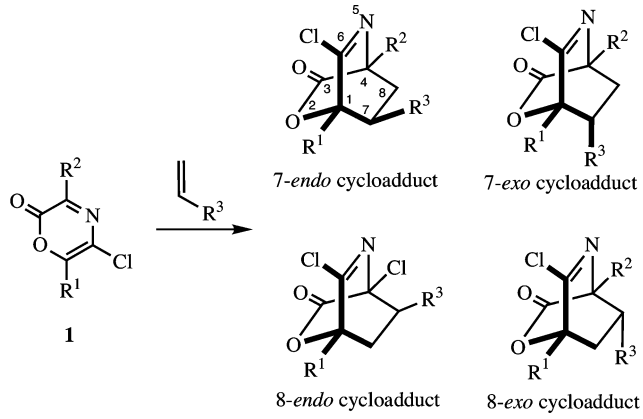
one, which having a chloro substituent at its 3-position can be considered an electron-deficient azadiene. Therefore, one of our key objectives was to prepare further examples of 2(*H*)-1,4-oxazin-2-one, particularly ones with electron-donating groups at the 3-position of the ring, and attempt their cycloadditions.[15]

3,5-Dichloro-2(*H*)-1,4-oxazin-2-ones **1**, **6**, and **7** were prepared by treatment of the corresponding cyanohydrins with oxalyl chloride in the presence of an external source of chloride ions (such as trimethylammonium chloride) according to Hoornaert's procedure (Scheme 3).[16] It is expected that the chloro substituent at the 3-position is more reactive than the one at the 5-position, and therefore, there were no issues relating to regioselectivity of further functionalization of these heterocyclic compounds. However, although aromatic chlorides undergo a diverse range of reactions, we found it useful to have access to potentially more reactive 3-bromo derivative **8**. This was prepared by treatment with hydrogen bromide in acetic acid. Stille coupling on 3,5-dichloro-2(*H*)-1,4-oxazin-2-ones afforded the corresponding 3-methyl- and 3-phenyl-2(*H*)-1,4-oxazin-2-ones **9**–**12**. However, introduction of allyl and vinyl groups by Stille coupling of allyl- and vinylstannane failed since both reagents undergo a more facile Diels–Alder cycloaddition, rather than a coupling. Nevertheless, the more reactive 3-bromo-5-chloro-2(*H*)-1,4-oxazin-2-one **8** did afford the corresponding 3-hydro and 3-stannyl derivatives **13** and **14**, but unfortunately, these proved to be highly sensitive compounds and decomposed quickly and, therefore, could not be used for further derivatization reactions or in cycloadditions.

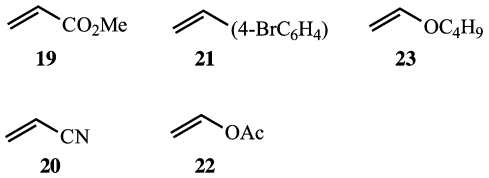
5-Chloro-3-methoxy-6-methyl-2(*H*)-1,4-oxazin-2-one **15** and 5-chloro-3-methoxy-6-phenyl-2(*H*)-1,4-oxazin-2-one **16** were prepared by treatment of **1** and **6** with methanolic hydrogen chloride.[10d,16c,19] 5-Chloro-3-phenylsulfenyl-6-methyl-2(*H*)-1,4-oxazin-2-one **17** and 5-chloro-3-phenylsulfenyl-6-phenyl-2(*H*)-1,4-oxazin-2-one **18** were prepared by treatment of **1** and **6** with thiophenol and aluminum trichloride (Scheme 3).[10d,16c,19]

(19) Meerpoel, L.; Joly, G. J.; Hoornaert, G. J. *Tetrahedron* **1993**, *49*, 4085.

SCHEME 4



Cycloadditions of 2(*H*)-1,4-Oxazin-2-one. The cycloadditions were carried out with a range of electron-deficient dienophiles methyl acrylate **19** and acrylonitrile **20**, electron-"neutral" dienophile 4-bromostyrene **21**, electron-rich dienophiles vinyl acetate **22**, and butyl vinyl ether **23**. It became immediately clear that 2(*H*)-1,4-



oxazin-2-ones are highly reactive azadienes and undergo cyloadditions with all these dienophiles at room temperature or with a relatively short reaction time at elevated temperatures. The cycloadditions were also highly efficient with only the cycloadducts (as well as unreacted starting materials, had the reaction not gone to completion) observed by NMR in crude product mixtures. The cycloadducts were quite stable; however, on prolonged exposure to silica gel during chromatography, we observed partial or significant decomposition in some cases, mainly due to hydrolysis of the imidoyl chloride function in the cycloadducts. The results of the cycloadditions are shown in Scheme 4 and Tables 1–3. The regio- and stereochemical assignment of the cycloadducts was based on the analysis of the NMR spectra of the cycloadducts according to the criteria which will be discussed shortly.

One of the first issues that we needed to address was whether the ratio of cycloadducts were determined by the thermodynamic stability of each configurational isomer. The issue of the kinetic or thermodynamic control in Diels–Alder reaction is complex. As a general rule with cyclic dienes, and particularly with 2(*H*)-pyran-2-ones and closely related 2(*H*)-pyridin-2-ones,[20] the *endo* cycloadducts are considered to be kinetic products whereas

(20) (a) Beteneli, L.; Shusherina, N. P.; Stepanyants, A. U.; Tarkhanova, E. A. *J. Org. Chem. USSR* **1977**, *13*, 1787. (b) Shusherina, N. P.; Pilipenko, V. S.; Kireeva, O. K.; Geller, B. I.; Stepanyants, A. U. *J. Org. Chem. USSR* **1980**, *16*, 2047. (c) Pilipenko, V. S.; Shusherina, N. P. *J. Org. Chem. USSR* **1981**, *17*, 1891. (d) Posner, G. H.; Vinader, M. V.; Afarinkia, K. *J. Org. Chem.* **1992**, *57*, 4088.

TABLE 1

Dienophile (Condition) [a]	Oxazinone Diene R^2	R^1	Cycloadduct ratio [b] 8-endo	7-endo	8-exo	7-exo
CO_2Me (A)	Cl	Me	35[c]	33[c]	32[c]	0[c]
	Cl	Ph	30	20	30	20
	Br	Me	32	50	18	0
$(4\text{-}BrC_6H_4)$ (A)	Cl	Me	53[d]	20[d]	18[d]	9[d]
	Cl	Ph	40	20	30	10
OAc (A)	Cl	Ph	40	20	30	10
	Br	Me	34	36	30	0
OBu (A) or (B)	Cl	Me	73[e]	0[e]	27[e]	0[e]
	Cl	Ph	30	20	30	20
	Br	Me	64	0	36	0

[a] Conditions A: Reaction was carried out for 2 days at 70 °C. Conditions B: Reaction was carried out for 4 days at room temperature. [b] Ratio of cycloadducts are normalized so as to total 100%. [c] Values taken from ref 10. [d] Values taken for the cycloaddition to styrene from ref 10. [e] Values taken for the cycloaddition to ethyl vinyl ether from ref 10.

TABLE 2

Dienophile (Condition) [a]	Oxazinone Diene R^2	R^1	Cycloadduct ratio [b] 8-endo	7-endo	8-exo	7-exo
CO_2Me (B)	Me	Me	55	18	27	0
	Me	Ph	68	16	16	0
	Ph	Ph	80	10	10	0
CN (A)	Me	Me	44	22	34	0
	Me	Ph	40	7	53	0
	Ph	Ph	77	8	15	0
$(4\text{-}BrC_6H_4)$ (A)	Me	Me	38	16	38	8
	Me	Ph	80	0	20	0
	Ph	Ph	>98	trace	trace	0
OAc (A)	Me	Me	64	14	22	0
	Me	Ph	55	18	27	0
	Ph	Ph	45	22	22	11
OBu (A)	Me	Me	60	0	40	0
	Me	Ph	71	0	29	0
	Ph	Ph	>98	0	trace	0

[a] Conditions A: Reaction was carried out for 2 days at 70 °C. Conditions B: Reaction was carried out for 4 days at room temperature. [b] Ratio of cycloadducts are normalized so as to total 100%.

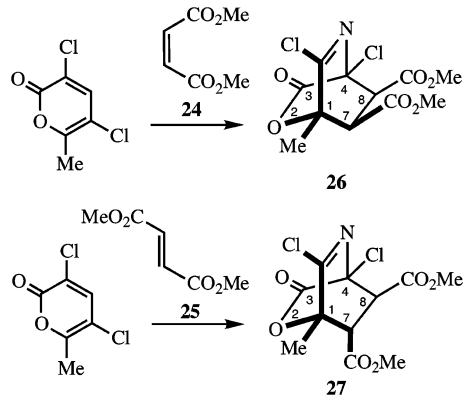
the *exo* products, which have less steric congestion, are considered to be the thermodynamic products. To ascertain this, we followed the progress of a typical thermal cycloaddition, that between **6** and butyl vinyl ether, by NMR. We found that the ratio of the cycloadduct products did not change as the reaction progressed, and once the reaction was complete, the ratio of the cycloadduct products did not change on prolonged heating. Furthermore, we analyzed the outcome of the thermal cycloaddition between **1** and dimethyl maleate **24** and dimethyl fumarate **25**, by NMR. We found that the stereochemistry

TABLE 3

Dienophile[a]	Oxazinone Diene R^2	R^1	Cycloadduct ratio [b,c] 8-endo	7-endo	8-exo	7-exo
CO_2Me	MeO	Me	67 (53)	0	33 (26)	0
	PhS	Me	50 (35)	0	50 (25)	0
	PhS	Ph	32 (27)	18 (15)	44 (38)	6 (1)
CN	MeO	Me	50 (46)	0	50 (44)	0
	PhS	Ph	50 (30)[d]	16 (4)[d]	34 (5)[d]	0
$(4\text{-}BrC_6H_4)$	MeO	Me	57 (46)	0	50 (44)	0
	PhS	Me	75 (69)	0	25 (15)	0
	PhS	Ph	58 (57)	18 (12)	14 (3)	10 (10)
OAc	MeO	Me	54[e]	trace[e]	46[e]	trace[e]
	PhS	Ph	33[e]	26[e]	33[e]	8[e]
OBu	MeO	Me	50 (38)	24 (18)	25(19)	trace
	PhS	Me	50 (18)[d,f]	12.5[d,f]	25 (10)[d,f]	12.5[d,f]
	PhS	Ph	48 (33)[d,f]	17 (13)[d,f]	35 (27)[d,f]	0[d,f]

[a] Conditions: Reaction was carried out for 2 days at 70 °C. [b] Ratio of cycloadducts are normalized so as to total 100%. [c] Values in brackets are the yield of isolated cycloadducts after purification by chromatography. [d] Cycloadducts partially decomposed during chromatography. [e] Cycloadducts decomposed during chromatography. [f] Using (2-chloroethyl) vinyl ether as dienophile.

SCHEME 5



of dimethyl maleate dienophile was preserved during cycloaddition affording exclusively *cis* cycloadduct **26** (Scheme 5). Had the reaction been a two-step process involving nucleophilic addition to dimethyl maleate as the first step, we would expect some *trans* cycloadduct **27**. However, this cycloadduct, an authentic sample of which is obtained in the cycloaddition of **1** and dimethyl fumarate **25** (Scheme 5), was absent from the reaction mixture. The results of this experiment further support an irreversible, single step cycloaddition step mechanism under the proposed reaction conditions.

As can be seen, the key features of the cycloaddition chemistry of 2(*H*)-1,4-oxazin-2-ones are as follows. 6-Alkyl- and 6-aryl-5-chloro-2(*H*)-1,4-oxazin-2-ones are ambident dienes reacting efficiently with examples of electron-rich, electron-deficient, and electron-neutral dienophiles. Introduction of substituents at the 3-position of 2(*H*)-1,4-oxazin-2-ones does not significantly affect the ambident reactivity of the azadiene. For example, 2(*H*)-1,4-oxazin-2-ones bearing an electron-donating substituent at their 3-position still react efficiently with electron-rich dieno-

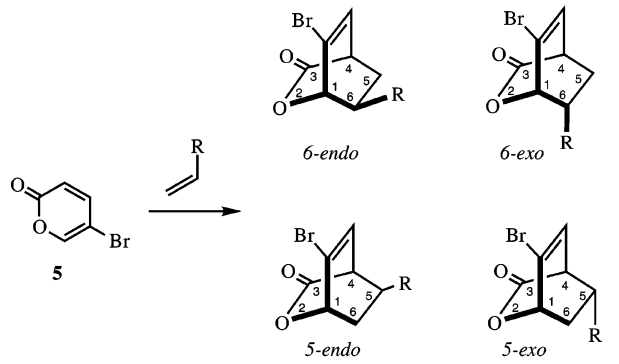
philes, and 2(*H*)-1,4-oxazin-2-ones bearing an electron-withdrawing substituent at their 3-position still react efficiently with electron-deficient dienophiles. However, matching the electronic demand of 2(*H*)-1,4-oxazin-2-ones with that of dienophiles can result in a significant improvement in regioselectivity of the reaction. For example, 2(*H*)-1,4-oxazin-2-ones bearing an electron-withdrawing substituent at their 3-position react efficiently with electron-deficient dienophiles to exclusively afford 8-substituted cycloadducts. An important observation which further confirms the role of matching the electron demand between dienophiles and 2(*H*)-1,4-oxazin-2-ones is that although the reactions are all efficient and afford near quantitative yield of cycloadducts, there is a significant difference between the rates of reactions. For example, using competition experiments we established that the rate of cycloaddition of butyl vinyl ether is at least five times faster with its electronically matched azadiene, 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **6**, than with 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **12**. Similarly, the rate of the cycloaddition of methyl acrylate is at least 10 times faster with its electronically matched azadiene, 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **12**, than with 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **6**.

In contrast, stereoselectivity of the cycloadditions remains modest even when the electron demand of the azadiene and dienophile are matched, except when the 2(*H*)-1,4-oxazin-2-one has a bulky substituent at its 3- and 6-positions. The role of sterically bulky substituents in improving the *endo* selectivity in cycloadditions of 2(*H*)-1,4-oxazin-2-ones is presumably related to similar observations by Sammes, who demonstrated that aryl substituents at the 3- and 6-position of 2(*H*)-pyridin-2-ones significantly improves the *endo* selectivity in their cycloadditions.[21]

However, the most important observation is that the preference in the cycloadditions of 2(*H*)-1,4-oxazin-2-one is for the cycloadducts with an 8-*endo* configuration regardless of the electronic demand of the dienophile.

Assignment of the Configuration of Cycloadducts. We were fortunate to obtain the major cycloadducts from the reactions of 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **12** with acrylonitrile **20**, 4-bromostyrene **21**, and butyl vinyl ether **23** as crystalline compounds. Hence, it was possible to confirm the relative configurations of all three by X-ray crystallography (see the Supporting Information). The configurations of all three of the major cycloadducts from the reaction between 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **12** and these three dienophiles were found to be 8-*endo*. In other words, *cycloadditions of* ***12*** *afforded the same configuration as the major cycloadduct regardless of the electronic demand of the dienophile*. Interestingly, this configuration is similar to the major one obtained in the cycloadditions of 3- and 5-bromo-2(*H*)-pyran-2-ones, the regio- and stereoselectivity of which are also independent of the electronic demand of the dienophile. It should be noted that the numbering system in cycloadducts from 2(*H*)-pyran-2-ones is different from the cycloadducts from 2(*H*)-1,4-oxazin-2-ones, which affords 2-oxa-5-azabicyclo[2.2.2]-oct-5-en-3-one. This confirms a strong similarity between the cycloaddition chemistry of 2(*H*)-pyran-2-ones and 2(*H*)-1,4-oxazinones.

SCHEME 6



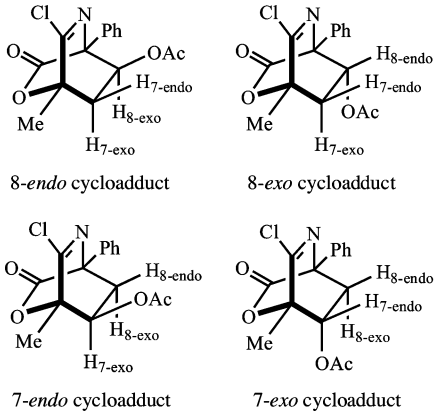
R = OBu, 5-endo : 6-endo : 5-exo : 6-exo = 65 : 0 : 35 : 0 (ref 20)
R = COMe, 5-endo : 6-endo : 5-exo : 6-exo = 89 : 11 : 0 : 0 (ref 20)

Although it was possible to obtain crystal structures of the major cycloadducts in the cycloadditions of **12** and hence absolutely prove the configurational assignment of the major cycloadducts in these cases, we needed to devise an alternative proof of structure which did not rely on crystallography. As part of the investigation of the Diels–Alder reaction of substituted 2(*H*)-pyran-2-ones, our group had established a protocol for the determination of the configuration of cycloadducts from 2(*H*)-pyrones.[11c,e,12] This protocol involves a comparison of the magnitude of the coupling constants between bridgehead protons (at position 1- or 4- of the 2(*H*)-pyrone cycloadduct and protons at position 5- or 6- of the 2(*H*)-pyrone cycloadduct, see Scheme 6). Since in the cycloadducts from 2(*H*)-1,4-oxazine-2-ones both bridgehead positions are substituted the relative configurations could not be determined by this protocol. Hoornaert had devised another protocol-based on long-range coupling between protons and ^{13}C of the bridging carboxyl function. Although this is an established protocol, it lacks practicality as large sample quantities are required. Therefore, we required another general, reliable, and robust protocol for assignment of the configuration of our cycloadducts.

The protocol that we have developed uses a combination of NOESY (Nuclear Overhauser Enhancement SpectroscopY) and observation of the chemical shifts of the protons at the 7- and 8-positions of the cycloadducts. To start, the signal due to the methyne and methylene protons at either the 7- or 8-position are easily distinguishable by the pattern of their couplings. Methylene protons have a large (11–13 Hz) geminal coupling to each other as well as a small (2–6 Hz) coupling to the adjacent *syn* or a medium (7–11 Hz) coupling to the adjacent *gauche* methyne. Similarly, the methyne proton has a small (2–6 Hz) coupling to the *syn* hydrogen and a medium (7–11 Hz) coupling to the *gauche* hydrogen of the adjacent methylene group. Analysis of the degree of nuclear Overhauser enhancement is then used to determine the regiochemistry of the cycloadduct. For example, a methyne proton signal showing significant enhancement with irradiation of C-4 substituent suggest that the cycloadduct is an 8-substituted isomer, whereas signifi-

(21) (a) Gisby, G. P.; Royall, S. E.; Sammes P. G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 169. (b) Sammes P. G.; Weller D. J. *Synthesis* **1995**, 1205.

CHART 1



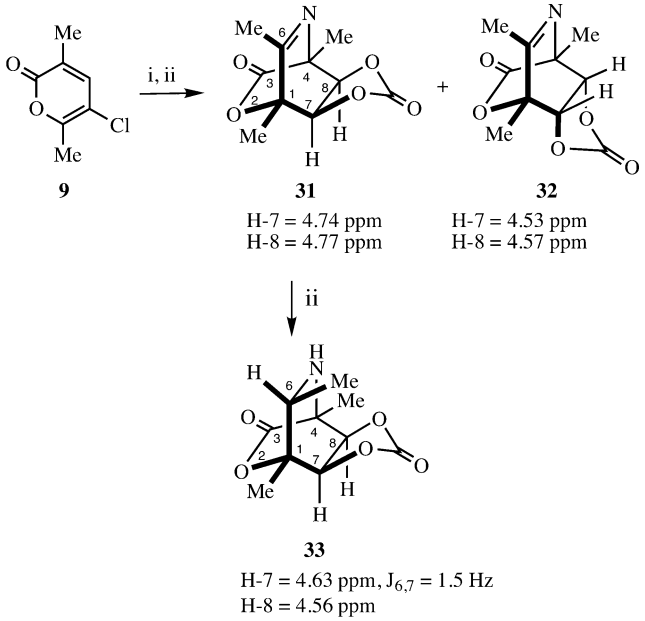
Cycloadduct configuration	Chemical shifts (coupling constants)			
	$H_{8\text{-endo}}$	$H_{8\text{-exo}}$	$H_{7\text{-endo}}$	$H_{7\text{-exo}}$
8-endo	-------	5.65 ppm (2.1 Hz, 8.1 Hz)	1.85 ppm (2.1 Hz, 15.1 Hz)	2.82 ppm (8.1 Hz, 15.1 Hz)
8-exo	4.87 ppm (3.7 Hz, 9.1 Hz)	--------	2.44 ppm (9.1 Hz, 14.6 Hz)	2.12 ppm (partly obscured, 14.6 Hz)
7-endo	1.80 ppm (obscured)	3.03 ppm (8.0 Hz, 14.5 Hz)	---------	5.22 ppm (3.7 Hz, 8.0 Hz)
7-exo	2.51 ppm (9.2 Hz, 14.8 Hz)	2.22 ppm (2.4 Hz, 14.8 Hz)	5.07 ppm (2.4 Hz, 9.2 Hz)	-------

cant enhancement of methylene proton signals with C-4 substituent suggest that the cycloadduct is a 7-substituted isomer. Although this rationale requires a proton containing substituent either at C-1 or C-4 bridgehead, in our experience this protocol was infallible in determination of regiochemistry of cycloadducts.

The key feature which allows us to assign the relative stereochemical configuration (*endo* versus *exo*) of a pair of regioisomeric cycloadducts is that due the magnetic anisotropy of the imine bond, protons at the *endo* position will always resonate at lower chemical shift than otherwise expected. This feature was first reported by Tomisawa and Hongo[22] in 2-aza[2.2.2]cyclooctenes (cycloadducts from 2(*H*)-pyridin-2-ones) and later by Hisano and Harano[23] and Posner[20d] in 2-oxa[2.2.2]cyclooctenes (cycloadducts from 2(*H*)-pyran-2-ones). For instance, as can be seen in the following example (Chart 1), the chemical shift of a proton at an *endo* position is always lower than that of the corresponding proton in an *exo* position.

We could further confirm the assignment of relative configuration of the cycloadducts by chemical manipulation. To demonstrate this, we carried out the cycloaddition of 5-chloro-3,6-dimethyl-2(*H*)-1,4-oxazine-2-one **9** with the symmetrically substituted dienophile, vinylene carbonate. The cycloaddiction afforded two cycloadducts in a ratio of 3:1 which could not be separated. However, after the chloro substituents in each of the cycloadduct had been replaced with a methyl group using palladium catalyzed Stille coupling, the two bridged bicyclic esterimines **31** and **32** were separable and were isolated in 65% and 27% yields respectively (Scheme 7). The major product was assigned an *endo* configuration based on the observation that the chemical shifts for H-7 and H-8 protons in this compound were 4.74 and 4.77 ppm, whereas the same protons resonate at 4.53 and 4.57 ppm in the minor product. Hydride reduction of the imine functionality of the *endo*-assigned bridged ester selectively gave a single product with the relative configuration given as amine **33**. The selectivity of the reduction step is precedented by earlier observations during hydrogenolysis of the structurally related bridged bicyclic lactones[14a] and is due to the steric encumbrance by the

SCHEME 7 [a]



[a] Key: (i) toluene, reflux, 24 h, vinylene carbonate, 74%; (ii) toluene, reflux, 48 h, Me_4Sn, $Pd(PPh_3)_4$, 92%; (iii) AcOH, $Na(AcO)_3BH$, rt, 24 h, 68%.

carbonate bridge. Close analysis of the NMR of compound **33** revealed a fine coupling (1.5 Hz) between H-6 and H-7. The presence of this W coupling strongly supports the proposed configuration of the reduction product and excludes other possible configurations.

To summarize, 6-alkyl-5-chloro-2(*H*)-1,4-oxazin-2-ones are ambident dienes reacting efficiently with examples of electron-rich, electron-deficient, and electron-neutral dienophiles. Introduction of electronically biased substituents at the 3-position of 2(*H*)-1,4-oxazin-2-ones does not significantly affect the ambident reactivity of azadiene. Matching the electronic demand of 2(*H*)-1,4-oxazin-2-ones with that of dienophiles can result in regiospecificity of the reaction; however, stereoselectivity of the cycloadditions remains modest except when the 2(*H*)-1,4-oxazin-2-one has bulky substituents at its 3- and 6-positions. Finally, the observed preference in the cycloadditions of 2(*H*)-1,4-oxazin-2-one is for the cycloadduct with an 8-*endo* configuration regardless of the electronic demand of the dienophile.

(22) Tomisawa, H.; Fujita, R.; Noguchi, K. J.; Hongo, H. *Chem. Pharm. Bull.* **1970**, *18*, 941. Also see: Tori, K.; Moneyuki, R.; Takano, Y.; Tanida, H.; Tsuji, T.; Hata, Y. *Can J. Chem.* **1964**, *42*, 926.

(23) Harano, K.; Aoki, T.; Eto, M.; Hisano, T. *Chem. Pharm. Bull.* **1990**, *38*, 1182.

A Comparison between the Cycloadditions of 2(*H*)-1,4-Oxazin-2-ones and 2(*H*)-Pyran-2-ones. It is clear from these observations that the reactivity, as well as regio and stereoselectivity of the cycloadditions of 2(*H*)-1,4-oxazin-2-ones does parallel closely those of 2(*H*)-pyran-2-ones. In particular, the favored cycloadduct in the cycloadditions of 2(*H*)-1,4-oxazin-2-ones has the corresponding configuration to those obtained in the cycloadditions of 2(*H*)-pyran-2-ones. Therefore, in a broad sense, 2(*H*)-1,4-oxazin-2-ones can be considered 2-azadiene analogues of 2(*H*)-pyran-2-one dienes. As such, highly advantageous synthetic methodologies based on cycloadditions of 2(*H*)-pyran-2-ones which afford highly substituted six-membered carbocycles can be translated to analogous methodologies based on cycloadditions of 2(*H*)-1,4-oxazin-2-ones to afford highly substituted piperidine rings. Indeed, both Hoornaert and we have shown the value of this methodolgy in target synthesis.[24]

However, the cycloaddition chemistry of 2(*H*)-1,4-oxazin-2-ones is clearly more subtle than that of 2(*H*)-pyran-2-ones both in the scope of dienophiles they react with, and in the role of ring substituents on the control of the electron demand of the cycloaddition. Since in cycloadditions of 2(*H*)-1,4-oxazin-2-ones a wider range of substituents are tolerated both on the diene and dienophile, this is a more versatile synthetic method and can afford a more diverse range of heavily substituted six-membered rings. 2(*H*)-1,4-Oxazin-2-ones are also more reactive than 2(*H*)-pyran-2-ones in the sense that they react with dienophiles regardless of their electronic demand, and sometimes even with their electronically mismatched dienophiles. This results in less stereoselectivity in cycloadditions, although it is possible to control the regiochemistry of cycloadditions by matching the electron demand between oxazinone diene and dienophiles.

Computational Results and Discussion

As discussed earlier, 2(*H*)-1,4-oxazin-2-ones undergo cycloaddition with dienophiles regardless of their electronic demand. In this sense, 2(*H*)-1,4-oxazin-2-ones appear to be 2-azadiene analogues of the well-established halo substituted 2(*H*)-pyran-2-ones. We had previously shown that the regio- and stereochemical outcome of the cycloadditions of 2(*H*)-pyran-2-one can be predicted computationally.[12] We decided to carry out a similar investigation of 2(*H*)-1,4-oxazin-2-ones in order to understand and predict the regio and stereoselectivity in their cycloadditions. Hence, we carried out a range of calculations on the four transition states (TS) leading to the four possible stereoisomers, namely the 8-*endo*, the 7-*endo*, the 8-*exo*, and the 7-*exo* cycloadducts, in the cycloadditions of 3,5-dichloro-6-methyl-1,4-oxazin-2-one, **1**, and 5-chloro-3-methoxy-6-methyl-1,4-oxazin-2-one, **15**, with methyl acrylate (MA) and methyl vinyl ether (MVE). Methyl vinyl ether was chosen as a typical electron-rich dienophile for computations. Although this was not one of the dienophiles used in the cycloaddition experiments, we are confident that the results obtained computationally for MVE can be used for comparison with results obtained experimentally for closely related butyl vinyl ether and 2-chloroethyl vinyl ether.[12] The partnering of electron-deficient 3,5-dichloro-6-methyl-1,4-oxazin-2-one, **1**, with methyl vinyl ether (MVE) represents a matching of electron demands between the diene and dienophile, whereas partnering of this 1,4-oxazin-2-one with methyl acrylate (MA) represents a "mismatch".

Calculations were performed using Gaussian 01.[25] All transition structures were initially optimized with AM1[26,27] and then reoptimized using B3LYP/6-31G*.[28] Frequency calculations were carried out at all computed B3LYP/6-31G* transition structures. Each was shown to have only one vibrational mode with an imaginary frequency. These were animated to confirm that they were transition structures for the reactions being investigated. This DFT method (model chemistry) has been previously shown by Houk to be a reliable method for predicting the regio- and stereoselectivity of the cycloaddition of Danishefsky's diene with acrylonitrile[29] and by us to be a reliable method for predicting the regio- and stereoselectivity of the cycloadditions of halogen-substituted 2(*H*)-pyran-2-ones.[12]

The calculated relative energies of transition states leading to the four possible cycloadducts from the reaction of each of the oxazin-2-ones with methyl acrylate (MA) and methyl vinyl ether (MVE), along with the yields of each cycloadduct obtained experimentally, are shown in Table 4 (yields of cycloaddition with butyl vinyl ether were used in place of that for methyl vinyl ether). Table 4 also contains information on the distance between the bond-forming atoms in diene and dienophile in each case. This information indicates the degree of asynchronicity in the bond formation during the Diels–Alder cycloaddition and is further evidence in support of the lack of significant change in electron demand of the cycloadditions.

The computational data can be used to proximately predict the ratio of the cycloadducts obtained in these reactions. We can expect that of the four transition states, the ones with the lower energy are likely to be favored and cycloadducts resulting from them will be observed in larger proportion in the final product mixture. Therefore, one expects a correlation between the calculated energy of the four transition states and the yield of the four cycloadducts.

As can be seen from the tables, the theory is partially successful in its predictions. For the cycloadditions of the

(24) Afarinkia, K.; Bahar A.; Neuss, J. *Synlett* **2003**, 2341.

(25) Gaussian 01, Development Version (Revision B.01): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Stratmann, R. E.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Iyengar, S.; Petersson, G. A.; Ehara, M.; Toyota, K.; Nakatsuji, H.; Adamo, C.; Jaramillo, J.; Cammi, R.; Pomelli, C.; Ochterski, J.; Ayala, P. Y.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 2001.

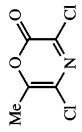
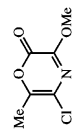
(26) Dewar, M. J. S., Zoebisch, E. G. *THEOCHEM* **1988**, *41*, 1.

(27) Dewar, M. J. S., Zoebisch, E. G.; Healy, E. F.; Stewart J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(28) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(29) Ujaque, G.; Norton, J. E.; Houk, K. N. *J. Org. Chem.* **2002**, *67*, 7179.

TABLE 4. Comparison between the Calculated Energy of Transition States Leading to the Four Possible Cycloadducts and the Experimentally Derived Ratios from the Reactions of 5-Chloro-6-methyl-1,4-oxazin-2-ones 1 and 5-Chloro-6-methoxy-1,4-oxazin-2-ones 15 with Methyl Acrylate (MA) and Methyl Vinyl Ether (MVE)

1,4-oxazin-2-one diene	Config.	Cycloaddition with MVE				Cycloaddition with MA			
		ΔE (Kcal/mol)[a]	Relative ratio[b]	C1-C7 (Å)	C4-C8 (Å)	ΔE (Kcal/mol)[a]	Relative ratio[b]	C1-C7 (Å)	C4-C8 (Å)
	8-endo	0.684	73	2.01	2.69	0.509	35	2.06	2.49
	8-exo	0.000	27	2.03	2.69	1.347	33	2.08	2.44
	7-endo	3.404	0	2.34	2.08	0.000	32	2.32	2.14
	7-exo	2.485	0	2.38	2.03	1.498	0	2.37	2.12
	8-endo	0.000	67	2.02	2.62	0.000	50	2.01	2.56
	8-exo	0.760	33	2.06	2.58	2.634	25	2.01	2.59
	7-endo	1.310	0	2.23	2.09	1.851	25	2.23	2.13
	7-exo	1.463	0	2.27	2.03	3.601	0	2.28	2.11

[a] Difference in the calculated barrier heights, with the lowest energy transition state taken as the energy zero. [b] Experimentally obtained (see Tables 1−3).

two 2(*H*)-oxazin-2-ones with electron rich dienophile methyl vinyl ether (MVE), the two observed products are those which theory predicted to have lower activation energies. Although the computations fail to correctly predict the major isomer in the cycloaddition of the matched diene/dienophile pair **1** and MVE, this can be put down to the relatively small energy gaps involved. For the cycloadditions of the two 2(*H*)-oxazin-2-ones with electron-deficient dienophile methyl acrylate (MA), again the two observed products are those which theory predicted to have lower activation energies. However, theory is less successful in predicting the ratio of the cycloadducts and significantly underestimates the likelihood of the formation of the 8-*exo* cycloadduct.

In other words, the model chemistry used in these computations, although not sophisticated enough to predict the exact ratios of cycloadducts of 2(*H*)-oxazin-2-ones, is able to predict which cycloadducts are *likely* to be formed. This is in contrast to the excellent agreement between computational and experimental results in the cycloadditions of halo substituted 2(*H*)-pyran-2-ones. Nevertheless, DFT (B3LYP/6-31G*) provides a useful tool for predicting the regio- and stereochemical preferences in the cycloadditions of 2(H)-oxazin-2-ones to first approximation.

Experimental Section

3,5-Dichloro-6-methyl-2(*H*)-1,4-oxazin-2-one **1**,[16b] 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **6**,[16b] 3,5-dichloro-2*(H)*-1,4-oxazin-2-one **7**,[16b] 3-bromo-5-chloro-6-methyl-2(*H*)-1,4-oxazin-2-one **8**,[10d] 5-chloro-3,6-dimethyl-2(*H*)-1,4-oxazin-2-one **9**,[10h] 5-chloro-6-methyl-3-phenyl-2(*H*)-1,4-oxazin-2-one **10**,[10d] and 5-chloro-6-methyl-3-phenylsulfenyl-2(*H*)-1,4-oxazin-2-one **17**[10d] were prepared according to literature procedures. An illustrative selection of experimental procedures for the preparation and cycloadditions of 2(*H*)-1,4-oxazin-2-ones is given below. For other experimental procedures, refer to the Supporting Information.

5-Chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one, 12. Trimethyl(phenyl)tin (0.19 mL, 1.10 mmol) and tetrakis(triphenylphosphine)palladium(0) (38 mg, 0.03 mmol) were added to a stirred solution of 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **6**[16b] (240 mg, 1.00 mmol) in dry toluene (20 mL) at room temperature under an inert atmosphere of argon. After 10 min, the mixture was brought to reflux. After approximately 48 h, the solvent was removed under reduced pressure and the yellow residue was purified by flash chromatography, eluting with 10% v/v ether in petrol ether (60−80 °C) to give 200 mg (71%) of a yellowish powder: mp 146−149 °C; ^{1}H NMR δ 7.42−7.61 (m, 6H, Ph), 7.99−8.01 (m, 2H, Ph), 8.40−8.42 (m, 2H, Ph); ^{13}C NMR δ 125.29 (C-5), 127.55 (2 × CH, Ph), 127.63 (2 × CH, Ph), 128.95 (2 × CH, Ph), 128.99 (C_{ipso}), 129.13 (2 × CH, Ph), 129.41 (C_{ipso}), 131.67 (CH, Ph), 132.31, CH, Ph), 133.16 (C-3), 146.87 (C-6), 152.88 (C-2); IR 1595, 1739 cm^{-1}; *m/z* 283 (M^+, 71), 255 (57), 220 (43); HRMS calcd for $C_{16}H_{10}NO_2{}^{35}ClNa$ (MNa^+) 306.0019, found 306.0035.

5-Chloro-3-methoxy-6-methyl-2(*H*)-1,4-oxazin-2-one, 15. 3,5-Dichloro-6-methyl-2(*H*)-1,4-oxazin-2-one **1**[16b] (1.00 g, 5.56 mmol) was dissolved in anhydrous methanol (30 mL) and cooled to 0 °C. To the ice-cold mixture was added acetic acid (30 mL) dropwise over 15 min. The mixture was warmed to room temperature and stirred for a further 2 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with 10% v/v ethyl acetate in petrol ether (60−80 °C) to give 760 mg (78%) of a white solid: mp 66−68 °C; ^{1}H NMR δ 2.27 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3); ^{13}C NMR δ 15.14 (CH_3), 54.69 (OCH_3), 120.62 (C-5), 141.10 (C-3), 148.79 (C-6), 149.28 (C-2); IR 1573, 1751 cm^{-1}; *m/z* 176 (MH^+, 29), 175 (M^+, 100), 132 (58); HRMS calcd for $C_6H_6NO_3{}^{35}ClNa$ (MNa^+) 197.9929, found 197.9936.

5-Chloro-6-phenyl-3-phenylsulfenyl-2(*H*)-1,4-oxazin-2-one 18. Aluminum chloride (0.61 g, 4.5 mmol) was added to a stirred solution of 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **6**[16b] (1.0 g, 4.1 mmol) in dichloromethane (50 mL) at room temperature over 15 min. Thiophenol (0.46 mL, 4.5 mmol) was added dropwise, and the reaction was allowed to stir overnight. The reaction mixture was quenched by pouring over ice and was extracted with chloroform (3 × 100 mL). The combined chloroform extracts were dried with $MgSO_4$, and solvent was removed under reduced pressure to afford a brown/orange solid. Recrystallization from hexane/chloroform mixture afforded 628 mg (48%) of the title compound as long yellow needles: mp 110−112 °C; R_f = 0.44 (10% ethyl acetate in petroleum); ^{1}H NMR δ 7.49−7.55 (6H, m, H_{Ph}), 7.60 (2H, t, H_{Ph}), 7.90 (2H, d, J = 1.43 Hz, H_{Ph}); ^{13}C NMR δ 126.51 (C-5), 128.86 and 129.89 (4 × $C_{Ph}H$), 128.90 and 130.55 (4 × $C_{Ph}H$), 129.41 ($C_{Ph-ipso}$), 130.24 ($C_{Ph-ipso}$), 131.11 ($C_{Ph}H$), 135.40 ($C_{Ph}H$), 144.35 (C-3), 152.22 (C-6), 154.73 (C-2); IR 1566, 1764 cm^{-1}; *m/z* 343 (4, M^+), 315 (9), 287 (4); HRMS calcd for $C_{16}H_{10}O_2N^{35}ClSNa$ (M^+Na) 338.0016, found 337.2340. Anal. Calcd for $C_{16}H_{10}O_2NClS$: C, 60.86; H, 3.19; N, 4.44. Found: C, 60.80; H, 3.11; N, 4.37.

Typical Cycloaddition: Reaction of 5-Chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one and Methyl Acrylate. A sealed pressure tube was charged with 5-chloro-3,6-phenyl-2(*H*)-1,4-oxazin-2-one **12** (176 mg, 0.62 mmol), methyl acrylate

(2.0 mL, 22 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (acting as anti-polymerization agent) and a small magnetic stirrer bar. The pressure tube was sealed and immersed in an oil bath maintained at 70 °C. After 2 days, the tube was cooled to room temperature and the contents were stripped of volatile materials. Chromatography using 10−15% v/v diethyl ether in petrol ether afforded methyl 6-chloro-1,4-diphenyl-3-oxo-2-oxa-5-azabicyclo[2.2.2]oct-5-ene-8_{endo}-carboxylate as a beige solid (229 mg, 100%): ^{1}H NMR δ 2.77 (1H, dd, J = 9.4, 13.8 Hz, H_{7-exo}), 3.00 (1H, dd, J = 3.6, 13.8 Hz, H_{7-endo}), 3.32 (3H, s, Me), 3.63 (1H, dd, J = 3.6, 9.4 Hz, H_{8-exo}), 7.40 (3H, m, H_{Ph}), 7.49 (2H, m, H_{Ph}), 7.59 (3H, m, H_{Ph}), 7.82 (2H, m, H_{Ph}); ^{13}C NMR δ 34.58 (C-7), 44.83 (C-8), 51.50 (C-12), 70.63 (C-4), 84.62 (C-1), 126.65−127.84 (9 × CH_{Ph}), 132.60 (C_{Ph}), 133.04 ($C_{Ph-ipso}$), 164.56 (C-6), 166.65 (C-3), 168.94 (C-9); IR 1610, 1736, 1767 cm^{-1}; *m/z* 369 (13, M^+), 325 (89), 290 (10); HRMS calcd for $C_{20}H_{16}ClNO_4Na$ (MNa^+) 392.0663, found 392.0643. Anal. Calcd for $C_{20}H_{16}ClNO_4$: C, 64.96; H, 4.36; N, 3.79. Found: C, 64.85; H, 4.16; N, 3.63.

Typical Cycloaddition: Reaction of 5-Chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one and 4-Bromostyrene. A sealed pressure tube was charged with 5-chloro-3,6-phenyl-2(*H*)-1,4-oxazin-2-one **12** (178 mg, 0.63 mmol), 4-bromostyrene (2.0 mL, 15.3 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (acting as anti-polymerization agent) and a small magnetic stirrer bar. The pressure tube was sealed and immersed in an oil bath maintained at 70 °C. After 2 days, the tube was cooled to room temperature, and the contents were stripped of volatile materials. Chromatography using 15% v/v diethyl ether in petrol ether afforded 8_{endo}-(4-bromophenyl)-6-chloro-1-methyl-4-phenyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one as a white solid (290 mg, 99%): mp 201 °C; ^{1}H NMR δ 2.71 (1H, dd, J = 4.4, 14.4, Hz H_{7-endo}), 3.17 (1H, dd, J = 9.8, 14.4 Hz, H_{7-exo}), 3.89 (1H, dd, J = 4.4, 9.8 Hz, H_{8-exo}), 6.75 (3H, m, H_{Ph}), 7.08 (2H, m, H_{Ph}), 7.29 (3H, m, H_{Ph}), 7.45 (2H, m, H_{Ph}), 7.76 (2H, m, H_{Ph}), 7.95 (2H, m, H_{Ph}); ^{13}C NMR δ 41.00 (C-7), 47.07 (C-8), 74.21 (C-4), 86.34 (C-1), 121.89 ($C_{Ph-ipso}$), 127.03−132.15 (14 × C_{Ph}H and C_{Ph}Br), 134.51, 135.01 and 137.48 ($C_{Ph-ipso}$), 165.54 (C-6), 169.03 (C-3); IR 1618, 1770 cm^{-1}; *m/z* 466 (39, MH^+), 422 (47), 387 (52), 105 (79); HRMS calcd for $C_{24}H_{17}{}^{81}Br^{35}ClNO_2Na$ (MNa^+) 488.0029, found 488.0013. Anal. Calcd for $C_{24}H_{17}BrClNO_2$: C, 61.50; H, 3.60; N, 3.00. Found: C, 61.78; H, 3.29; N, 2.97.

Typical Cycloaddition: Reaction of 5-Chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one and Butyl Vinyl Ether. A sealed pressure tube was charged with 5-chloro-3,6-phenyl-2(*H*)-1,4-oxazin-2-one **12** (175 mg, 0.62 mmol), butyl vinyl ether (2.0 mL, 15.5 mmol), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (acting as anti-polymerization agent) and a small magnetic stirrer bar. The pressure tube was sealed and immersed in an oil bath maintained at 70 °C. After 2 days, the tube was cooled to room temperature and the contents were stripped of volatile materials. Chromatography using 10−15% v/v diethyl ether in petroleum ether afforded 8_{endo}-butoxy-4,6-dichloro-2-oxa-1-phenyl-5-azabicyclo[2.2.2]oct-5-en-3-one as a beige solid (233 mg, 98%): mp 137−138 °C; ^{1}H NMR δ 0.71 (3H, t, CH_3, J = 7.3 Hz), 0.83 (2H, m, $MeCH_2$), 1.10 (2H, m, $EtCH_2$), 2.57 (1H, dd, J = 2.0, 14.3 Hz, H_{7-endo}), 2.90 (2H, m, CH_2O), 2.93 (1H, dd, J = 7.7, 14.3 Hz, H_{7-exo}), 4.38 (1H, dd, J = 2.0, 7.7 Hz, H_{8-exo}), 7.26 (3H, m, H_{Ph}), 7.47 (2H, m, H_{Ph}), 7.68 (3H, m, H_{Ph}), 7.87 (3H, m, H_{Ph}); ^{13}C NMR δ 14.25 (CH_3), 19.44 ($MeCH_2$), 32.27 ($EtCH_2$), 40.99 (C-7), 72.00 (CH_2O), 76.01 (C-4), 78.28 (C-8), 85.11 (C-1), 126.66−129.57 (10 × C_{Ph}H), 134.49 and 136.45 ($C_{Ph-ipso}$), 164.52 (C-6), 168.48 (C-3); IR 1678, 1770 cm^{-1}; *m/z* 383 (53, M^+), 355 (47), 320 (73), 105 (97); IR 1678, 1770 cm^{-1}; *m/z* 383 (53), 355 (47), 320 (73), 105 (97); HRMS calcd for $C_{22}H_{22}ClNO_3Na$ (MNa^+) 406.1183, found 406.1144. Anal. Calcd for $C_{22}H_{22}ClNO_3$: C, 68.84; H, 5.78; N, 3.65. Found: C, 69.00; H, 5.70; N, 3.67.

Acknowledgment. We thank Oxford GlycoSciences (UK) Ltd. (now part of UCB) for financial support (A.B.).

Supporting Information Available: Experimental procedures and characterization of all previously unreported compounds. Drawings, crystal data, and coordinates of all crystal structures. Coordinates of all transition states and absolute energies of all transition states. Figures showing the computed transition structures leading to the cycloadducts of 3,5-dichloro-6-methyl-1,4-oxazin-2-one, **1**, with MVE and MA and the cycloadducts of 5-chloro-3-methoxy-6-methyl-1,4-oxazin-2-one, **15**, with MVE and MA. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051646I