Face Selectivity of the Nitrile Oxide Cycloaddition to Unsaturated Sugars

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Nitrile oxides cycloadd to unsaturated sugars **1a–h**, to give the anti adduct with 73.5–96.8% π-facial stereoselectivity. The highest values of face selectivity were observed with dipolarophiles bearing an ether group in the homoallylic position. This finding was rationalized by considering the influence of the substituent lone pairs on the relative energies of the possible transition states. The minimum-energy conformations of the dipolarophiles and the relative energies of model transition states were evaluated by MM2 calculations. The structure of the major products, assigned by X-ray analysis, features a transition state that confirms the model proposed by Houk.

Introduction

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes provides a valuable tool for the synthesis of 2-isoxazolines as natural products and as unnatural compounds possessing a biological activity.[2] In addition, this heterocycle has been employed in numerous multistep syntheses since it represents the masked form of an array of different functionalities related by a well-defined stereochemistry.[2,3]

Among the different forms of isomerism associated with the 1,3-dipolar strategy, i.e., regiochemistry, periselectivity, etc.,[4] a great deal of attention has been devoted to the study of the stereoselectivity of nitrile oxide cycloadditions to alkenes bearing a stereocenter in the allylic position.[5] Since knowledge of the factors involved in these additions is of utmost importance in achieving control of the adducts' stereochemistry, different model transition states have been proposed to rationalize the experimental results.[5a–c] The most recent and general, proposed by Houk and workers,[5c] features a transition-state geometry with the "large" group anti to the incoming nitrile oxide and the "medium" group in the inside position (Figure 1). Recently this model was extended to the intramolecular 1,3-dipolar cycloaddition of 1,2-disubstituted alkenes, and the influence of the double-bond configuration on the stereochemical outcome of the reaction has been discussed.[6]

Table I. Diastereomeric Ratios of the Cycloaddition between Nitrile Oxides 2–4 and Unsaturated Sugars 1a–h

dipolarophile	nitrile oxide	product	diastereomeric ratio
1a	**2**	**5a:6a**	73.5:26.5
1b	**2**	**5b:6b**	78.2:21.8
1c	**2**	**5c:6c**	96.5:3.5
1d	**2**	**5d:6d**	96.8:3.2
1e	**2**	**5e:6e**	96.5:3.5
1f	**2**	**5f:6f**	91.4:8.6
1g	**2**	**5g:6g**	96.6:3.4
1h	**2**	**5h:6h**	87.1:12.9
1b	**3**	**7b:8b**	86.6:13.4
1d	**3**	**7d:8d**	94.2:5.8
1b	**4**	**9b:10b**	82.6:17.4
1d	**4**	**9d:10d**	85.5:14.5

In our efforts devoted to the application of the 1,3-dipolar cycloaddition of nitrile oxides to the synthesis of biologically active compounds,[2d,7] we needed the diastereoselective production of chiral heterocyclic derivatives. Consequently, we undertook a systematic investigation of the cycloaddition of three nitrile oxides to a series of unsaturated sugars.

Scattered results in this field have been reported in the past, but the stereoselectivity of the cycloaddition has never been discussed in detail.[8] The results of our cycloadditions are analyzed on the basis of the conformational minima of the dipolarophiles as well as of model transition-state structures, all calculated by molecular mechanics (MM2).

Results and Discussion

Nitrile oxides **3** and **4** were prepared by the in situ technique from the corresponding hydroximic acid chlorides, while the stable mesitonitrile oxide (**2**), was used as such. Dipolarophiles **1a–h** were prepared by known procedures[9–12] or from **1b** by simple functionalizations of its hydroxyl group. All the cycloaddition reactions, reported in Scheme I, were run under comparable conditions with a slight excess of the 1,3-dipole. The reactions were continued until disappearance of the dipolarophile; in the case of **3** and **4**, the mixture contained, besides the two isoxazoline diastereomers, variable amounts of 3,4-disubstituted

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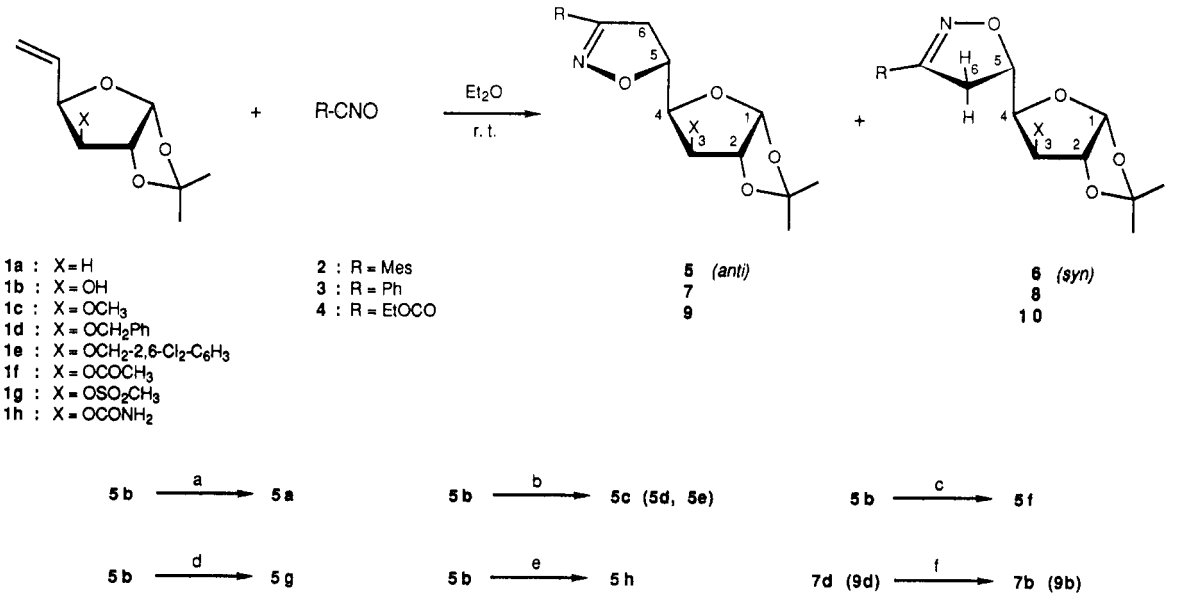
Scheme I[a]



[a] Reagents: (a) (1) NaH, CS_2, MeI, (2) n-Bu_3SnH, toluene reflux; (b) NaH, RX, THF; (c) Ac_2O, NEt_3; (d) $MeSO_2Cl$, NEt_3; (e) (1) $ClSO_2NCO$, THF, (2) H_2O; (f) H_2, Pd/C 5%.

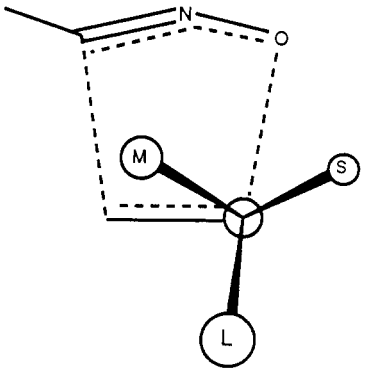


Figure 1.

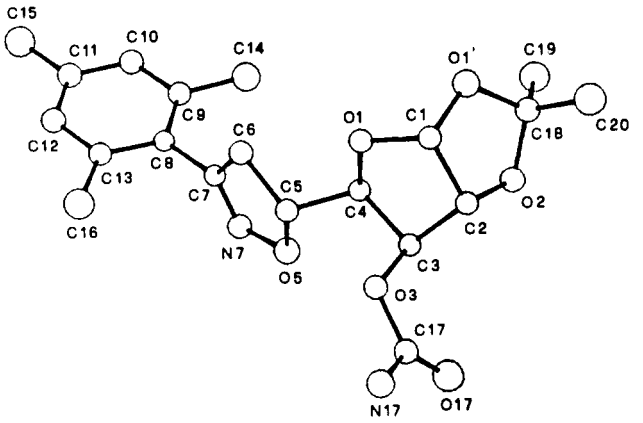


Figure 2. ORTEP[13] plot of **5h** derived from the X-ray coordinates with hydrogens omitted for clarity. The spheres are contoured to enclose 20% of the electron density.

furazan N-oxide. The separation was achieved through column chromatography, and the isomeric ratios, reported in Table I, were deduced from GLC or HPLC analysis of the crude reaction mixtures. The major isomers **5a,c–h** were correlated to each other through standard transformations of **5b** (Scheme I), whereas **7d** and **9d** were transformed into **7b** and **9b**, respectively, by catalytic hydrogenation. The assignment of stereochemistry at C(5) is based on single-crystal X-ray data for **5h**. Figure 2 is a computer-generated perspective drawing of **5h** from the final X-ray coordinates showing the absolute stereochemistry of the stereocenter C(5). ^1H NMR data such as chemical shifts, coupling constants, and NOE difference signals failed to provide clear evidence on the structure of the adducts.

The theoretical approach used in these studies to account for the experimental results was first to derive minimum-energy conformations in the ground state of the dipolarophiles and then to evaluate the relative energies of model transition-state structures as proposed by Houk and co-workers.[5b,c]

Minimum-energy conformations (Figure 3) were calculated by using Allinger's MM2 program.[14,15] As expected,[16]

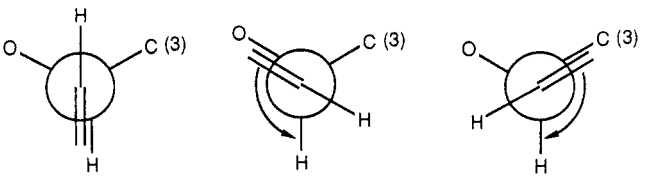


Figure 3.

Table II. Conformational Energies, Relative Abundances, and C=C—CH Dihedral Angle

compd	rel energy, kcal mol^{-1}	rel abundance, %	conformatn	dihedral angle ϕ, deg
1a	0.00	37	I	+5
1a	0.06	34	II	−111
1a	0.16	29	III	+103
1c	0.12	31	I	+23
1c	0.00	38	II	−113
1c	0.11	31	III	+87

1a and **1c** exhibited three minima, whose relative energies and dihedral angles ϕ are gathered in Table II. It is worth

(13) Johnson, C. K. "ORTEP"; Report ORNL-3794; Oak Ridge National Laboratory, Oak Ridge, TN, 1965.
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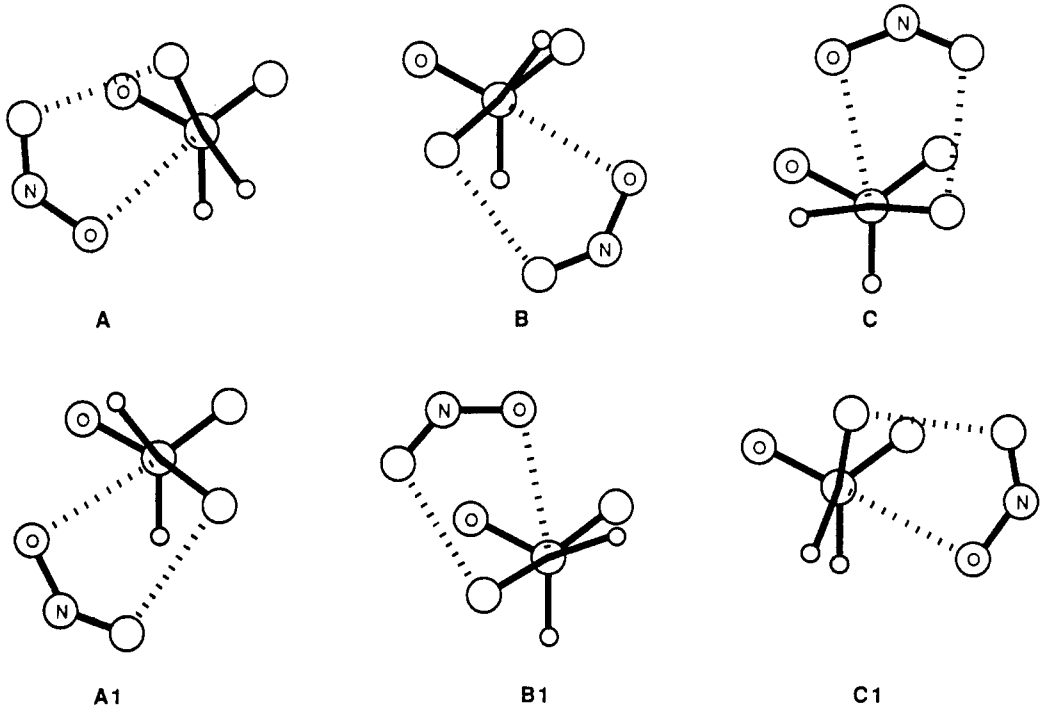

Figure 4. The Newman projections along the C(4)–C(5) bond of the six staggered transition-state structures for the cycloaddition of HCNO to **1a** (**1c**).

Table III. Relative Energies (E_{rel}, kcal/mol) and Torsional Angles [H(4)–C(4)–C(5)–C(6), deg] of the Transition-State Models of Nitrile Oxide Cycloadditions Calculated by MM2

			transition state						5:6	
entry	reactn		A	B	C	A_1	B_1	C_1	calcd	exptl
1[a]	**1a** + HCNO	E_{rel}	0.0	0.1	1.5	0.2	1.2	0.9	65:35	73.5:26.5
		ϕ	−157	−49	+81	+50	−67	+162		
2[b]	**1a** + HCNO	E_{rel}	0.0	0.3	1.6	0.2	1.1	1.0	60:40	73.5:26.5
		ϕ	−149	−45	+89	+47	−75	+151		
3[a]	**1c** + HCNO	E_{rel}	0.0	0.4	2.9	0.2	3.3	1.5	67:33	96.5:3.5
		ϕ	−155	−48	+87	+50	−60	+175		
4[b]	**1c** + HCNO	E_{rel}	0.0	0.5	3.1	0.2	3.1	1.9	65:35	96.5:3.5
		ϕ	−148	−45	+95	+47	−68	+165		

[a] Model transition state from 3-21G basis set.[17] [b] Model transition state from 4-31G basis set.[18]

pointing out that the calculated geometries of the three conformational minima for both **1a** and **1c** deviate from eclipsed arrangements; this deflection increases on passing from **1a** to **1c**. The presence of a methoxy group at C(3) particularly affects the geometry of those conformations where this group contracts a steric interaction with the vinylic C–H bond (conformation I) or with the CC double bond (conformation III). The energy minima for both **1a** and **1c** possess very close values, and consequently, stereoselectivity of the related 1,3-dipolar cycloadditions cannot be foreseen from the conformational profile of the alkenes in the ground state. These results confirm similar observations on related systems reported by Houk and co-workers[5c] where the structure of the major adduct features an attack of the nitrile oxide on the more hindered face of the preferred conformation of the isolated dipolarophile. In the alternative approach, we performed MM2 calculations on model transition states. The coordinates of the atoms involved in the formation of the isoxazoline moiety were taken from the fulminic acid–ethylene transition-state structure, calculated with either the RHF/3-21G[17] or MCSCF/4-31G[18] methods, and the position of the substituents was optimized with the MM2 program. The six staggered transition-state conformational minima for the cycloaddition of fulminic acid to **1a** and **1c** are depicted in Figure 4 and defined in Table III. The percentage of each diastereoisomer was calculated by taking into account the Boltzmann distribution of all six conformations. Inspection of the data reported in Table III shows that either for **1a**, which carries a hydrogen at C(3), or for **1c**, which bears a methoxy group and represents a model for all the substrates containing an oxygen in the homoallylic position, three conformations play the major role: conformations A and B possessing the allylic oxygen "inside" and anti, respectively, and conformation A_1 presenting the same group "outside" with the "large" substituent (C(3)) in the anti position. Conformations A and B yield the major isomer **5** (or **7**, **9**) while A_1 produces the minor isomer **6** (or **8**, **10**). A comparison of the experimental and calculated diastereomeric ratios (Table III) shows that, whereas the preference for stereoisomer **5** is well-predicted for the nitrile oxide cycloaddition to both **1a** and **1c**, the extent of the stereoselectivity, which is sufficiently accurate

(15) The conformation of the bicyclic portion of dipolarophiles **1a** and **1c**, calculated with the MM2 program, fits perfectly that deduced from the X-ray analysis of adduct **5h**.
(16) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.
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for the cycloaddition to **1a** (73.5:26.5 vs 65:35 or 60:40), presents a substantial difference for **1c** (96.5:3.5 vs 67:33 or 65:35). It is worth pointing out that a slight change in the geometry of the transition state[19] (entry 1 vs 2 or 3 vs 4) does not significantly affect the predicted ratios.

Since molecular mechanics calculations take into account the sole steric effects, we should admit, in the case of **1c**, the intervention of an additional stereoelectronic factor, the lone pairs of the homoallylic heteroatom. A through-space interaction, lone-pair/π-bond, was proposed by Paddon-Row and co-workers[20] to explain the accelerating effect of a methoxy group on the reactivity of a double bond toward Diels–Alder cycloadditions and epoxidation reactions. By analogy, the higher selectivity of some intramolecular nitrile oxide cycloadditions was interpreted as due to a through-space interaction of the homoallylic oxygen lone pair with the CC double bond.[6a] A close inspection of the geometry of the main conformations A, B, and A_1 shows that whereas A and A_1 present the homoallylic oxygen near the reacting double bond (O(3)–C(5) distance: 2.8 Å), anti to the incoming nitrile oxide, B possesses the same group far away from the π-bond. A through-space interaction between the above-mentioned groups might cause destabilization of transition states A and A_1. The increased weight of B gives a reason for the observed higher stereoselectivity of the nitrile oxide cycloaddition to all the dipolarophiles carrying an oxygen in the homoallylic position, with the sole exception of **1b**.

We remark the close similarity of transition-state B with the solid-state conformation of adduct **5h** (Figure 2). This observation supports the idea[5c] of a transition state for the 1,3-dipolar cycloaddition that is reactant-like in terms of bond making and product-like in terms of conformational preferences. The increased stereoselectivity of both intra-[6a] and intermolecular cycloadditions brought about by the homoallylic oxygen will be studied in the near future on dipolarophiles containing, in the same position, a rigidly oriented heteroatom and will be reported in due course.

A final consideration applies to dipolarophile **1b**, which, through its hydroxyl group, might form a hydrogen bonding with the incoming nitrile oxide oxygen. The presence of hydrogen bonding has been proposed to explain the variation in face selectivity observed in cyclic[21] and acyclic[5b] allylic alcohols as well as in cyclic homoallylic alcohols.[22] Figure 4 shows that, among the most populated transition-state structures (A, A_1, and B), the sole B, which yields the main isomer **5**, could be stabilized by the above-mentioned interaction. Nevertheless, the distance between the oxygen in the 3-position and the nitrile oxide oxygen (3.6–3.7 Å) is too large for the existence of an effective hydrogen bonding. A reasonable explanation of the results obtained with **1b** takes into account either the presence of a weak intramolecular hydrogen bond between the OH group and the CC double bond or the repulsion between the hydroxy lone pair and the π-bond (conformations A and A_1). Both these effects favor the conformation with the hydroxylic hydrogen pointing inward (Figure 5). The result is a decrease of the interaction between the hydroxy lone pair and the CC double bond, bringing the system to a situation that resembles that of the C(3)-unsubstituted derivative **1a**. The existence of a conformational equilibrium such as that depicted in Figure 5 was previously reported to explain the influence of a hydroxy vs a methoxy group on the reactivity of a double bond toward a Diels–Alder reaction.[20] Furthermore, the conformational profile of 3-buten-2-ol, calculated at the 6-31G//3-21G level,[23] clearly evidences that the most stable conformers possess the hydroxylic hydrogen positioned above the double bond.

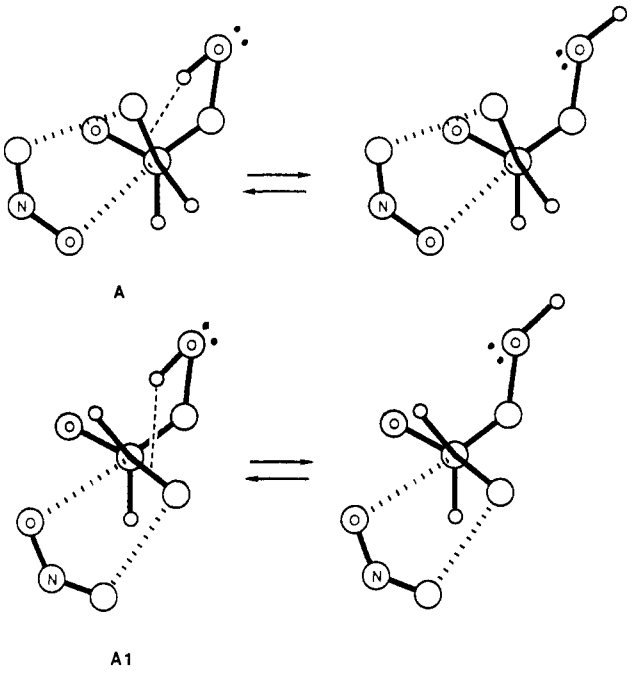
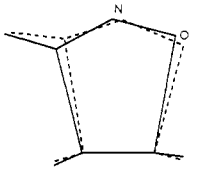


Figure 5. The Newman projections along the C(4)–C(5) bond of transition states A and A_1 for the HCNO–**1b** cycloaddition showing the feasible hydrogen bonding between the 3-OH group and the C=C bond.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker WP 80 or a Varian XL-200 spectrometer with $CDCl_3$ as solvent: chemical shifts in parts per million; coupling constants J in hertz. Optical rotations were measured on a Perkin-Elmer 241 polarimeter coupled with a Haake N3-B thermostat. High-performance liquid chromatography was carried out on a Perkin-Elmer Series 3 instrument fitted with a Waters μ-Porasil column, using an 85:15 mixture of *n*-heptane-2-propanol as the mobile phase. Capillary GLC analyses were performed on a Carlo Erba HRGC 5160 Mega Series gas chromatograph equipped with on-column injector, flame-ionization detector, and a Shimadzu integrator. A fused silica gel column with (a) SP2330 (15 m, 0.20 μm) or (b) SPB-1 (15 m, 0.25 μm) liquid phase was employed. Elemental analyses were carried out on a Carlo Erba elemental analyzer Model 1106. All new compounds gave satisfactory elemental analyses (C, H, N,

(19) The concerted transition state of the cycloaddition HCNO–ethylene is asynchronous with both the methods. However, a direct comparison of the calculated geometries, as depicted below, shows that they predict a different timing of bond formation: the forming C---C bond is longer than the C---O bond in RHF/3-21G calculations[17] (---) and shorter in MCSCF/4-31G calculations[18] (—).



(20) Paddon-Row, M. N.; Patney, H. K.; Warrener, R. N. *J. Org. Chem.* **1979**, *44*, 3908.

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(22) Substantial amounts of the syn adducts were obtained in the cycloaddition of nitrile oxides to *endo-cis*-5,6-dihydroxy- and *endo*-5-hydroxybicyclo[2.2.2]oct-2-ene: Gandolfi, R., unpublished results.

(23) Kahn, S. D.; Pau, C. F.; Chamberlain, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.

Table IV. Analytical Data for Compounds 5–10

compd	mp, °C	$[\alpha]^{20}_D$ in $CHCl_3$	R_f[a]
5a	oil	−87.79 (*c* 1.0)	0.47
6a	oil	+6.4 (*c* 0.5)	0.38
5b	120–1	−161.78 (*c* 1.0)	0.22
6b	140–1	+130.00 (*c* 1.0)	0.14
5c	111–3	−167.46 (*c* 1.1)	0.52
6c	oil	+60.38 (*c* 1.1)	0.37
5d	114–8	−103.87 (*c* 1.2)	0.72
6d	127–9	+34.10 (*c* 1.2)	0.55
5e	152 dec	−95.50 (*c* 1.0)	0.58
6e	220–2	+7.50 (*c* 0.9)	0.44
5f	118–9	−139.80 (*c* 1.0)	0.40
6f	118–20	+97.30 (*c* 0.7)	0.33
5g	181–2	−151.10 (*c* 1.0)	0.38
6g	188–9	+38.30 (*c* 0.5)	0.23
5h	202–4 dec	−128.46 (*c* 1.0)	0.17[b]
6h	218–20	+63.30 (*c* 1.0)	0.10[b]
7b	195–6	−157.44 (*c* 1.0)	0.23
8b	211–4 dec	+127.27 (*c* 1.1)	0.11
7d	125–7	−122.42 (*c* 1.1)	0.67
8d	134–5	+38.64 (*c* 1.1)	0.49
9b	136–8	−142.40 (*c* 1.0)	0.14
10b	141–3	+113.12 (*c* 1.9)	0.07
9d	oil	−102.92 (*c* 1.9)	0.54
10d	oil	+32.93 (*c* 1.1)	0.35

[a] Eluent: cyclohexane/ethyl acetate, 7:3. [b] Eluent: cyclohexane/ethyl acetate, 3:2.

≤0.3). Melting points were determined in open capillaries on a Büchi apparatus and are uncorrected. TLC were carried out on commercial silica gel GF_{254} plates. Molecular mechanics calculations were performed with a BASIC version of MM2 translated from the FORTRAN version of QCPE program No. 395. The program was run on an IBM AT personal computer.

Materials. Unsaturated sugar **1b** was prepared according to the previously reported procedure.[9] The known dipolarophiles **1a**,[10] **1c**,**d**,[11] and **1g**[12] were prepared from **1b** as reported in the references cited thereafter. In analogy, the new derivatives **1e** (oil), **1f**, and **1h** (mp 114–5 °C) were prepared by reacting **1b** with 2,6-dichlorobenzyl bromide, acetyl chloride, and chlorosulfonyl isocyanate,[24] respectively. Mesitonitrile oxide (**2**) and the hydroximic acid chloride precursors of nitrile oxides **3** and **4** were prepared according to the methods collected in a monograph.[25]

X-ray Analysis. A colorless crystal (0.55 × 0.45 × 0.38 mm) was mounted on a Philips PW1100 four-circle diffractometer with graphite-monochromated Mo Kα radiation (0.7107 Å); 2061 independent reflections were collected up to $2\theta = 50°$ using an ω-scan technique. The intensities were corrected for Lp effects and semiempirically for absorption;[26] there were 1607 observed reflections with $I \geq 3\sigma(I)$.

The space group is PZ_1 with two molecules ($C_{20}H_{26}O_6N_2$) in the unit cell, $D_{calcd} = 1.26$ g/cm^3. The lattice parameters were determined from a least-squares analysis on 24 reflections ($7.4 \leq 2 \leq 37.6$): $a = 13.401$ (3) Å, $b = 9.620$ (2) Å, $c = 8.016$ (2) Å, $\beta = 91.51$ (2)°. The structure was solved by direct methods (MULTAN 80).[27] The full-matrix least-squares refinement[28] with anisotropic non-hydrogen atoms and fixed isotropic hydrogens leads to a crystallographic $R = 0.0374$ and $wR = 0.0343$ for all observed reflections.

Standard Procedures for the Preparation of Isoxazolines 5–10. (a) Anhydrous ethereal solutions (1 mmol in 50 mL) of the unsaturated sugar and 1.5 equiv of mesitonitrile oxide were mixed and stirred at room temperature until disappearance of the dipolarophile. The reaction was monitored by TLC. After evaporation to dryness, the residue was column chromatographed and allowed the isolation of the pure diastereomers reported in Table IV.

(b) To a stirred ethereal solution of the hydroximic acid chloride (2 equiv) and the unsaturated sugar (1 equiv) was added a 3-fold excess of triethylamine in ether dropwise at room temperature. The mixture was left at room temperature with stirring for 4 h and then poured into cold water; the organic layer was separated, dried, and evaporated. The pure stereoisomers, reported in Table IV, were obtained by column chromatography of the residue.

Determination of Isomeric Proportions. The diastereomeric ratios reported in Table I were determined directly by capillary GLC analysis of the reaction mixtures in the cases of **1a**, **1c**, **1d**, **1e**, **1g** (column b), and **1f** (column a) with mesitonitrile oxide (**2**) in addition to the reactions of **1d** with nitrile oxides **3** and **4** (column a). The adducts derived from the cycloaddition of **1b** to **2–4** were transformed quantitatively into the corresponding acetyl derivatives and then analyzed by GLC (column a). Finally the isomeric ratio **5h**:**6h** was determined by HPLC.

Chemical Correlations. Synthesis **of 5a.** (a) To a stirred suspension of NaH (21 mg, 0.9 mmol) in 10 mL of dry THF (10 °C, N_2) were added carbon disulfide (83 μL, 1.5 mmol), methyl iodide (29 μL, 0.9 mmol), imidazole (4 mg), and adduct **5b** (160 mg, 0.46 mmol). The reaction mixture was stirred until disappearance of the starting material (TLC analysis), and then the excess NaH was destroyed with glacial acetic acid. The solvents were removed in vacuo, and the residue was extracted with ether (3 × 15 mL), washed with aqueous $NaHCO_3$, and dried over Na_2SO_4. Removal of the ether yielded the crude xanthate, which was not purified but directly used in the following step.

(b) To tributyltin hydride (0.27 mL) in dry refluxing toluene (10 mL), under a N_2 atmosphere, was added the crude xanthate in toluene (20 mL). The solution was refluxed for 16 h, and then the toluene was removed at reduced pressure. The residue, submitted to column chromatography, yielded 120 mg of **5a**, which was identical with the main isomer of the cycloaddition of **1a** with mesitonitrile oxide.

Synthesis of 5c. To a stirred suspension of 99% NaH (70 mg, 1.47 mmol) in dry THF (25 mL) was added **5b** (0.500 g, 1.44 mmol) in dry THF (25 mL) at room temperature. The mixture was stirred until evolution of gas ceased, and then 180 μL (2.88 mmol) of methyl iodide was injected through the rubber septum. The mixture was stirred until disappearance of the starting material (TLC analysis) and then submitted to the usual workup, yielding 436 mg (84%) of adduct **5c**.

Synthesis of 5d. To a stirred suspension of NaH (35 mg, 1.47 mmol) in 15 mL of dry THF was added adduct **5b** (0.326 g 0.94 mmol) in THF (15 mL) at room temperature. The mixture was stirred for 1 h at room temperature before the addition of benzyl bromide (174 μL, 1.47 mmol) and tetrabutylammonium iodide (10 mg). The reaction mixture was left aside, with stirring, for 3 h, and then, after the usual workup, the residue was submitted to column chromatography and yielded 361 mg (88%) of **5d**.

Synthesis of 5e. Following the procedure reported for **5d**, 0.245 g of **5b** was reacted with 2,6-dichlorobenzyl bromide and yielded 0.282 g (79% yield) of **5e**.

Synthesis of 5f. To an ice-cooled solution of **5b** (160 mg, 0.46 mmol) and acetic anhydride (90 μL, 0.92 mmol) in methylene chloride (20 mL) was added 260 μL of triethylamine with stirring. After the usual workup, **5f** was collected in quantitative yield.

Synthesis of 5g. Following the procedure reported for **5f**, 200 mg (0.58 mmol) of **5b** was reacted with 67.6 μL of methanesulfonyl chloride and 122 μL of triethylamine and yielded 194 mg (79% yield) of **5g**.

Synthesis of 5h. A solution of **5b** (100 mg, 0.288 mmol) in anhydrous THF (40 mL) was placed in a 100-mL Erlenmeyer flask fitted with a magnetic stirring bar and a rubber septum. Chlorosulfonyl isocyanate (75 μL) was injected with stirring and cooling in an ice–salt bath. Stirring was continued for 5 h at room temperature, and then water (20 mL) was added to the reaction mixture. The organic solvent was removed under vacuum and the residue extracted with CH_2Cl_2. After drying and removal of the solvent, 47 mg (42% yield) of **5h** was recovered.

Hydrogenation of 7d and 9d. A mixture of **7d** (or **9d**) and Pd/C 5% in EtOH was hydrogenated at room temperature until

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1 equiv of hydrogen was absorbed. After filtration and washing of the solid with EtOH, evaporation of the combined filtrates gave **7b** (or **9b**) in 80% yield.

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Registry No. **1a**, 96852-88-9; **1b**, 7284-07-3; **1c**, 19877-09-9; **1d**, 19877-13-5; **1e**, 89755-67-9; **1f**, 17225-57-9; **1g**, 74152-53-7; **1h**, 118226-52-1; **2**, 2904-57-6; **3**, 873-67-6; **4**, 51983-62-1; **5a**, 118226-53-2; **5b**, 118226-54-3; **5b** (xanthate), 118246-93-8; **5c**, 118226-55-4; **5d**, 118332-52-8; **5e**, 118226-56-5; **5f**, 118226-57-6; **5g**, 118226-58-7; **5h**, 118226-59-8; **6a**, 118332-53-9; **6b**, 118332-54-0; **6c**, 118332-55-1; **6d**, 118332-56-2; **6e**, 118332-57-3; **6f**, 118332-58-4; **6g**, 118332-59-5; **6h**, 118332-60-8; **7b**, 118226-60-1; **7d**, 118332-61-9; **8b**, 118332-62-0; **8d**, 118332-63-1; **9b**, 118226-61-2; **9d**, 118226-62-3; **10b**, 118332-64-2; **10d**, 118374-38-2; PhC(=NOH)Cl, 698-16-8; EtOCOC(=NOH)Cl, 14337-43-0.

Supplementary Material Available: Tables of positional parameters, anisotropic thermal parameters for non-hydrogen atoms, bond distances and angles for adduct **5b**, ^{1}H NMR chemical shifts and coupling constants for adducts **5–10**, Eu(fod)$_3$-induced shifts in ^{1}H NMR spectra of **5b** and **6b**, NOE difference data on adducts **5d** and **6d**, and elemental analyses of adducts **5–10** (10 pages). Ordering information is given on any current masthead page.

Solvatochromic Studies of Novel Azo Merocyanine Dyes. The π^*_{azo} Scale of Solvent Polarity†

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Six novel azo merocyanine dyes (**1–6**) have been synthesized and their UV–vis spectra recorded in 29 solvents. These dyes exhibit positive solvatochromism (bathochromic shift) with increasing solvent polarity, i.e., $\mu_g < \mu_e$. The spectral data obtained were used as *primary data* in a parameter optimization program (Teetor Totter method) to arrive at averaged results in 19 select solvents, which led to the formulation of a new solvent polarity scale, the π^*_{azo} scale. Subsequently, π^*_{azo} values of ten secondary solvents were determined. The π^*_{azo} values thus obtained were correlated with 20 solvent polarity scales and the spectral data of 59 indicator solutes. The correlation coefficients were found to be in the region 0.900 to 0.995, indicating the overall validity of the procedure adopted in the formulation of the π^*_{azo} scale. The correlations of the π^*_{azo} scale with solvent polarity scales such as Brooker's χ_R scale, based on compounds that are structurally similar to the azo dyes, were found to be better than the correlations of Kamlet and Taft's π^* scale with the above polarity scales. The spectral data of the azo merocyanines **1–6** were also used as *secondary data* with Kamlet's π^* and α parameters as well as with 20 other polarity scales. Of the various scales considered, the π^* scale and Brooker's χ_R scale were found to correlate best with the spectral data of **1–6**. The π^* value of a new solvent, *N,N'*-dimethyl-*N,N'*-trimethyleneurea (DMPU), has been determined as 1.08 (π^*_{azo} = 0.99). Various structure–spectral property relationships among the azo merocyanine dyes are considered. Based on the correlations observed in the present work, it is suggested that a "Universal primary set of solutes", comprising representative compounds from important classes of compounds, be chosen to formulate a π^*_U (Pi Star Universal) scale. Alternatively, though less desirably, a dozen diversified π^*_X scales (X representing various families of compounds) could be designed.

Introduction

Solvent as a medium for chemical and physical processes has always played a very important role in chemistry. Interest in describing solvent properties has focused mainly on the polarity aspect, a term that has not been defined precisely. In a broader sense, solvent polarity relates to the overall solvating capability of a solvent.[1,2] Numerous reports on solvent polarity scales have appeared in the literature in the past 30 years.[1-6] These scales have been designed on single and multiple parameter approaches.

The scales based on the single parameter approach include Dimroth and Reichardt's E_T,[4a] Brooker's χ_R,[4b] Drougard and Decroocq's log k_2,[4c] Walther's ϵ_K,[4d] Knauer and Napier's $\mathcal{A}_n$,[4e] Allerhand and Schleyer's G,[4f] Brownstein's S,[4g] Kosower's Z,[4h] Winstein and Grunwald's Y,[4i] Berson, Hamlet, and Mueller's Ω,[4j] Dong and Winnick's Py,[4k] and Dubois and Bienvenüe's ϕ scale.[4l] These scales, being based on spectral data of a single indicator dye, are

† Studies of Azo and Azoxy Dyestuffs. 19. For 18, see: Buncel, E.; Onyido, I. *Can. J. Chem.* **1986**, *64*, 2115.

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