able to obtain virtually complete backbone assignments for the 156-residue protein, which will be reported elsewhere.

Major practical problems with 3D spectroscopy are the long measuring time needed to get sufficient digitization in the F_1 and F_2 dimensions of the 3D spectrum and the large size of the 3D matrix. We have used folding of some of the resonances in both the F_1 and F_2 dimensions and employed an unfolding procedure[12] in the F_1 dimension (based on shifting the F_1 carrier position during data processing[13]) to obtain maximum resolution with a relatively small number of t_1 and t_2 increments. The minimum measuring time also depends on the number of scans needed for phase cycling or each set of t_1,t_2 values and on the overhead time needed to write the data to disk at the end of an acquisition. In principle, replacing the first ^{1}H 90° pulse by a frequency-selective pulse could reduce the minimum measuring time (or increase digitization),[3] but this would eliminate informative correlations from the 3D spectrum. We therefore believe that the heteronuclear 3D experiment discussed here is best executed in a nonselective fashion. The sensitivity of the heteronuclear 3D technique is excellent, and resonance overlap in the S. Nase 3D spectrum is minimal, despite the relatively coarse digitization. The three-dimensional NMR experiment reported here should be applicable to proteins significantly larger than S. Nase.

Acknowledgment. This work was supported by the Intramural AIDS Antiviral Program of the Office of the Director of the National Institutes of Health. L.E.K. and D.M. acknowledge financial support from the Medical Research Council, Canada, and from the CNRS/NIH exchange agreement, respectively. We thank Rolf Tschudin for technical support.

Supplementary Material Available: Three figures giving the projection of the 3D spectrum on the F_2/F_3 plane, a F_1/F_3 slice taken at F_2 = 121.8 ppm, and an identical region of the regular 2D NOESY spectrum (4 pages). Ordering information is given on any current masthead page.

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A General Solution To Implementing the 4π Participation of 1-Aza-1,3-butadienes in Diels-Alder Reactions: Inverse Electron Demand Diels-Alder Reactions of α,β-Unsaturated *N*-Benzenesulfonyl Imines

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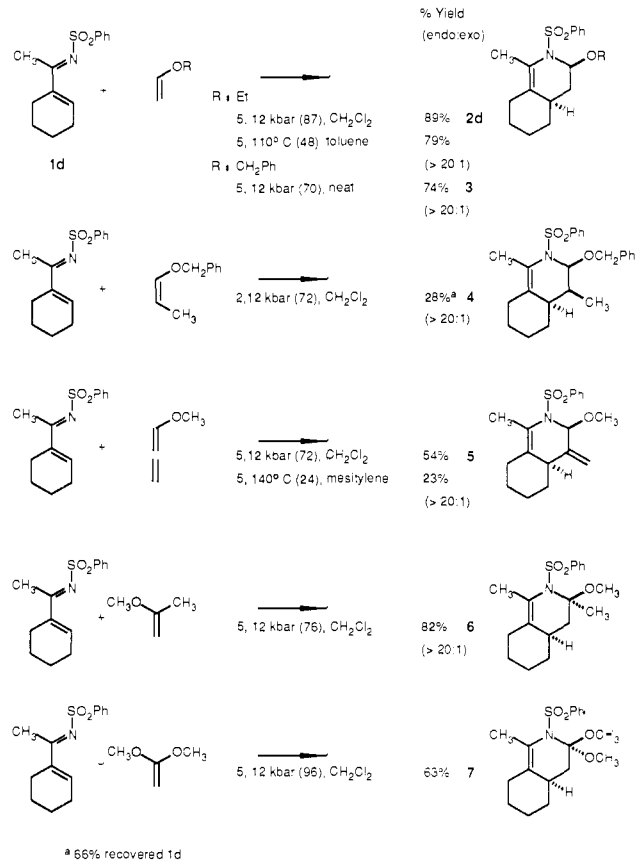
The Diels-Alder 4π participation of simple α,β-unsaturated imines is rarely observed and typically suffers low conversions, competitive imine addition, and/or imine tautomerization precluding [4 + 2] cycloaddition.[2] Consequently only a limited number of 1-aza-1,3-butadiene structural variations and modified or restricted reaction conditions have been introduced that have permitted the productive 4π participation of selected α,β-unsaturated imines in [4 + 2] cycloaddition reactions.[3-7] In the conduct of synthetic efforts on natural and synthetic quinoline-5,8-quinones including streptonigrone,[8] we have examined alternative approaches to predictably control and accelerate the intermolecular 4π participation of 1-aza-1,3-butadienes in [4 + 2] cycloaddition reactions. The complementary N-1 or C-3 substitution of an α,β-unsaturated imine with an electron-withdrawing substituent would be expected to accentuate the electron-deficient nature of the 1-aza-1,3-butadiene and accelerate its potential [4 + 2] cycloaddition reaction with electron-rich dienophiles in $LUMO_{diene}$-controlled Diels-Alder reactions.[2] In addition, a bulky, electron-withdrawing N-1 1-aza-1,3-butadiene substituent would be expected to preferentially decelerate 1,2-imine addition relative to [4 + 2] cycloaddition and convey [4 + 2] cycloaddition product stability to the reaction conditions while enhancing the electron-deficient nature of the diene. Herein we detail a comparative study of the 4π participation of N[1]-substituted α,β-unsaturated imines in $LUMO_{diene}$-controlled Diels-Alder reactions which has revealed the general, well-defined 4π participation of α,β-unsaturated *N*-benzenesulfonyl imines in regio- and endo-specific inverse electron demand Diels-Alder reactions suitable for the diastereoselective preparation of substituted *N*-benzenesulfonyl-1,2,3,4-tetrahydropyridines.

Scheme I



[a] 66% recovered 1d

Representative results of initial studies employing stable imine derivatives of 1-acetylcyclohexene[9] are summarized in eq 1 and

(1) National Institutes of Health research career development award recipient (CA 01136), 1983-1988. Alfred P. Sloan research fellow, 1985-1989.
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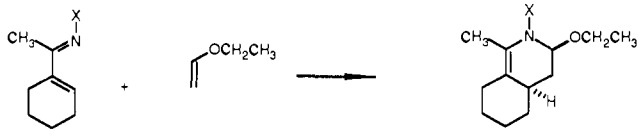
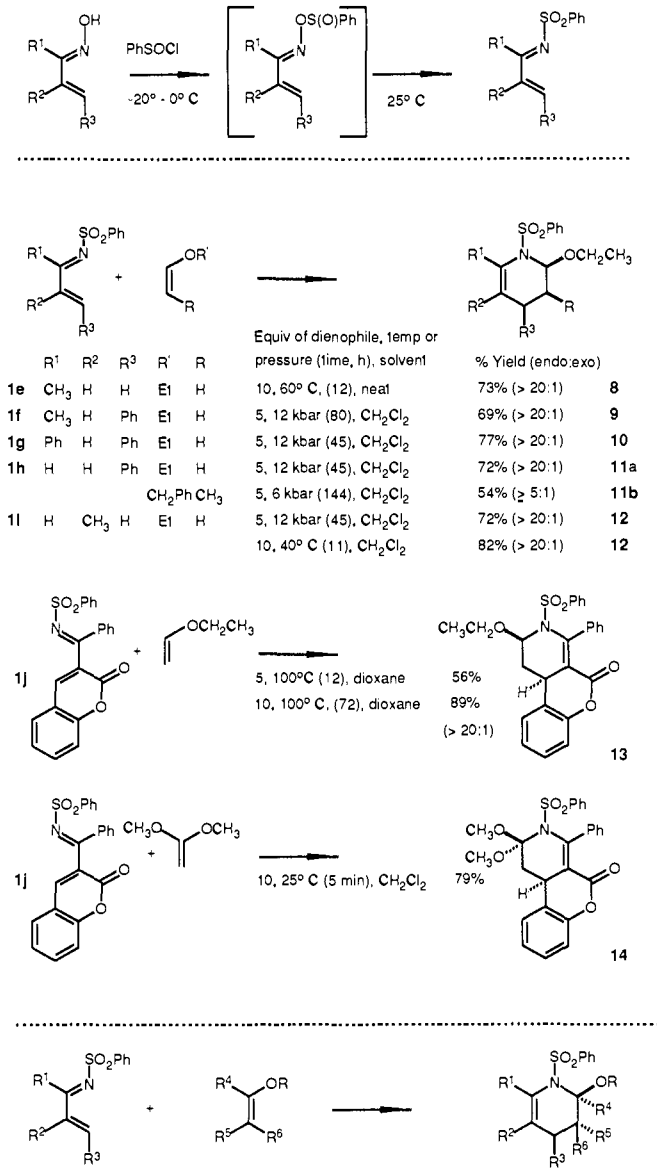


(1)

1a	X = OH	5, 12 kbar (72), CH_2Cl_2	**2a** no reaction
1b	X = OCH_3	5, 12 kbar (72), CH_2Cl_2	**2b** no reaction
1c	X = $P(O)Ph_2$	5, 12 kbar (135), CH_2Cl_2	**2c** 75%
1d	X = SO_2Ph	5, 12 kbar (87), CH_2Cl_2	**2d** 89%
		5, 110° C (48), toluene	79%

demonstrated that N^1-substitution of a 1-aza-1,3-butadiene with an electron-withdrawing substituent facilitates its participation in $LUMO_{diene}$-controlled Diels–Alder reactions: *N*-benzenesulfonyl imine[10] = *N*-diphenylphosphinyl imine[11] ≫ oxime, *O*-methyl oxime. The results of a study of the full scope of the Diels–Alder 4π participation of the α,β-unsaturated *N*-benzenesulfonyl imine **1d** with a range of electron-rich dienophiles are summarized in Scheme I. The diene **1d**, which represents a rigorous test of the generality of the 1-aza-1,3-butadiene Diels–Alder reactions,[9] exhibited excellent thermal reactivity toward ethyl vinyl ether and 1,1-dimethoxyethylene (110 °C) cleanly providing the [4 + 2] cycloadducts.[12] Both the thermal and pressure-promoted [4 + 2] cycloaddition reactions proved to proceed predominately *if not exclusively* (≥95%)[13] through an endo transition state with the apparent full preservation of the dienophile olefin geometry.[14] Even in instances when the endo [4 + 2] cycloaddition is decelerated by destabilizing steric interactions introduced by an additional dienophile cis substituent, the exclusive (**4**) or predominate (**11b**) formation of the product derived from [4 + 2] cycloaddition through an endo transition state was observed.[15]

Scheme II



The initial results of a study of the extension of these observations to the [4 + 2] cycloaddition reaction of ethyl vinyl ether with a full range of *N*-benzenesulfonyl 1-aza-1,3-butadienes are summarized in Scheme II. The *N*-benzenesulfonyl imines were found to be readily accessible through the clean, homolytic rearrangement of in situ generated oxime *O*-phenylsulfinyl[10] compounds or through the direct condensation of benzenesulfonamide with selected α,β-unsaturated aldehydes.[15] The thermal- or pressure-promoted [4 + 2] cycloadditions of **1e–j** proved to proceed predominantly *if not exclusively* (≥95%)[13] through an endo transition state, *N*-benzenesulfonyl aldimines (R^1 = H) proved more reactive than *N*-benzenesulfonyl ketimines ($R^1 = CH_3 > R^1 = C_6H_5$), and the complementary addition of C-3 electron-withdrawing substituent ($R^2 = CO_2R \gg R^2$ = H) substantially further accelerated the *N*-benzenesulfonyl 1-aza-1,3-butadiene participation in the Diels–Alder reaction. Thus, the reaction of N^1-benzenesulfonyl imine **1j** possessing the additional C-3 electron-withdrawing substituent was found to react with 1,1-dimethoxyethylene *within 5 min at 25 °C* to provide the Diels–Alder adduct **14** (79%). In addition, even the α,β-unsaturated N^1-benzenesulfonyl imines which preferentially exist in the extended

(9) The relative increased population of the s-cisoid (*s-Z*) versus s-transoid (*s-E*) conformation of acyclic 1-aza-1,3-butadienes has been related to the observed, but not general, $HOMO_{diene}$-controlled [4 + 2] cycloaddition reactions of the nontautomerizable *N,N*-dimethylhydrazone of methacrolein.[5] The selection of stable imine derivatives of 1-acetylcyclohexene for study represents a rigorous test 1-aza-1,3-butadiene system (1) capable of imine tautomerization, (2) which possesses no selected (*s-Z*)- versus (*s-E*)-diene conformational bias, (3) which presents substantial diene–dienophile steric interactions in the developing [4 + 2] transition state (N-1, C-2, C-3, and C-4 diene substituents), and (4) which suffers from the introduction of $A^{1,2}$-strain accompanying the [4 + 2] cycloaddition. This latter effect generally conveys a preference for 1,2- versus 1,4-addition to such systems.

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(12) The [4 + 2] cycloaddition products **2–13** were purified by chromatography on Florisil and have proven somewhat unstable to silica gel. The cycloadducts **5–7** are not completely stable to this method of purification, and **14** proved unstable to chromatography on Florisil. To date we have not detected epimerization of the cycloadduct C-2 center resulting from the conditions of purification, and the products have proven configurationally stable.

(13) A single-crystal X-ray structure determination of **9** unambiguously established the C-2/C-4 cis relative stereochemistry which must arise through endo [4 + 2] cycloaddition. Full details of the X-ray structure determination are provided as Supplementary Material and includes an ORTEP representation of the structure which illustrates the C-2/C-4 relative stereochemistry, the axial orientation of C-2 OEt, the pseudo axial orientation of C-4 phenyl, and the near planar N^1-nitrogen which lies approximately 0.21 Å above the plane of the attached substituents syn to the C-2 OEt. The conformation of the X-ray crystal structure **9** was consistent with the spectroscopically (^{1}H NMR) assigned structures and stereochemistry ($J_{H2eq,H3ax} \leq$ 2–2.5 Hz, $J_{H2eq,H3eq} \leq$ 4 Hz, $J_{H3ax,H4eq}$ = 7–9 Hz, $J_{H3eq,H4eq} \cong$ 4 Hz, $^1J_{C2,H2}$ = 160–165 Hz). For **9**: $J_{2,3ax}$ = 2.3 Hz, $J_{2,3eq}$ = 4 Hz, $J_{3ax,4}$ = 8.6 Hz, $J_{3eq,4}$ = 4 Hz, $^1J_{C2,H2}$ = 163 Hz.

(14) The all-cis stereochemistry for **11b** and the axial C-2 OEt orientation was established spectroscopically: $J_{2,3ax}$ = 2.3 Hz; $J_{3ax,4eq}$ = 7.7 Hz; $^1J_{C2,H2}$ = 166 Hz. The predominate (**11b**) and exclusive (**4**) formation of the cis cycloadducts derived from an endo transition state for the [4 + 2] cycloaddition with preservation of the olefin geometry is characteristic of but does not require a concerted Diels–Alder reaction. The minor diastereomer accompanying **11b** proved to be the cycloadduct derived from exo [4 + 2] cycloaddition.

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(*s*-*E*)-diene conformation; e.g., **1h**, were found to participate readily in the $LUMO_{diene}$-controlled Diels–Alder reactions.[9] The stereochemistry of the [4 + 2] cycloaddition reaction products was established by spectroscopic techniques and was unambiguously confirmed with the single-crystal X-ray structure determination of adduct **9**.[13,14]

Studies of full scope of the inter- and intramolecular [4 + 2] cycloaddition reactions of α,β-unsaturated *N*-benzenesulfonyl imines as well as their applications are in progress and will be reported in due course.

Acknowledgment. This work was assisted through the financial support of the National Institutes of Health (CA 42056) and the Alfred P. Sloan Foundation. We thank Professor S. M. Weinreb for helpful discussions and Dr. P. Fanwick of the Purdue University X-ray Crystallography facility for the prompt experimental treatment of the X-ray structure determination of **9**.

Supplementary Material Available: General experimental procedures and full spectroscopic and physical characterization of **1a–j**, **2c–d**, **3–14** and full details of the X-ray structure determination of **9** are provided (30 pages). Ordering information is given on any current masthead page.

Oxaphosphetane Pseudorotation: Rates and Mechanistic Significance in the Wittig Reaction

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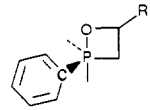
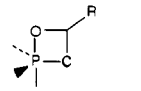
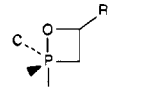
Theoretical investigations suggest a small energy advantage for the oxaphosphetane **1** vs **2** (hypothetical gas-phase species),[1] but the choice of **1** over **2** as the favored Wittig intermediate *in solution* has not been proved and is based on ^{1}H NMR chemical shifts and solid-state analogies.[2,3] The structures of unusually stable pseudorotamers **3**,**3′**, **4**,**4′**, and related compounds were likewise assigned by analogy.[4–6] We now report ^{13}C NMR evidence that **1** is indeed the favored solution species, together with the kinetics of pseudorotamer interconversion.

The NMR spectra of oxaphosphetanes **5**,**5′** (from $Ph_2MeP{=}CH_2$ + 3-pentanone; ^{1}H NMR, toluene-d_8: ring CH_2, δ 3.56, d, ^1J = 16.4 Hz; CH_3P, δ 1.91, d, ^1J = 13.7 Hz), **8a**,[7] or the analogous **8b** (^{13}C spectra; Table I) at −83 °C or above showed only one set of signals, indicating either a single pseudorotamer or rapid interconversion. However, the ^{1}H spectrum of dibenzophosphole (DBP) analogue **9**,**9′** (from (Me)DBP=CH_2 + 3-pentanone, −53 °C) contained two signals for the ring methylene protons (^{1}H NMR, CD_2Cl_2; ring CH_2, δ 3.92, d, ^1J = 16.5 Hz; δ 2.81, d, ^1J = 15.5 Hz; CH_3P, δ 1.72, d, ^1J = 14.1 Hz) and coalescence was observed near room temperature. Line shape analysis[8] (five points from −3 to +40 °C) gave the free energy $\Delta G^{\ddagger}_{PSDRTN}$ = 13.1 kcal/mol, but the fast exchange limit could not be reached due to competing Wittig decomposition to alkene and phosphine oxide, $\Delta G^{\ddagger}_{DEC}$ = 25 kcal/mol (43–55 °C, monitored by NMR).

Table I. ^{13}C NMR Data for Oxaphosphetanes **5**, **8**, and **9**

carbon	chemical shifts (coupling)			
	8a[a]	**8b**[a]	**9**[b]	**5**[c]
	obscured	133.8 ppm (125.0 Hz)	134.3 ppm (132.3 Hz)	148.8 ppm (70.5 Hz)
	54.3 ppm (87.4 Hz)	61.2 ppm (85.6 Hz)	54.5 ppm (82.2 Hz)	60.3 ppm (83.0 Hz)
	28.3 ppm (98.1 Hz)	29.6 ppm (99.0 Hz)	21.9 ppm (98.1 Hz)	24.4 ppm (96.4 Hz)

[a] Spectrum at −30 °C, deuterated toluene. [b] Spectrum at −53 °C, CD_2Cl_2. [c] Spectrum at −53 °C, deuterated toluene.

The detailed structure of oxaphosphetane **9**,**9′** (−53 °C, slow exchange) is defined by the ^{13}C spectrum. Three quaternary aromatic (DBP) carbons (δ 152.7, d, J = 12 Hz; 143.1, d, J = 18 Hz; 135.9, d, J = 14 Hz) cannot be assigned with certainty, but a fourth signal at δ 134.3 ppm is unique because of the large ^{13}C–^{31}P coupling (^1J = 132 Hz), characteristic of an equatorial sp^2 carbon in the trigonal bipyramid.[9] Equally informative is the ^{13}C–^{31}P coupling constant of $^1J_{P-C}$ = 82 Hz for the ring C-3 signal (δ 54.5). The J value is consistent with **9** or **9′**, but not with the equatorial oxygen isomer **10** where apical C-3 should have $^1J_{P-C}$ < 20 Hz.[9]

The characteristic ^{13}C–^{31}P coupling constants **9**,**9′** can be used to evaluate the geometry of unconstrained oxaphosphetanes. For example, the averaged ^{13}C NMR spectrum of pseudorotamers **5**,**5′** has nearly the same $^1J_{P-C}$ = 83 Hz for C_3 as in **9**,**9′** (82 Hz), indicating that the population of **7** is negligible.[10] The quaternary aryl C–P coupling of 70.5 Hz is close to the mean estimated if **5**/**5′** are dominant relative to **6** at equilibrium (0.5[$^1J_{equat}$ = ca. 132 Hz + $^1J_{apical}$ = ca. 15 Hz] = 74 Hz). Similarily, the ^{13}C NMR spectra of **8a** and **8b** (Table I) correspond to dominant pseudorotamers having apical oxygen and the DBP unit spanning apical–equatorial sites. These results confirm the conventional oxaphosphetane representations **1**, **5**, **9**, etc. as orginally assumed for typical Wittig intermediates.[2]

Pseudorotation rates (k_{PSDRTN} = 5.6 × 10^3 sec^{-1})[11] and decomposition rates k_{DEC} = 7.3 × 10^{-5} s^{-1}) for **9** at 43 °C differ by a factor of ca. 10^8 and the corresponding free energies of activation differ by 11.5 kcal/mol. Only the minimum pseudorotation rate of **5** can be estimated ($k_{PSDRTN} \geq 3 \times 10^3$ s^{-1} at −83 °C) since the coalescence temperature could not be reached, but the activation barrier for alkene formation $\Delta G^{\ddagger}_{DEC}$ is again greater than ca. 10 kcal/mol above the pseudorotation barrier. Therefore, pseudorotation does not control the rate of the Wittig decomposition step.

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(6) **3** and **3′** decompose at 120 °C without interconversion. **4** and **4′** pseudorotate rapidly at 20 °C because one oxygen can always occupy an apical site; see: Ramirez, F.; Ugi, I. *Adv. Phys. Org. Chem.* **1971**, *9*, 25; and ref 5a.

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