$(\delta A_2/\delta\lambda_i)\Delta\lambda_i = 81.9$ kJ/mol. This value indicates that if the GROMOS[4] atomic partial charges for the *N*-acetylserine *N*-methylamide peptide are substituted by the atomic partial charges in the AMBER[7] potential, the free energy of *N*-acetylserine *N*-methylamide in methanol is increased substantially. However, an increase by approximately the same magnitude ($\sum(\delta A_1/\delta\lambda_i)\Delta\lambda_i = 78.5$ kJ/mol) is found for the *N*-acetylthreonine *N*-methylamide peptide when the AMBER[7] charges are used instead of the GROMOS[4] charges. The resulting $\Delta\Delta A = \sum(\delta A_2/\delta\lambda_i)\Delta\lambda_i - \sum(\delta A_1/\delta\lambda_i)\Delta\lambda_i$, which reflects the response of the free energy difference ΔA to the changes in the atomic partial charges $\Delta\lambda_i$, has a relatively small value of 3.4 kJ/mol. This analysis indicates that cancellations of errors can occur when the free energy difference between two similar systems is calculated. The free energies A_1 and A_2 do not change as much when the GROMOS[4] atomic partial charges for the "dipeptides" are substituted by those in the OPLS[6] potential, as suggested by $\sum(\delta A_2/\delta\lambda_i)\Delta\lambda_i = -16.9$ kJ/mol and $\sum(\delta A_1/\delta\lambda_i)\Delta\lambda_i = -8.3$ kJ/mol. These values indicate that the free energies of the "dipeptides" are decreased when the OPLS[6] charges are used for the "dipeptides" instead of the GROMOS[4] charges. The $\Delta\Delta A$ value now becomes -8.6 kJ/mol. One can use the variation of $\Delta\Delta A$ values obtained when different potentials (e.g., AMBER,[7] OPLS[6]) are used for V_a to estimate the uncertainty of a free energy result (i.e., ΔA).

The above example shows that one can use the SSAM to estimate the uncertainty of a free energy difference (ΔA) as a result of the use of nonoptimal parameters in a potential energy function. By analyzing the sensitivity coefficients, one can also study how a small change in each parameter in a potential energy function affects a free energy result. When larger $\Delta\lambda_i$'s are involved, one can improve the estimate of $\Delta\Delta A$ by including higher order terms in the Taylor series expansion (eq 1). Extension to include other potential parameters (e.g., Lennard-Jones parameters) is straightforward. To study the effects of changing potential energy functional forms, the formalism can be generalized by using functional calculus.

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Remarkable Catalysis of Intersystem Crossing of Singlet (Pentafluorophenyl)nitrene

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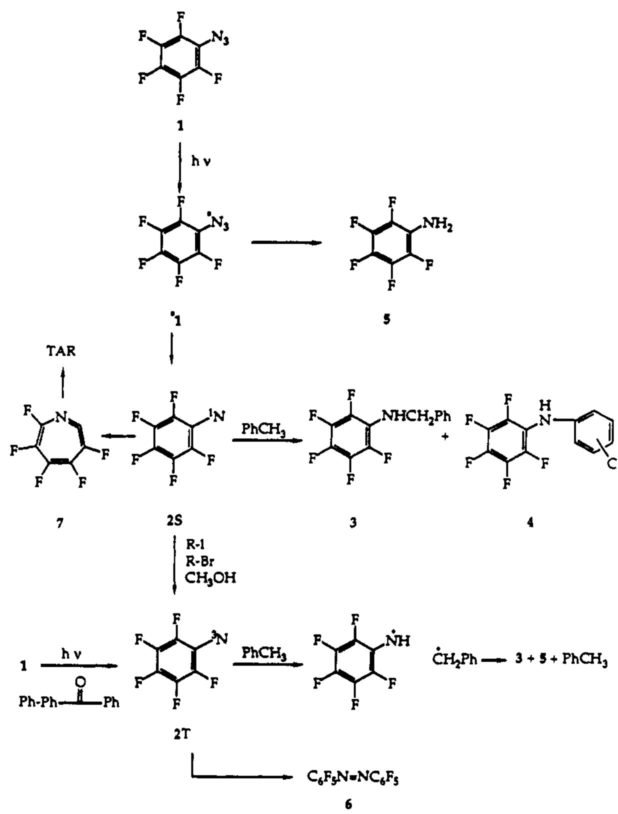
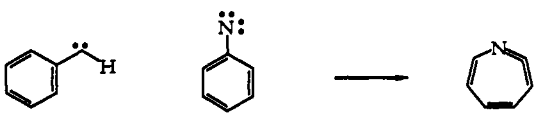
Scheme I



Phenylcarbene (PC)[4] and phenylnitrene (PN)[5] are both reactive intermediates which have triplet ground states and low-lying singlet states. The triplet states are well characterized by low-temperature matrix isolation spectroscopy.[6] Brauman and Drzaic determined that ^{1}PN is 4.3 kcal/mol higher in energy than ^{3}PN.[7] The energy gap in PC is not known but must be very small as the two states rapidly interconvert.[8] Although ^{1}PC is readily intercepted by external trapping reagents,[4] ^{1}PN is not,[5] apparently due to the ease of ring expansion of the latter species to form a ketenimine (KET), in solution at ambient temperature.[9]



PC PN KET

(Pentafluorophenyl)nitrene (**2S**, **2T**, Scheme I) is also a ground-state triplet species;[6,9c] however, the singlet-triplet energy separation of this species remains undetermined. Banks discovered that this nitrene undergoes intermolecular reactions in solution.[10,11]

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(2) Support of a graduate fellowship provided by the Eastman Kodak Company administered by the Organic Division of the American Chemical Society, and support of a graduate fellowship provided by the Amoco Corporation are gratefully acknowledged.

(3) Ohio State University Graduate School Postdoctoral Fellow.

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Table I. Distribution of Products Formed on Photolysis of **1** in the Presence of Toluene at Ambient Temperature[a]

solvent	3	4-ortho	4-para	5	6
neat toluene (T)[b,c]	4.0	32	14	12	–
T[d] + BBP[e]	9.7	–	–	26	5.7
7.1 M T, CH_2Cl_2[c]	2.6	12	6.1	10	–
4.7 M T, CH_2Cl_2[c]	2.0	10	7.2	8.2	–
3.3 M T, CH_2Cl_2[c]	2.0	9.6	6.0	10	–
2.4 M T, CH_2Cl_2[c]	1.8	9.5	5.2	10	–
6.3 M T, CH_3CH_2I, IP[f,g] (0.5 M)	–	–	–	64.5	–
6.3 M T, CH_3CH_2I, IP[f,g] (0.133 M)	–	–	–	57	–
4.7 M T, CH_3CH_2I	–	–	–	44	10
6.6 M T, $CH_3(CH_2)_3Br$	–	28	6	36	–
7.5 M T, CH_3OH	18	24	8	19	–
5.6 M T, CH_3OH	6	6	–	23	–
3.8 M T, CH_3OH	–	–		37	–
neat CH_3OH	–			–56	–

[a] Absolute yields determined by GC. [b] 9.4 M. [c] 0.03 M **1**. [d] 0.0125 M **1**. [e] 0.01 M *p*-benzoylbiphenyl as triplet sensitizer. [f] Isoprene. [g] 0.01 M **1**.

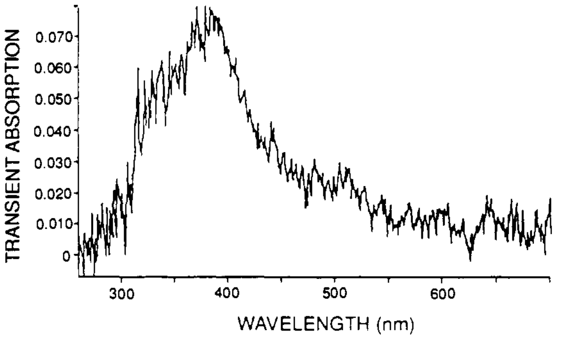

Figure 1. The transient absorption spectrum of either **2S** or **7** (λ_{max} = 385 nm) produced by LFP of **1** in CH_2Cl_2 at 20 °C. The spectrum was recorded 400 ns after the laser pulse over a window of 500 ns. The shoulder at 330 nm may be due to a small amount of triplet nitrene **2T**.

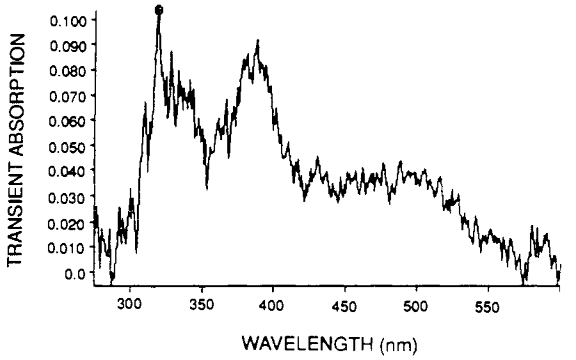

Figure 2. Transient absorption spectrum of **2T** obtained by LFP of azide **1** in CH_3OH at 20 °C. The spectrum was recorded over a window of 500 ns, taken 400 ns after the laser flash. The band at 370–390 nm may contain contributions from both **2S** and **2T**.

Our earlier work indicated that **2S** is surprisingly discriminating, implying that it is a relatively long-lived intermediate.[12] Herein we report additional chemical and dynamical information which indicates that **2S** does not undergo intersystem crossing (ISC) at an appreciable rate in solution, but that ISC can be catalyzed by heavy atoms and by methanol.

Photolysis of **1** in neat toluene (9.4 M) produces formal insertion adducts.[10m,12] Adduct **3** can be formed in principle from **2S** or **2T**, but adducts **4** (ortho and para isomers) are clearly derived from capture of singlet nitrene **2S** (Scheme I). Adducts **4**-ortho and **4**-para are not formed upon triplet photosensitized decomposition of **1** in toluene; instead the yields of benzylic insertion adduct **3**, pentafluoroaniline **5**, and azo compound **6** are enhanced. The absence of **6** in the mixture of products formed upon direct photolysis of **1** indicates that very little **2T** has been intercepted. The modest yield of **5** produced by direct photolysis of **1** is probably due to a small amount of triplet nitrene chemistry and to photoreduction of **1*** as in the case of the aroyl azides.[13] Dilution of toluene with the inert solvent CH_2Cl_2 leads to little change in the distribution of volatile products formed photochemically, but to an increase in the yield of polymeric tar.[14] This indicates that relaxation of **2S** to the lower energy triplet state **2T** is slow.[15] However, dilution of toluene with CH_3CH_2I or $CH_3(CH_2)_3Br$ dramatically alters the distribution of products (Table I). Insertion adducts **3** and **4** are completely absent in CH_3CH_2I, even in the presence of isoprene, a quencher of putative triplet excited state $^{3}\mathbf{1}^{*}$. This result indicates that the heavy-atom effect[15] is catalyzing ISC of singlet nitrene **2S**, and not **1S*** → **1T***, followed by extrusion of nitrogen to form **2T**.

Amazingly CH_3OH has the same effect on the product distribution as the heavy-atom cosolvents, implying that the alcohol can also catalyze the ISC process. This interpretation is supported by laser flash photolysis (LFP) experiments. LFP of **1** in CH_2Cl_2 produces a transient with $\lambda_{max} \approx$ 385 nm (Figure 1) which is attributed to either **2S** or ketenimine **7**.[9] This spectrum differs from the matrix spectrum[9c] of **2T** but is similar to the spectrum of KET produced by flash photolysis of phenyl azide.[9c] The carrier of the transient spectrum of Figure 1 is quenched by dimethyl sulfide, a known scavenger of **2S**. On the other hand, LFP of **1** in CH_3OH produces a transient spectrum (Figure 2) which contains the known matrix spectrum of **2T**.[9c]

How does methanol catalyze nitrene ISC? We speculate that hydrogen bonding plays a key role, as ethers such as tetrahydrofuran[17] and polar solvents such as acetonitrile do not catalyze ISC in this system. Unlike carbenes, which are divalent and undergo ISC with rates close to 10^{10} s^{-1},[18] monovalent nitrenes lack bending vibrations which can couple to and assist the ISC process. It is convenient to think of the nitrene nitrogen as sp hybridized. There is a doubly occupied nonbonding sp orbital colinear with the C–N bond and two orthoganol pure p orbitals. We speculate that hydrogen bonding to the two doubly occupied nonbonding orbitals of the singlet nitrene provides low-frequency

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[11] Singlet (pentafluorophenyl)nitrene is known to undergo ring expansion over platinum in the gas phase at 300 °C: Banks, R. E.; Venayak, N. D. *J. Chem. Soc., Chem. Comm.* **1980**, 900.

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[14] Polymeric tar is likely formed in a reaction initiated by reaction of ketenimine **7** with itself or with **1**, as in the reaction of KET with parent phenyl azide; see ref 9a.

[15] Jones, M., Jr.; Rettig, K. R. *J. Am. Chem. Soc.* **1965**, *87*, 4013.

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[17] Photolysis of **1** in toluene containing THF does not produce triplet-derived products; instead, an adduct of **2S** with THF is formed. LFP of **1** in acetonitrile produces **2S**; the results are included as supplementary material.

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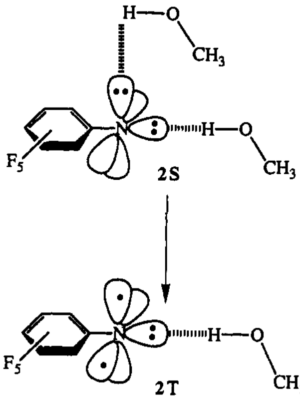
bending modes and can thereby catalyze the ISC process. Alternatively methanol may preferentially stabilize the singlet state of the nitrene which forms two hydrogen bonds, relative to the triplet state which forms only a single hydrogen bond.[19] Reducing the singlet-triplet energy gap is expected to result in an increased rate of ISC.[18] Experiments are in progress with other nitrenes to establish the generality of the alcohol effect.



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Supplementary Material Available: A matrix spectrum of **2T**, a solution-phase transient spectrum of **2S** or **7** in acetonitrile, the matrix spectrum of ^{3}PN, and a transient spectrum of KET (4 pages). Ordering information is given on any current masthead page.

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(19) Effects of this type are responsible for shifting $n \rightarrow \pi^*$ absorption maxima of ketones. The absorption maximum of acetone is shifted from 279 to 264.5 nm between hexane and water, an amount corresponding to 5 kcal/mol; $n \rightarrow \pi^*$ excitation destroys one hydrogen bonding interaction. See: Jaffé, H. H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*; Wiley: New York, NY, 1962; p 187.

Correlation Spectroscopy at a Bargain: SIMPLE-COSY[†]

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Correlation spectroscopy (COSY) of *J*-coupled spins was the first representative[1,2] of multidimensional experiments, which have revolutionized NMR spectroscopy.[3] Various methods have been developed to get pure-phase spectra with quadrature detection in both dimensions. Multiple-quantum filtering is frequently used[4] resulting in diagonal peaks also of pure absorption phase, as well as reduced cross-peak multiplet structure.[5] Attempts have been made to suppress diagonal peaks in homonuclear correlations.[6] However, each of these experimental modifications results in a more complicated acquisition scheme and increases the minimum number of scans to be acquired.

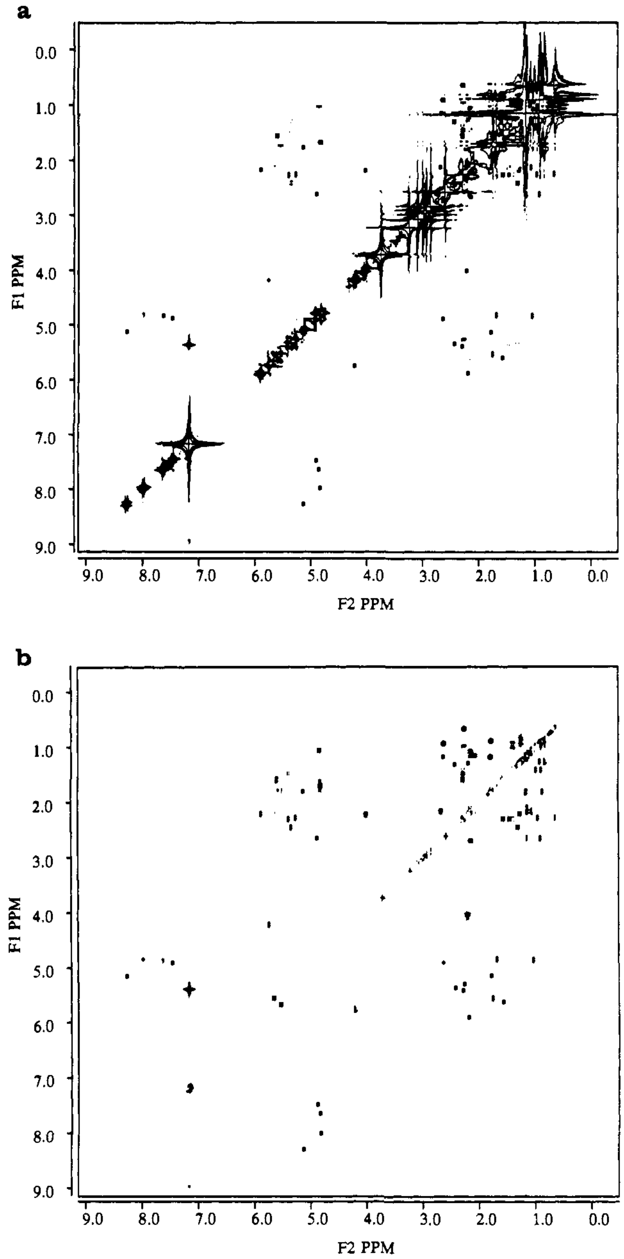

Figure 1. Two stages of the SIMPLE-COSY procedure for cyclosporin A, measured in C_6D_6 at 303 K at 500.1 MHz on a GN-500 spectrometer: (a) pure-phase spectrum with huge dispersive diagonal peaks, (b) which are removed via the method described in the text. One percent of the full spectrum was zeroed along the diagonal. Some residual intensities at higher fields are due to incompletely suppressed truncation of more intense overlapping signals.

Recently, a witty simplification has been introduced to substitute MQ filtering with substraction of a reference 2D set containing only the diagonal peaks.[7] Marion and Bax have improved this approach by synthesizing the latter reference 2D from a carefully adjusted 1D spectrum.[8] This P.COSY has been proven to be the most economical and fastest way to get a pure absorption phase COSY spectrum, so far.

We present here an even faster and the most simple way to create a full-power pure-phase COSY spectrum (SIMPLE-COSY or S.COSY). This approach does not need extra care in setting up the experiment and requires less effort in computation in

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[†] Dedicated to Dr. Szabó, J. A., Szeged, Hungary.

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