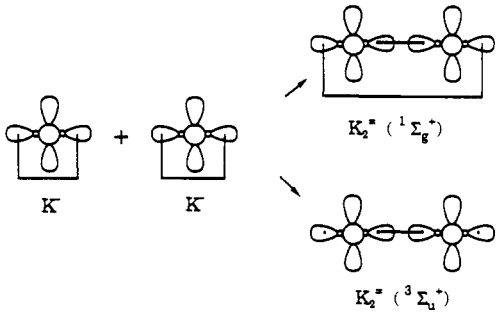
into a σ bond and leaving the remaining two electrons localized on very different orbitals on each K ion.



The observed K^- to K^- distance in I is 4.90 Å, considerably longer than the 4.00 Å that we calculate. This suggests that the particular electrostatic potential we have used overestimates the positive potential experienced by K_2^{2-}. While we are exploring[5] more realistic potentials based on the observed crystal structure, we feel that these calculations suggest that a reasonable mechanism for the anion–anion bonding in alkalides is the stabilization of K_2^{2-} by the internal electric fields in the crystal.

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(5) Tientega, F.; Dye, J. L.; Harrison, J. F. The Electronic Structure of Na_2^{2-} and K_2^{2-}, in preparation.

Systematic Sensitivity Analyses in Free Energy Perturbation Calculations

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The use of free energy perturbation calculations is increasing gradually in chemistry and biochemistry.[1] Since the potential energy functions used in these calculations are approximate, it is important to examine the sensitivity of simulation results to the choice of the parameters in these potentials. The response of a free energy result ($\Delta A = A_2 - A_1$: the free energy difference between state 2 and state 1) to a small change in a potential parameter can be obtained by recalculating ΔA with two or more values of the parameter. However, this would be an expensive procedure by which to examine the response of ΔA to each parameter in the potential energy function. An alternative based on the systematic sensitivity analysis method[2] (SSAM) commonly used in engineering problems is proposed here for the analyses of free energy results. The advantage of the method is that it requires only two simulations to find out the sensitivity of ΔA to a small change in each parameter in the potential energy function.

Using the sensitivity analysis approach,[2] one approximates the response ($\Delta\Delta A$) of ΔA to parameter changes by a truncated Taylor series:

$$\Delta\Delta A = \sum(\delta\Delta A/\delta\lambda_i)\Delta\lambda_i \quad (1a)$$

$$= \sum(\delta A_2/\delta\lambda_i)\Delta\lambda_i - \sum(\delta A_1/\delta\lambda_i)\Delta\lambda_i \quad (1b)$$

where $\Delta\lambda_i$ represents a small change in the parameter λ_i. The partial derivatives $\delta\Delta A/\delta\lambda_i$'s, which are known as sensitivity coefficients, can be calculated by using the finite difference formula:

$$\delta\Delta A/\delta\lambda_i = -[1/(2\beta\, d\lambda_i)] \times \{\ln\{\langle\exp[-\beta(H_2(\lambda_i + d\lambda_i) - H_2(\lambda_i))]\rangle_{2/\lambda_i}/\langle\exp[-\beta(H_2(\lambda_i - d\lambda_i) - H_2(\lambda_i))]\rangle_{2/\lambda_i}\} - \ln\{\langle\exp[-\beta(H_1(\lambda_i + d\lambda_i) - H_1(\lambda_i))]\rangle_{1/\lambda_i}/\langle\exp[-\beta(H_1(\lambda_i - d\lambda_i) - H_1(\lambda_i))]\rangle_{1/\lambda_i}\}\} \quad (2)$$

where β = (Boltzmann constant × absolute temperature)$^{-1}$, $H_i(x)$ is the classical Hamiltonian of the state i evaluated by using the potential parameter x, and $\langle\ldots\rangle_{j/\lambda_i}$ represents an ensemble average over the state j simulated by using the potential parameter λ_i. $d\lambda_i$ is a small finite change in the paramter λ_i. Similar finite difference formulas have been used to calculate enthalpy and entropy changes.[3]

The SSAM was tested by taking ΔA to be the free energy difference between *N*-acetylserine *N*-methylamide (state 2) and *N*-acetylthreonine *N*-methylamide (state 1) in methanol. Results for $\delta A_2/\delta\lambda_i$, $\delta A_1/\delta\lambda_i$, and $\delta\Delta A/\delta\lambda_i$ in which λ_i's are the atomic partial charges of the "dipeptides" are shown in Figure 1. Since corresponding atoms in the two "dipeptides" have similar free energy responses to small changes in the atomic partial charges (i.e., $\delta A_2/\delta\lambda_i \approx \delta A_1/\delta\lambda_i$), $\delta\Delta A/\delta\lambda_i$'s have values close to 0. Equation 1a then suggests that ΔA is not sensitive to small parameter changes. To quantify this further, it is useful to take each $\Delta\lambda_i$ as $\Delta\lambda_i = \lambda_i(V_a) - \lambda_i(V_b)$ where $\lambda_i(V_a)$ and $\lambda_i(V_b)$ are the atomic partial charges from force fields V_a and V_b, respectively (V_b is the force field used in the simulation; see figure caption). One can then estimate $\sum(\delta A_2/\delta\lambda_i)\Delta\lambda_i$, $\sum(\delta A_1/\delta\lambda_i)\Delta\lambda_i$, and $\Delta\Delta A$ in eq 1b. When V_a is taken to be the AMBER[7] force field, $\sum$-

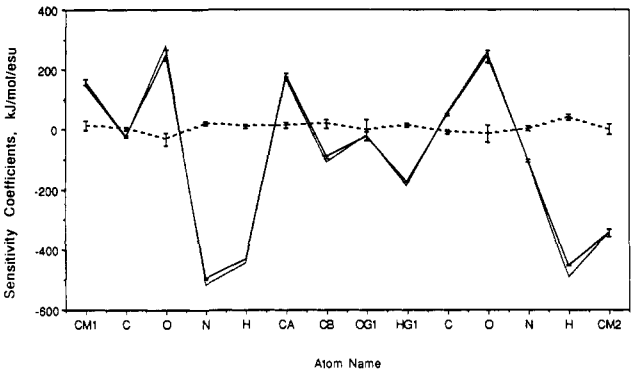

Figure 1. $\delta A_2/\delta\lambda_i$ (dotted line), $\delta A_1/\delta\lambda_i$ (solid line), and $\delta\Delta A/\delta\lambda_i$ (dashed line); see text for description. The molecular dynamics simulation of the threonine "dipeptide" was performed with the GROMOS[4] molecular modeling package using a time step of 2 fs. The SHAKE algorithm[5] was used to constrain the covalent bond lengths. Periodic boundary conditions were used in the simulation. The threonine "dipeptide" was put in a box of 230 equilibrated methanol molecules. After 25ps of careful equilibration, the sensitivity coefficients were calculated using data from the next 30ps (i.e. 25–55ps). Each error bar was estimated from the difference of corresponding sensitivity coefficients calculated from two 15ps segments. At 55ps, the threonine "dipeptide" was "mutated" into a serine "dipeptide". The system was allowed to relax for 10ps and sensitivity coefficients were calculated from data of the next 30ps. For clarity, error bars of $\delta A_2/\delta\lambda_i$ are not shown. The error bar of each $\delta\Delta A/\delta\lambda_i$ is obtained by adding the error bars of $\delta A_2/\delta\lambda_i$ and $\delta A_1/\delta\lambda_i$. The OPLS[6] parameters were used for the methanol molecules. The GROMOS[4] parameters were used for the "dipeptides". The combination rules described in reference 4 were used to construct the interaction potential between the "dipeptides" and the methanol molecules.

(1) McCammon, J. A.; Harvey, S. C. *Molecular Dynamics of Proteins and Nucleic Acids*; Cambridge University Press: New York, 1987. Beveridge, D. L.; DiCapua, F. M. *Annu. Rev. Biophys. Chem.* **1989**, *18*, 431. Kollman, P. A.; Merz, K. M. *Acc. Chem. Res.* **1990**, *23*, 246. Brooks, C. L., III; Fleischman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 3307. Jorgensen, W. L. *Acc. Chem. Res.* **1989**, *22*, 184. Warshel, A.; Sussman, F.; King, G. *Biochemistry* **1986**, *25*, 368. Also see references in the above articles.

(2) Franck, P. *Introduction to System Sensitivity Theory*; Academic Press: New York, 1978. Rabitz, H. *Chem. Rev.* **1987**, *87*, 101.

(3) Fleischman, S. H.; Brooks, C. L., III. *J. Chem. Phys.* **1987**, *87*, 3029.

(4) van Gunsteren, W. F. *GROMOS*; Univeristy of Groningen: Groningen, 1987. Hermans, J.; Berendsen, H. J. C.; van Gunsteren, W.; Postma, J. P. M. *Biopolymers* **1984**, *23*, 1513.

(5) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327.

(6) Jorgensen, W. L. *J. Phys. Chem.* **1986**, *90*, 1276. Jorgensen, W. L. *J. Am. Chem. Soc.* **1984**, *106*, 6638.

(7) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765.

0002-7863/91/1513-3208$02.50/0

$(\delta A_2/\delta\lambda_i)\Delta\lambda_i$ = 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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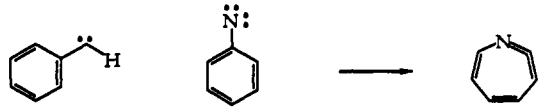
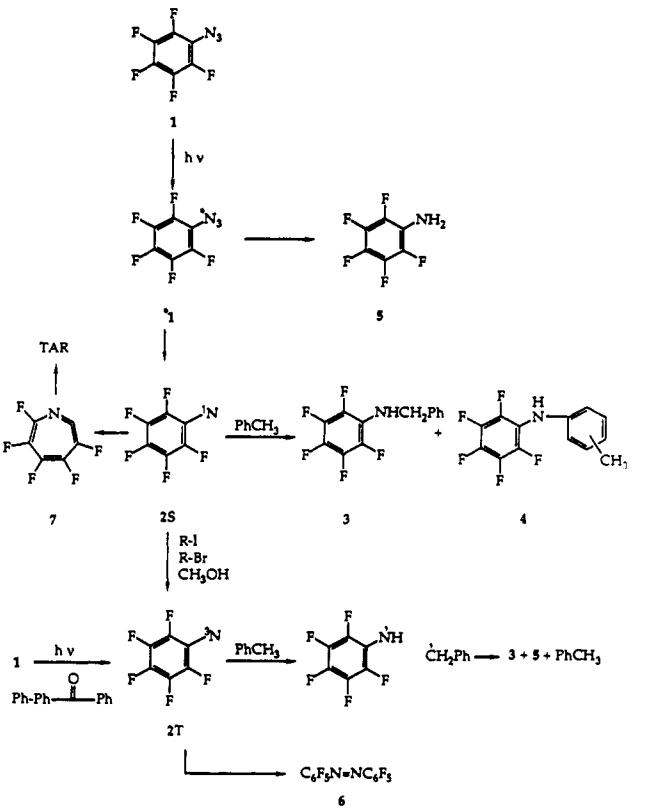
Phenylcarbene (PC)[4] and phenylnitrene (PN)[5] are both reactive intermediates which have triplet ground states and low-lying singlet states. The triplet states are well characterized by low-temperature matrix isolation spectroscopy.[6] Brauman and Drzaic determined that ^{1}PN is 4.3 kcal/mol higher 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]

Scheme I



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(4) For reviews of phenylcarbene chemistry and leading references, see: (a) Platz, M. S. *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum: New York, NY, 1990; p 143. (b) Baron, W. J.; DeCamp, M. R.; Hendrick, M. E.; Jones, M., Jr.; Levin, R. H.; Sohn, M. B. *Carbenes*; Jones, M., Jr., Moss, R. A., Eds.; Academic: New York, NY, 1973; Vol. 1, p 1.

(5) For a review of phenylnitrene chemistry, see: Smith, P. A. S. *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic: New York, NY, 1984; p 95.

(6) (a) Trozzolo, A. M.; Murray, R. W.; Wasserman, E. *J. Am. Chem. Soc.* **1962**, *84*, 4991. (b) McMahon, R. J.; Chapman, O. L. *J. Am. Chem. Soc.* **1987**, *109*, 683. Chapman, O. L.; Johnson, J. W.; McMahon, R. J.; West, P. R. *J. Am. Chem. Soc.* **1988**, *110*, 5a. Wasserman, E. *Prog. Phys. Org. Chem.* **1971**, *8*, 319. (e) Platz, M. S. *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic: New York, NY, 1984; p 359. (f) Reiser, A.; Frazer, V. *Nature (London)* **1965**, *208*, 682.

(7) Drzaic, P. S.; Brauman, J. I. *J. Am. Chem. Soc.* **1984**, *106*, 3443.

(8) (a) Baer, T. A.; Gutsch, C. D. *J. Am. Chem. Soc.* **1971**, *93*, 5180. (b) Moss, R. A.; Dolling, U.-H. *J. Am. Chem. Soc.* **1971**, *93*, 954.

(9) (a) Li, Y.-Z.; Kirby, J. P.; George, M. W.; Poliakoff, M.; Schuster, G. B. *J. Am. Chem. Soc.* **1988**, *110*, 8092. (b) Schrock, A. K.; Schuster, G. B. *J. Am. Chem. Soc.* **1984**, *106*, 5234. (c) Leyva, E.; Platz, M. S.; Persy, G.; Wirz, J. *J. Am. Chem. Soc.* **1986**, *108*, 3783.

(10) (a) Birchall, J. M.; Haszeldine, R. N.; Parkinson, A. R. *J. Chem. Soc.* **1962**, 4966. (b) Kaskin, A. V.; Bakhmutov, Y. L.; Marchenko, N. N. *Zh. usesoyuz Khim. Obshehest* **1970**, *15*, 58. (c) Birchall, J. M.; Haszeldine, R. N.; Jones, M. E. *J. Chem. Soc. C* **1971**, 1343. (d) Banks, R. E.; Sparkes, G. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2964. (e) Banks, R. E.; Prakash, A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1365. (f) Banks, R. E.; Prakash, A. *Tetrahedron Lett.* **1973**, 99. (g) Banks, R. E.; Medany, I. M. *J. Fluorine Chem.* **1990**, *47*, 527. (h) Banks, R. E.; Prakash, A.; Venayak, N. D. *J. Fluorine Chem.* **1980**, *16*, 325. Keana, J. F. W.; Cai, S. X. *J. Org. Chem.* **1990**, *55*, 3640. Keana, J. F. W.; Cai, S. X. *J. Fluorine Chem.* **1989**, *43*, 151. (k) Cai, S. X.; Keana, J. F. W. *Tetrahedron Lett.* **1989**, *30*, 5409. (l) Leyva, E.; Young, M.-J. T.; Platz, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 8307. (m) Leyva, E.; Munoz, D.; Platz, M. S. *J. Org. Chem.* **1989**, *54*, 5938.

0002-7863/91/1513-3209$02.50/0