J|A|C|S

A R T I C L E S

Dimerizations of Nitrile Oxides to Furoxans Are Stepwise via Dinitrosoalkene Diradicals: A Density Functional Theory Study

Zhi-Xiang Yu,[†] Pierluigi Caramella,[‡] and K. N. Houk*,[†]

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, USA and Dipartimento di Chimica Organica, Universita degli Studi di Pavia, Viale Taramelli, 10, I-27100 Pavia, Italy

Received July 16, 2003; E-mail: houk@chem.ucla.edu

Abstract: Density functional theory calculations at the B3LYP/6-31G* level on the dimerization reactions of acetonitrile oxide and para-chlorobenzonitrile oxide to form furoxans indicate that these processes are stepwise involving dinitrosoalkene intermediates that have considerable diradical character. The rate-determining steps for these two reactions correspond to C−C bond formation. The retardation of dimerization in aromatic nitrile oxides arises from the interruption of conjugation between the nitrile oxide and aryl groups in the C−C bond formation step. The present study also suggests that the isomerization of single-ring furoxans occurs via a diradical intermediate mechanism.

1. Introduction

Nitrile oxides are widely used participants in 1,3-dipolar cycloadditions to generate five-membered ring heterocycles.[1] Nitrile oxides (especially for lower aliphatic and acyl nitrile oxides) easily dimerize to form 1,2,5-oxadiazole-2-oxides, commonly known as furoxans or furazan oxides (reaction 1 in Scheme 1).[1] Under acidic or basic conditions, nitrile oxides can also dimerize to give either 1,2,4-oxadiazole-4-oxides or symmetric 1,4-dioxa-2,5-diazines (reactions 2 and 3 in Scheme 1).[2]

Two paths have been proposed for the dimerization of nitrile oxide to furoxans, but the detailed mechanism is not known.[3] The most widely accepted mechanism is a concerted 1,3-dipolar cycloaddition process, where one nitrile oxide acts as a dipole while the C−N multiple bond in the other nitrile oxide acts as a dipolarophile (Scheme 2). A (closed-shell) stepwise mechanism, often called the carbene mechanism, has also been proposed. In the carbene mechanism, the first step corresponds to bond formation between the carbenoid carbons of two nitrile oxides to form a dinitroso alkene intermediate, which then cyclizes to the furoxan. Huisgen, the originator of the field of

Scheme 1
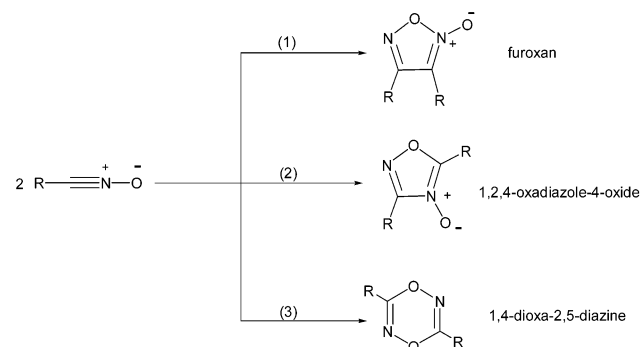
Scheme 2
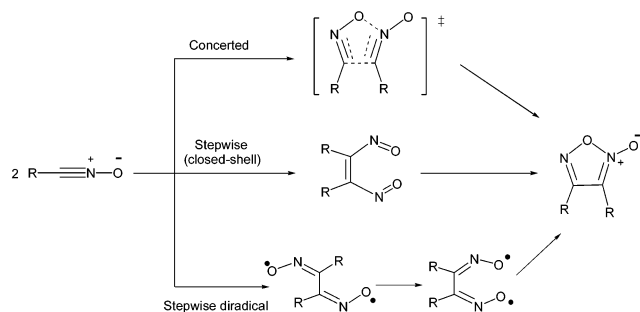
1,3-dipolar cycloadditions, and Dondoni, have given evidence in favor of the concerted mechanism.[3,4] Early experimental support for the stepwise mechanism came from Mallory's experimental work on the interconversions of two methylphenylfuroxans and two ethylmethylfuroxans, in which they have assumed the existence of dinitrosoalkene intermediates during

† UCLA.

‡ Universita degli Studi di Pavia.

(1) For recent reviews, see: (a) Jager, V.; Colinas, P. A. Nitrile Oxides. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley & Sons Inc.: New York; 2002, Vol. 59, *The Chemistry of Heterocyclic Compounds*. (b) Caramella, P.; Grunanger, P. Nitrile Oxides and Imines. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons Inc.: New York, 1984. (c) Grundmann C.; Grunanger, P. *The Nitrile Oxides*; Springer-Verlag: Berlin, 1971.

(2) (a) Speroni, G.; Bartoli, M. *Sopra Gli Ossidi di Benzonitrile, Nota VIII*; Stabilimento Tipografico Marzocco, Florence, 1952. (b) Morrocchi, S.; Ricca, A.; Selva, A.; Zanarotti, A. *Chim. Ind. (Milan)* **1968**, *50*, 558. (c) Morrocchi, S.; Ricca, A.; Selva, A.; Zanarotti, A. *Gazz. Chim. Ital.* **1969**, *99*, 165. (d) De Sarlo, F.; Guarna, A. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 2793, and references therein.

(3) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633.

(4) (a) Dondoni, A.; Mangini, A.; Ghersetti, S. *Tetrahedron Lett.* **1966**, 4789. (b) Barbaro, G.; Battaglia, A.; Dondoni, A. *J. Chem. Soc. (B)*, **1970**, 588.

the tautomerization.[5] Recently, Pasinszki and Westwood[6] reported gas-phase spectroscopic and density functional theory (DFT) studies on the decomposition of dimethylfuroxan to acetonitrile oxide; their calculations predicted a two-step mechanism for the dimerization with a reasonable activation barrier of 16.6 kcal/mol.[6a,7] Very recently, Himmel, Rauhut, and co-workers observed an aliphatic dinitroso alkene intermediate during the photoinduced isomerization and decomposition of dimethylfuroxan.[8a] DFT calculations gave the geometry of the dinitrosoalkene intermediate.[8] These experimental and theoretical investigations[6,8] imply that dimerization of nitrile oxides to furoxans adopt the (closed-shell) stepwise carbene mechanism. However, all the previously reported calculations[6,8-10] on the isomerization and decomposition of furoxan are based on restricted wave functions, and the diradical character of the dinitrosoalkene has been overlooked (although Pasinszki and Westwood do refer to the "Firestone-type intermediate", and Firestone has been the champion of diradical intermediates[11] in cycloaddition of nitrile oxides). Here, we report density functional theory calculations on the dimerizations of acetonitrile oxide and para-chlorobenzonitrile oxide. Theory predicts that the formation of furoxans involves stepwise reactions through dinitrosoalkene intermediates, which have substantial diradical character (stepwise diradical mechanism, Scheme 2). The origin of the slower rate of dimerization of arylnitrile oxides to furoxans has also been explored computationally.

2. Computational Methods

All of calculations were performed with the *Gaussian 98* program except for **2**(ctt), **2**(ttt), **TS4**, **9**(ctt), **TS10** and **TS11**, which were located using the *Gaussian 03* program.[12] The hybrid B3LYP functional[13] in conjunction with the 6-31G* basis set[14] were applied for the optimization of all the stationary points in the gas phase except those singlet diradical transition states and intermediates, which were located at the UB3LYP/6-31G* level. Frequency calculations at the same level have been performed to confirm each stationary point to be either a minimum or a transition structure. Solvent effects were estimated with the PCM model[15] implemented in the *Gaussian 98* using the gas-phase optimized structures. $\Delta G_{solvent}$ and ΔG_{298} are calculated relative free energies in

various solvents (CCl_4, CH_2ClCH_2Cl, CH_2Cl_2, CH_3OH, and H_2O) and the gas phase, respectively. ΔE_0 are the zero-point energy (ZPE) corrected relative electronic energies in the gas phase. For all diradical transition states and intermediates, a spin-projection scheme has been used to estimate energies of singlet diradical structures.[16]

3. Results and Discussion

3.1. Dimerization of Acetonitrile Oxide. Figure 1 shows the potential energy surface for the dimerization of acetonitrile oxide to form dimethylfuroxan in the gas phase, together with the B3LYP/6-31G* computed structures. No concerted 1,3-dipolar cycloaddition transition state for the formation of furoxan could be found. Instead, the dimerization is stepwise via a dinitrosoalkene. The first step corresponds to the formation of intermediate **2**(ctc)[17] via a singlet diradical **TS1**, in which the forming C1−C4 bond is 1.957 Å.[18] Two salient features of the structure of **TS1** are worthy of mention. One is that the two N=O groups in **TS1** are trans to each other in order to avoid electrostatic repulsions. In addition, both NO groups are bent toward the forming bond so that the nitrogen lone pairs avoid electrostatic repulsion with the π electrons involved in the forming C1 and C4 bond. All efforts to locate the transition state leading to **2**(ccc), with nitroso groups in cis, always led to **TS1** with the ctc configuration. No transition structure with ttt conformation could be found using B3LYP and UB3LYP methods.

The generation of **2**(ctc) from two nitrile oxides is exothermic by 11.9 kcal/mol in the gas phase. Although we are tempted to write dinitrosoalkene **2** as an alkene, it is in fact a singlet diradical species, as evidenced by the C1−C4 bond length of 1.479 Å, a distance characteristic of an sp^2–sp^2 single bond. Intermediate **2**(ctc) is found to be a σ, σ diradical, as is evident from the radical orbitals that are composed of the in-plane p orbitals of N and O (Scheme 3); **2**(ctc) consists of two iminoxy radicals, which are also σ radicals (Scheme 3).[19] A closed-shell singlet structure of **2**(ctc) is higher in energy than its singlet diradical structure by 22.7 kcal/mol. The spin distributions of

(5) (a) Mallory, F. B.; Manatt, S. L.; Wood, C. S. *J. Am. Chem. Soc.* **1965**, *87*, 5433. (b) Mallory, F. B.; Cammarata, A. *J. Am. Chem. Soc.* **1966**, *88*, 61. (c) Hoffmann, R.; Gleiter, R.; Mallory, F. B. *J. Am. Chem. Soc.* **1970**, *92*, 2, 1460.
(6) Pasinszki, T.; Westwood, N. P. C. *J. Phys. Chem. A* **2001**, *105*, 1244. (b) Pasinszki, T.; Westwood, N. P. C. *J. Phys. Chem. A* **1998**, *102*, 4939.
(7) However, their computed activation barrier for decomposition of furoxan to acetonitrile oxides is 51.6 kcal/mol.[6] This value is too high given the fact that thermolysis of furoxans can be used to generate nitrile oxides, which can participate in 1,3-dipolar cycloadditions with dipolarophiles. (a) Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W. *Adv. Heterocycl. Chem.* **2001**, *78*, 65. (b) Curran, D. P.; Fenk, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 5310.
(8) (a) Himmel, H.-J.; Konrad, S.; Friedrichsen, W.; Rauhut, G. *J. Phys. Chem. A* **2003**, *107*, 6731. (b) Stevens, J.; Schweizer, M.; Rauhut, G. *J. Am. Chem. Soc.* **2001**, *123*, 7326.
(9) (a) Seminario, J. M.; Concha, M. C.; Politzer, P. *J. Comput. Chem.* **1992**, *13*, 177. (b) Sedano, E.; Sarasola, C.; Ugalde, J. M.; Irazabalbeitia, I. X.; Guerrero, A. G. *J. Phys. Chem.* **1988**, *92*, 5094.
(10) Studies of tautomerization of benzofuroxans have also attracted attention. For reviews, see: (a) Boulton, A. J.; Ghosh, P. B. *Adv. Heterocycl. Chem.* **1969**, *10*, 1. (b) Gasco, A. J.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1981**, *29*, 251. (c) Katritzky, A. R.; Gordeev, M. F. *Heterocycles* **1993**, *35*, 483. For experimental researches on this field, see ref 5a and the following. (d) Bulacinski, A. B.; Scriven, E. F. V.; Suschitzky, H. *Tetrahedron Lett.* **1975**, 3577. (e) Lin, S.-K. *J. Photochem. Photobiol. A. Chem.* **1988**, *45*, 243. (f) Hacker, N. P. *J. Org. Chem.* **1991**, *56*, 5216. (g) Gallos, J. K.; Lianis, P. S.; Rodios, N. A. *J. Heterocycl. Chem.* **1994**, *31*, 481. For theoretical studies, see: (h) Ponder, M.; Fowler, J. E.; Schaefer, H. F. J., III *Org. Chem.* **1994**, *59*, 6431. (i) Friedrichsen, W. *J. Phys. Chem.* **1994**, *98*, 12933. (j) Rauhut, G. *J. Comput. Chem.* **1996**, *17*, 1848.
(11) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81, and references therein.
(12) 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.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; 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.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
(13) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37,* 785.
(14) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(15) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.
(16) (a) Yamaguchi, K.; Jensen, F.; Houk, K. N. *Chem. Phys. Lett.* **1988**, *149*, 537. (b) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036.
(17) For both the dimerization transition states and the dinitrosoalkene intermediates, three letters are used to define the relative conformation. For example, for **2**(ctc), the first and third c mean that the O3−N2−C1−C4 and O6−N5−C4−C1 are both in s-cis conformations and the middle t means that two N=O groups are trans to each other (Figure 2). This nomenclature is the same as that of Rauhut[8b] for a convenient comparison of their RB3LYP calculations with the present study.
(18) A closed-shell singlet **TS1*** can also be located, but it is higher than **TS1** by 2.5 kcal/mol in terms of ΔE_0 (before the spin-projection, **TS1*** is still higher than **TS1** by 0.7 kcal/mol in terms of ΔE_0). Compared to **TS1***, the singlet diradical **TS1** is an earlier transition state with longer C1−C4 bond length (1.957 vs 1.875 Å). The computed structure of **TS1*** is given in the Supporting Information. **TS1*** has also been located previously by Pasinszki and Westwood.[6]
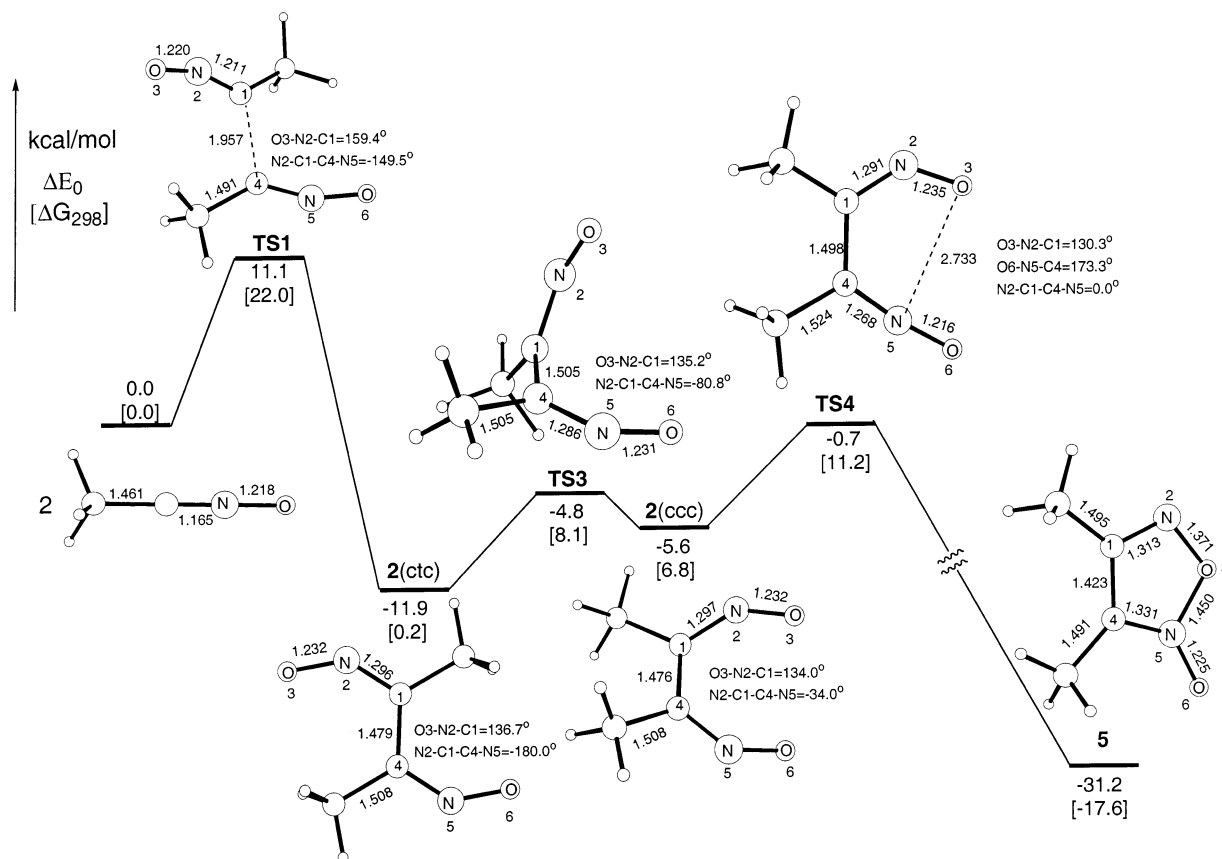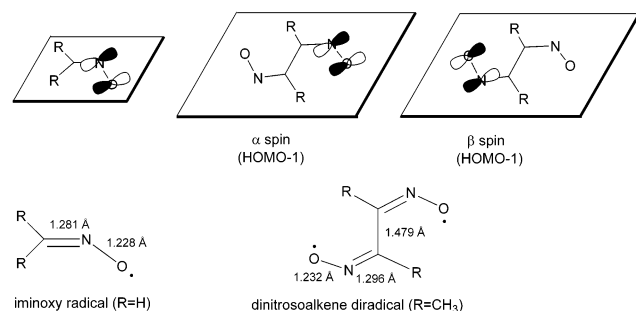
Figure 1. Potential energy surface for the dimerization of acetonitrile oxide to furoxan **5** computed by the (U)B3LYP/6-31G* method in the gas phase. Numbers in parentheses are free energies. Bond distances in Å.

Scheme 3

2(ctc) and its other conformers, some of which are slightly lower in energy, are given in Figure 2.[20−22]

To form a furoxan, the two N=O groups must rotate to the ccc conformation. This process requires only 7.1 kcal/mol. In the rotation transition state **TS3**, the dihedral angle, N2−C1−

C4−N5, is 81°. Conformer **2**(ccc) is nonplanar due to the O3−O6 repulsion. This O3−O6 repulsion also raises the energy of **2**(ccc) with respect to **2**(ctc) by 6.3 kcal/mol in terms of ΔE_0. Both **2**(ctc) and **2**(ccc) have very low-lying triplet states: their triplet states are higher in energy than their singlet states by only 1.7 kcal/mol for **2**(ctc) and 0.3 kcal/mol for **2**(ccc), respectively.[23]

Once **2**(ccc) is formed, it can be transformed to furoxan by forming either the O3−N5 or O6−N2 bonds. The located transition structure **TS4** is also a diradical species for this step. This planar transition state corresponds to the bending of the O6−N5−C4 bond and the formation of the O3−N5 bond. The transformation of **2**(ccc) to furoxan is very facile with an activation energy of 4.9 kcal/mol in the gas phase.[24]

The dimerization is very exothermic (31.2 kcal/mol) and has a rate-determining transition state, **TS1**, which is only 11.1 kcal/mol higher than the reactants. Aliphatic nitrile oxides can easily dimerize to furoxans via this diradical intermediate mechanism.

(19) For discussions of iminoxy radicals, see: (a) Thomas, J. R. *J. Am. Chem. Soc.* **1964**, *86*, 1446. (b) Bethoux, M.; Lemaire, H.; Rassat, A. *Bull. Soc. Chim. Fr.* **1964**, 1985. (c) Symons, M. C. R. *J. Chem. Soc.* **1965**, 2276. (d) Norman, R. O. C. *J. Chem. Soc. B* **1966**, 86. (e) Bordwell F. G.; Zhang, S. *J. Am. Chem. Soc.* **1995**, *117*, 4858. For DFT studies, see: (f) Jaszewski, A. R.; Jezierska, J.; Jezierski, A. *Chem. Phys. Lett.* **2000**, *319*, 611. (g) Kudoh, S.; Uechi, T.; Takayanagi, M.; Nakata, M.; Frei, H. *Chem. Phys. Lett.* **2000**, *328*, 283. (h) Uechi, T.; Kudoh, S.; Takayanagi, M.; Nakata, M. *J. Phys. Chem. A* **2002**, *106*, 3365.

(20) The computed structures of **2** are given in Figure S4 of the Supporting Information. The other conformers of singlet dinitrosoalkene reported by Rauhut and co-workers[8b] can only be located using restricted DFT instead of unrestricted DFT method. Rauhut found the most stable conformer of dinitrosoethene is in ttt conformation at the B3LYP/6-311++G** level. By using UB3LYP/6-311++G**, we found that the ctc conformer (singlet diradical) of dinitrosoethene is more stable in energy than the ttt conformer (closed-shell) by 9.9 kcal/mol (without ZPE and spin-projection corrections).

(21) Other conformers of dinitrosoethene (except its ctc and ccc conformers) have been studied by Politzer and co-workers using the MP2/6-31G* method.[9a] We think MP2 is not appropriate to study the present system. At the (U)MP2/6-31G* level, the singlet diradical dinitrosoethene in ctc conformation is higher in energy than its closed-shell ttt conformer by 29.2 kcal/mol. This energy difference is questionable because we found that the restricted and unrestricted Hartree−Fock wave functions of these two conformers are not stable.[22]

(22) Carsky, P.; Hubak, E. *Theo. Chim. Acta* **1991**, *80*, 407.

(23) The triplet and singlet diradical states have not been corrected by spin projection method. Their computed structures are given in the Supporting Information.

(24) The Hoffmann−Gleiter−Mallory[5c] suggested nonplanar transition state for furoxan opening, which is the reverse step of **2**(ccc) to furoxan **5**, can also be located at the closed-shell RB3LYP/6-31G* level. However, this transition state is less stable than **TS4** by 18.4 kcal/mol and therefore can be excluded for consideration.
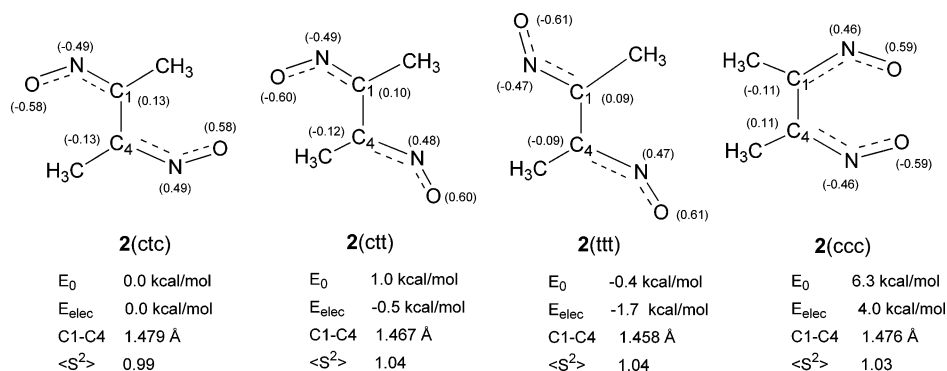
2(ctc)

E_0	0.0 kcal/mol
E_{elec}	0.0 kcal/mol
C1-C4	1.479 Å
$\langle S^2 \rangle$	0.99

2(ctt)

E_0	1.0 kcal/mol
E_{elec}	-0.5 kcal/mol
C1-C4	1.467 Å
$\langle S^2 \rangle$	1.04

2(ttt)

E_0	-0.4 kcal/mol
E_{elec}	-1.7 kcal/mol
C1-C4	1.458 Å
$\langle S^2 \rangle$	1.04

2(ccc)

E_0	6.3 kcal/mol
E_{elec}	4.0 kcal/mol
C1-C4	1.476 Å
$\langle S^2 \rangle$	1.03

Figure 2. Computed relative energies in terms of E_0 and E_{ele} (ZPE and spin projection corrections have been included in E_0 but not in E_{ele}), $\langle S^2 \rangle$ and C1−C4 distances of **2** with different conformations. The values in parentheses are computed spin densities. Structures **2**(cct) and **2**(tct) cannot be located.
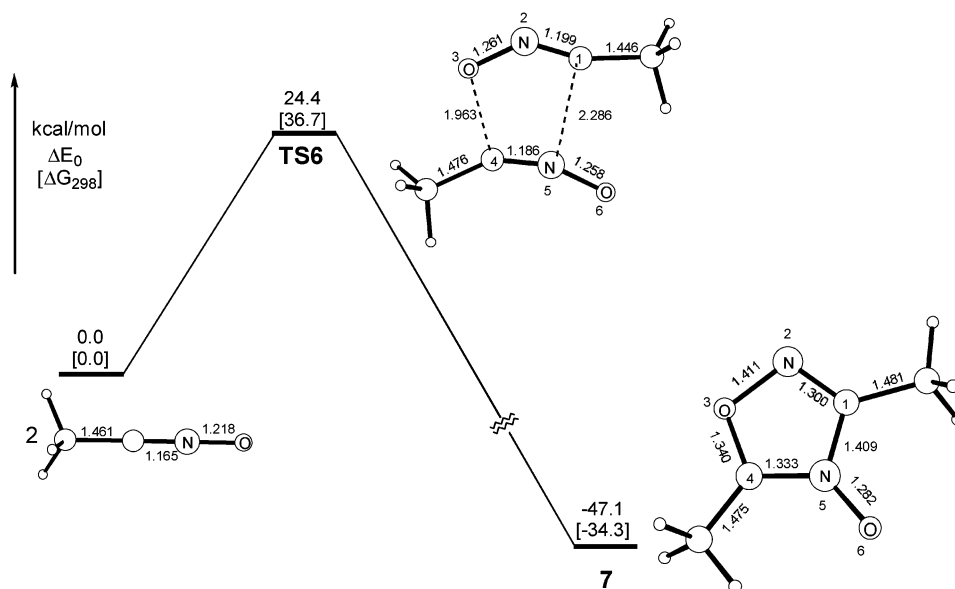

Figure 3. Dimerization process of acetonitrile oxide to 1,2,4-oxadiazole-4-oxide **7** computed by the B3LYP/6-31G* method in the gas phase.

Table 1. Energetics of Stationary Points Involved in the Dimerization of Acetonitrile Oxide to Furoxan **5** and 1,2,4-Oxadiazole-4-oxide **7** in the Gas Phase and Various Solvents[a−d]

	E_0	G_{298}	G_{CH2Cl2}	$G_{CH2ClCH2Cl}$	G_{CCl4}	G_{CH3OH}	G_{H2O}
CH₃CNO	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS1	11.1	22.0	25.7	22.9	21.4	26.3	23.9
2 (tcc)	−11.9	0.2	1.9	1.3	0.3	5.6	3.1
TS3	−4.8	8.1	10.1	9.6	7.0	13.0	10.6
2 (ccc)	−5.6	6.8	7.6	7.0	5.7	11.0	8.9
TS4[c]	−0.7	11.2	15.0	15.8	11.8	15.8	14.5
5[c]	−31.2	−17.6	−15.4	−15.6	−18.0	−14.7	−16.1
TS6	24.4	36.7	37.7	37.1	35.8	40.0	38.1
7	−47.1	−34.3	−35.1	−35.8	−32.9	−32.7	−36.9

[a] The standard states are 1 atm in the gas phase and 1 M in solution, respectively. [b] All the solvation free energies were computed by the PCM model implemented in *Gaussian 98* except for **TS4** and **5**, which were calculated by the PCM model in *Gaussian 03*, as **TS4** cannot be located by Gaussian 98. [c] The relative solvation free energies of **TS4** and **5** with respected to acetonitrile oxide were computed by the PCM model in *Gaussian 03*. [d] The computed activation free energies in solution were overestimated. After removal of the overestimation of entropy, the activation barriers were estimated to range from 18.4 to 19.5 kcal/mol.[26]

Solvent effects have been considered using the PCM model. Table 1 shows that in all solvents except CCl₄, the dimerization reaction is slower than in the gas phase. The reason for this is that the reactants are more polar than the transition state **TS1**; the dipole moment of acetonitrile oxide is 4.2 D, whereas **TS1** has a dipole moment of only 1.7 D. Table 1 shows that

dimerization in very nonpolar solvents such as CCl₄ has a lower activation barrier than for polar solvents such as methanol and water.

Figure 1 also has some implications for the long-standing debate about the tautomerization of furoxans. The above study clearly shows that tautomerization of furoxans occurs via a diradical transition state to give the dinitrosoalkene intermediate in ccc conformation, which then can be converted to a more stable ctc conformation via facile C−C bond rotation. The computed activation energy for the tautomerization in the gas phase is 30.5 kcal/mol. In solution, the activation energies (ΔE_0^+(sol)) are 32.1, 33.1, 31.5, 32.2, and 32.3 kcal/mol in dichloromethane, dichloroethane, tetrachloromethane, methanol, and water, respectively.[25] These values are very close to the activation energy of 35.3 kcal/mol found for the isomerization of ethylmethylfuroxan in tetrachloroethane by Mallory and co-workers.[5b] The present study also suggests that further study is needed to confirm the conformation of dinitrosoalkene obtained by Himmel, Rauhut, and co-workers.[8]

We have also investigated the reaction path for forming 1,2,4-oxadiazole-4-oxide from acetonitrile oxide. As shown in Figure 3, this process is concerted and has an activation energy of 24.4

(25) The activation energies in different solvents are estimated by the formula: ΔE_0^+(sol)=ΔE_0^+(gas) + $\Delta\Delta G^{\ddagger}$(sol) Here $\Delta\Delta G^{\ddagger}$(sol) is the Gibbs energy of solvation computed by the PCM method.
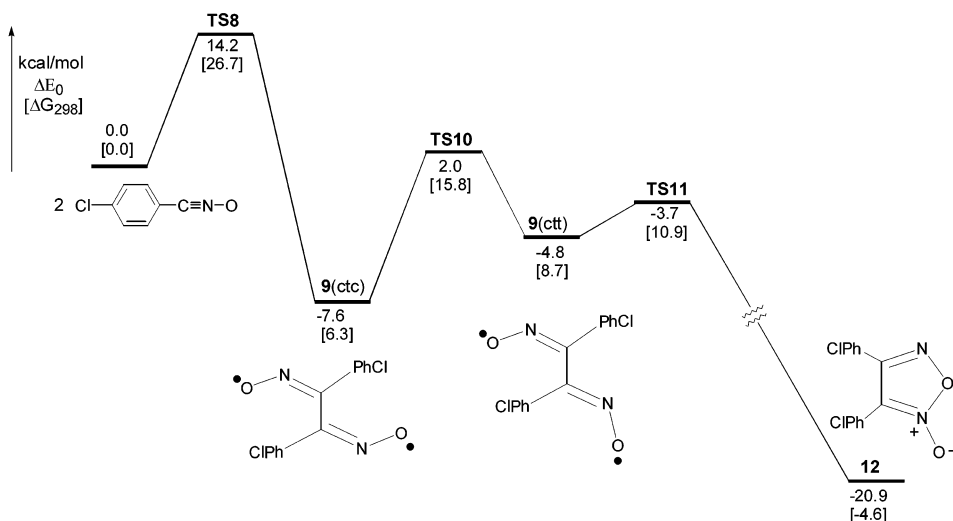
Figure 4. Potential energy surface for the dimerization of para-chlorobenzonitrile oxide to furoxan **12** computed by the (U)B3LYP/6-31G* method in the gas phase.
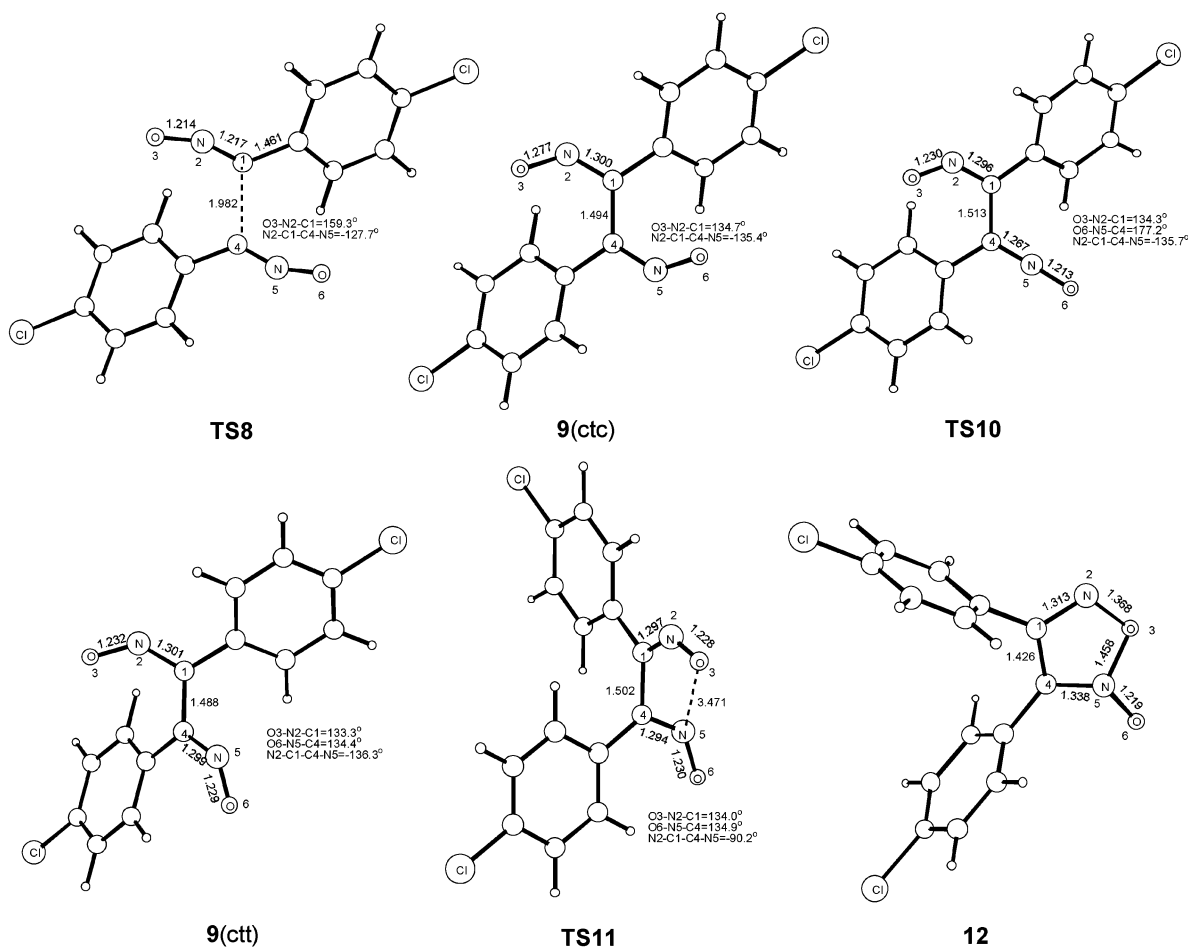

Figure 5. Computed geometries of transition states and intermediates for the dimerization of para-chlorobenzonitrile oxide to furoxan **12** computed by the (U)B3LYP/6-31G* method in the gas phase.

kcal/mol, more normal for a concerted pericyclic reaction. This is 13.3 kcal/mol higher than the activation energy for formation of furoxan that involves the relatively stable diradical intermediate. Comparison of Figures 1 and 3 shows the dimerization to furoxan is kinetically but not thermodynamically favored, because the formation of 1,2,4-oxadiazole-4-oxide is more exothermic by 15.9 kcal/mol than the formation of furoxan. The

lower stability of furoxan than 1,2,4-oxadiazole-4-oxide is probably due to its weak O3−N5 bond, as manifested by its long bond length (1.450 Å) and small bond order (0.8) (see Figures 1 and S3 (bond orders) in the Supporting Information).

3.2. Dimerization of Para-Chlorobenzonitrile Oxide. To investigate whether aromatic nitrile oxides dimerize to furoxans in the same way as aliphatic nitrile oxides, and to determine

why aromatic nitrile oxides are usually less reactive than the aliphatic nitrile oxides in this process, we have computed the potential energy surface for the dimerization of para-chlorobenzonitrile oxide. Figure 4 shows the energetics of this process in the gas phase. The computed transition states and intermediates are given in Figure 5. The formation of furoxan is again stepwise involving a diradical intermediate. The rate-determining step is the first transition state **TS8**, which is higher in energy than the reactants by 14.2 kcal/mol in the gas phase. The activation energy for this reaction is 3.1 kcal/mol greater than the dimerization of acetonitrile oxide. The higher barrier for the dimerization of aromatic nitrile oxides is attributed to the reduction of the conjugation between phenyl group and the CNO group of the nitrile oxide in **TS8.** The first step of the dimerization results in the formation of diradical intermediate **9** in the ctc conformation. It is expected that **9**(ctc) can be easily transformed to another conformer **9**(ccc) via rotation because **9**(ccc) is only 2.9 kcal/mol higher in energy than **9**(ctc). However, to form furoxan, **9**(ctc) first undergoes O6−N5−C4 bending via transition structure **TS10** to generate **9**(ctt), which has its O6−N5 bond trans to the C4−C1 bond. The final step to close the ring is through **TS11** and requires only 1.1 kcal/mol. **TS11** has the two C−N−O fragments approximately perpendicular to each other. The transition structure **TS11** resembles a rotation transition state to transform **9**(ctt) to **9**(cct) conformer. Actually, the process of **9**(ctt) to furoxan **12** occurs first via rotation via **TS11** to form **9**(cct), which is not a minimum and will directly collapse to the final product. The dimerization process is exothermic by 20.9 kcal/mol in the gas phase.

The solvent effects on the reaction rates have been investigated by computing the relative energies of rate-determining **TS8** with respect to two para-chlorobenzonitrile oxides in various solvents. As with acetonitrile oxide, the dimerization of the aromatic nitrile oxide is also slower in solution than in the gas phase. The computed activation energies in CH_2Cl_2, CH_2ClCH_2Cl, CCl_4, CH_3OH, and H_2O are 19.0, 18.3, 17.0, 17.6, and 17.7 kcal/mol, respectively.[25] These barriers range from 17.0 to 19.0 kcal/mol, very close to the values (16.0 to 18.1 kcal/

mol) obtained experimentally,[4] suggesting the present B3LYP method is alike to reproduce this reaction adequately.

4. Conclusions

The dimerizations of aliphatic and aromatic nitrile oxide to form furoxans are stepwise via diradical intermediates.[28] The rate-determining step corresponds to the bond formation between two carbenoid carbons of nitrile oxides. The intermediates formed are dinitrosoalkenes, which are diradicals. These diradical intermediates are formed first in the trans conformation. The formation of furoxan is a kinetically favored process compared to the formation of 1,2,4-oxadiazole-4-oxides. The reluctance of aromatic nitrile oxides to dimerize with respect to aliphatic nitrile oxides is attributed to conjugative stabilization of the former. The dimerization processes in solution are slower than in the gas phase, and polar solvents retard the reaction rates.

Supporting Information Available: The computed structures and energies for the reactant, intermediates and transitions states are available. This material is available free of charge via the Internet at http://pubs.acs.org.

JA037325A

(26) The computed entropy contribution for a bimolecular reaction in solvent is sometimes overestimated by the procedure used here. For example, it was found that the entropy contribution in aqueous solution for bimolecular reaction is found to be overestimated by 50−70%.[27] The computed activation energy of dimerization of para-chlorobenzonitrile in the gas phase is 3.1 kcal/mol higher than that required for dimerization of acetonitrile oxide (14.2 vs 11.1 kcal/mol). Therefore, the activation free energies for CH_3CNO is also approximately 3.1 kcal/mol lower than that of para-chlorobenzonitrile, which has activation free energies 21.5−22.6 kcal/mol in various solvents,[4] on the range of 18.4 and 19.5 kcal/mol.

(27) For discussions of entropy overestimation in bimolecular reactions in aqueous solution, see: (a) Strajbl, M.; Sham, Y. Y.; Villa, J. V.; Chu, Y. Y.; Warshel, A. *J. Phys. Chem. B* **2000**, *104*, 4578. (b) Hermans, J.; Wang, L. *J. Am. Chem. Soc.* **1997**, *119*, 2707. (c) Amzel, L. M. *Proteins* **1997**, *28*, 144.

(28) The diradical carbene mechanism of nitrile oxides has also been found in the intramolecular 1,3-dipolar ene reactions between nitrile oxides and alkenes, see: Yu, Z.-X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 13825.