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## Structural Study of 3,4-Bis(2-chlorophenyl)furazan *N*-Oxide and Speculation on the Fragmentation<sup>†</sup>

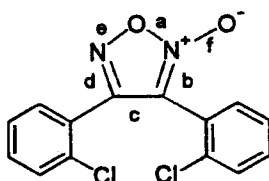
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The reactions for nitric oxide (NO) generation have been explored in regard to some biological activities: tumoricidal and bactericidal activities by macrophage,<sup>1</sup> a mediator of blood vessel relaxation,<sup>2</sup> and a signal transducing agent in neurotransmission in the brain.<sup>3</sup> In an effort of seeking NO precursors, several 3,4-disubstituted furazan *N*-oxides (furoxans) were prepared and confirmed to give nitric oxide by the fragmentations in mass spectrometer.<sup>4</sup> However, the high energy involved in electron-impacted fragmentation of a furoxan limited its application as a probe for NO-related physiology or a potential pharmaceutical agent for NO involved diseases. In an effort to release of NO by the fragmentation using relatively low energy, we have interested in the structure related fragmentation of the furoxan. Therefore, we studied carefully structural data of some furoxan derivatives. Here, we would like to report an X-ray crystal structure of 3,4-bis(2-chlorophenyl)furoxan (DCF, 1), and any implication from the structure.



Structure 1

### Experimental

**Preparation and Measurements.** DCF was prepared as reported previously.<sup>4</sup> 2-Chlorophenyl nitrile oxide was dimerized after *in situ* generation by the reaction of the corresponding *N*-hydroxyiminoyl chloride with Et<sub>3</sub>N. It was recrystallized in hexane-EtOAc and confirmed by <sup>13</sup>C NMR (CDCl<sub>3</sub>), IR (KBr pellet), and elemental analysis. A Enraf-

Nonius CAD4/Turbo diffractometer equipped with a rotating anode generator and a graphite monochromator was used for preliminary experiments and for the subsequent collection of diffraction intensities, all at 294(1) K (Kyungpook National University). Preliminary experiment for the cell parameters and orientation matrix was carried out by least-squares methods, using the setting angles of 25 centered reflections. The structure was refined by full-matrix least-squares procedures. Crystal parameters and procedural information are in the Table 1. Final atomic coordinates and isotropic thermal parameters are given in Supplementary Material. The molecular structure of DCF is shown in Figure 1. Bond distances and angles are given in Table 2.

### Results and Discussion

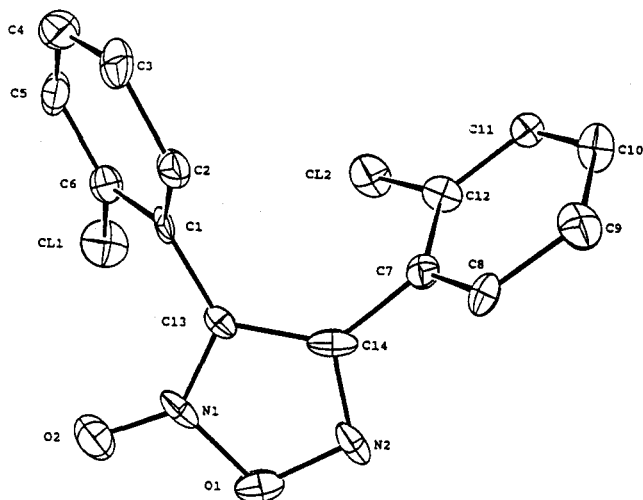
Some comparisons between the bond distances of DCF and those of other furazan *N*-oxide derivatives are made as shown in Table 3. The O(1)-N(1) bond distance (1.44(2) Å) of DCF is similar to those of other derivatives, suggesting a more or less single bond character,<sup>5</sup> while the O(1)-N(2) bond distance (1.34(2) Å) is somewhat shorter than the corresponding bonds (1.367-1.406 Å) of other derivatives. The O(1)-N(1) bond (a in Table 3) is longer than the O(1)-N(2) bond (e). The difference between bonds a and e of DCF is approximately 0.10 Å, which is larger than those (0.010-0.077 Å) in most of other derivatives except in 3-Me-4-NO<sub>2</sub> furoxan. This fact may support that the bond a of DCF is more labile than the bond e (*vide infra*). The C(1)-C(2) bond distance (c, 1.44(2) Å) in DCF is somewhat longer than other furoxans except in 3-Br-4-adamantyl derivative (see Table 3). Since much of generalization with induction effect cannot be made,<sup>6</sup> this fact may be due to the steric hindrance. The N(1)-C(1) (b) and N(2)-C(2) (d) bond distances in DCF are 1.29(2) and 1.35(2) Å, respectively. This

**Table 1.** Summary of crystallographic data and intensity collection for DCF (1)

Empirical formula	Cl <sub>2</sub> O <sub>2</sub> N <sub>2</sub> C <sub>14</sub> H <sub>10</sub>
Fw	309.15
Crystal system	orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub> (#19)
Z	4
Cell parameters	
a (Å)	7.201(4)
b (Å)	12.280(7)
c (Å)	15.178(5)
V (Å <sup>3</sup> )	1342(8)
Dcalc. (g/cm <sup>3</sup> )	1.520
μ (cm <sup>-1</sup> with Mo-Kα)	4.8
Transmission factor	0.79-1.00
Scan type	ω-2θ
Scan width (ϖ) (deg)	3.02+1.24tan (θ)
2(θ) <sub>max</sub> (deg)	60.88
No. of reflections measured	2596
No. of reflections observed (I>3σ(I))	762
F(000)	632
No. of variables	181
Discrepancy indices	
R <sup>a</sup>	0.0734
R <sub>w</sub> <sup>b</sup>	0.0775
Goodness of fit indicator <sup>c</sup>	2.43
Maximum shift in final cycles	less than 0.01

<sup>a</sup>  $R = \sum |F_o| - |F_c| / \sum |F_o|$ . <sup>b</sup>  $R_w = [(\sum W(|F_o| - |F_c|)^2) / \sum W(F_o^2)]^{1/2}$ , where  $w = 4F_o^2 / \sum^2(F_o^2)$ . <sup>c</sup> Standard deviation of an observation of unit weight:  $[(\sum W(|F_o| - |F_c|)^2) / (N_o - N_v)]^{1/2}$ , where  $N_o$  = number of observations and  $N_v$  = number of variables.

result (**b**<**d**) is opposite to the MNDO calculation (**b**=1.397, **d**=1.350 Å).<sup>4</sup> In most of other derivatives except 3-Br-4-adamantyl, the bond **b** is longer than the bond **d** (**b**≥**d**). The extracyclic N(1)-O(2) bond (**f**, 1.21(2) Å) in DCF is much shorter than the intracyclic N(1)-O(1) (**a**, 1.44(2) Å) and N(2)-O(1) (**e**, 1.34(2) Å) bonds suggesting a double bond

**Figure 1.** An ORTEP plot of 3,4-bis(2-chlorophenyl)furan *N*-oxide (DCF, 1) with the atomic numbering scheme.**Table 2.** Bond distances (Å) and bond angles (deg) in DCF (1)<sup>a</sup>

O(1)-N(1)	1.44(2)	N(1)-C(1)	1.29(2)	C(1)-C(2)	1.44(2)
O(1)-N(2)	1.34(2)	N(2)-C(2)	1.35(2)	O(2)-N(1)	1.21(2)
C(1)-C(3)	1.45(2)	C(3)-C(4)	1.40(2)	C(4)-C(5)	1.38(2)
C(5)-C(6)	1.41(3)	C(6)-C(7)	1.36(2)	C(7)-C(8)	1.44(3)
C(3)-C(8)	1.44(2)	C(2)-C(9)	1.50(2)	C(9)-C(10)	1.37(2)
C(10)-C(11)	1.41(2)	C(11)-C(12)	1.44(3)	C(12)-C(13)	1.35(2)
C(13)-C(14)	1.44(2)	C(9)-C(14)	1.37(2)	Cl(1)-C(4)	1.70(2)
Cl(2)-C(10)	1.68(2)				
Bond angles (deg)					
O(1)-N(1)-C(1)	109.0(1)	N(1)-C(1)-C(2)	106.0(2)		
C(1)-C(2)-N(2)	111.0(2)	C(2)-N(2)-O(1)	106.0(1)		
N(1)-O(1)-N(2)	109.0(1)	O(1)-N(1)-O(2)	117.0(2)		
O(2)-N(1)-C(1)	135.0(2)	N(1)-C(1)-C(3)	125.0(2)		
C(2)-C(1)-C(3)	129.0(1)	C(1)-C(2)-C(9)	130.0(1)		
N(2)-C(2)-C(9)	119.0(2)	C(1)-C(3)-C(4)	122.0(2)		
C(1)-C(3)-C(8)	117.0(2)	C(4)-C(3)-C(8)	121.0(1)		
C(3)-C(4)-C(5)	121.0(2)	C(4)-C(5)-C(6)	120.0(2)		
C(5)-C(6)-C(7)	120.0(2)	C(6)-C(7)-C(8)	122.0(2)		
C(7)-C(8)-C(3)	116.0(2)	C(2)-C(9)-C(10)	120.0(1)		
C(2)-C(9)-C(14)	115.0(1)	C(9)-C(10)-C(11)	121.0(1)		
C(10)-C(11)-C(12)	115.0(1)	C(11)-C(12)-C(13)	123.0(2)		
C(12)-C(13)-C(14)	120.0(2)	C(13)-C(14)-C(9)	116.0(1)		
C(14)-C(9)-C(10)	124.0(2)	Cl(1)-C(4)-C(3)	120.0(1)		
Cl(1)-C(4)-C(5)	119.0(2)	Cl(2)-C(10)-C(9)	122.0(1)		
Cl(2)-C(10)-C(11)	117.0(1)				

<sup>a</sup>The numbers in parentheses are the estimated standard deviations in the units of the least significant digit given for the corresponding parameters.

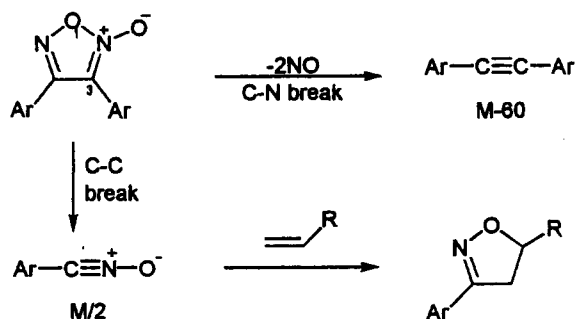
character of the bond **f**. In addition, the C-C bonds in phenyl ring are a little bit longer (1.36(2)-1.44(3) Å) than those of 3-Cl-4-phenyl derivative (1.362(4)-1.390(4) Å).<sup>7</sup> This indicates some localization of the π-electrons on the phenyl ring. It is notable that in most furoxans the C(1)-C(2)-N(2) angle, which is farther from the extracyclic N-O bond, is much larger than the C(2)-C(1)-N(1) angle, closer to the extracyclic N-O bond. This fact is true even for the furoxan with no substituent.<sup>5</sup>

As seen in Figure 1, the furazan and the phenyl rings are

**Table 3.** Bond distances (Å) of 3,4-substituted furazan *N*-oxide derivatives

	<b>a</b> <sup>i</sup>	<b>b</b>	<b>c</b>	<b>d</b>	<b>e</b>	<b>f</b>	ref
3-Me-4-NO <sub>2</sub>	1.479	1.332	1.401	1.288	1.367	1.220	13
3-NO <sub>2</sub> -4-Ph	1.440	1.316	1.410	1.314	1.386	1.204	14
3-Ph	1.439	1.318	1.417	1.289	1.369	1.239	15
3-Ph-4-Cl	1.452	1.326	1.420	1.301	1.375	1.219	7
3-Cl-4-Ph	1.433	1.317	1.413	1.307	1.384	1.229	7
3-Me-4-NH <sub>2</sub> <sup>ii</sup>	1.416 (0.918)	1.310 (1.469)	1.426 (1.031)	1.306 (1.561)	1.406 (0.974)	1.249 (1.286)	5
3-Br-4-adamantyl	1.45	1.31	1.43	1.32	1.40	1.21	6
3,4-bis-(2'-ClPh)	1.44(2)	1.29(2)	1.44(2)	1.35(2)	1.34(2)	1.21(2)	this work

<sup>i</sup>Bonds as labeled in DCF structure (1). <sup>ii</sup>Bond order values in parentheses are calculated by *ab initio* and MNDO/3.



Scheme 1.

not coplanar as in mono-phenyl derivatives of furoxan.<sup>5,7</sup> Two chlorine atoms on the phenyl rings of DCF are placed in the same side with respect to the furazan ring (aparted +2.27 and +2.33 Å for Cl1 and Cl2 atoms, respectively, from the least-squares plane of the furazan ring). Apparently, there is no intramolecular or intermolecular reinforcement causing the two bulky chlorine atoms to face in: because it is hard to believe that the solvent hexane-EtOAc influenced the molecular orientation during crystallization. This fact could imply a mechanistic threshold on the dimerization of 2-chlorophenyl nitrile oxide via [3+2] cycloaddition. 3,4-Diphenyl furoxan has been reported to be cleaved thermally into phenyl nitrile oxide: 1,3-dipolar cycloreversion,<sup>8</sup> *i.e.* [5 → 3+2]. Applying the similar reasoning to the reverse reaction, *i.e.* dimerization the 2-chlorophenyl nitrile oxide, two chlorine atoms might face in each other at the end of the concerted cycloaddition.

The fragmentation of the furoxan might be dependent on its structure: the furoxan containing a strained furazan ring by bulky substituents at 3-, or 4-positions assumably results in facile fragmentation. Without any dipolarophile, the furoxan can be fragmented to the corresponding nitrile oxide (cycloreversion)<sup>9</sup> or nitric oxide (NO generation)<sup>4</sup> by the cleavage of a C-C bond or a C-N bond, respectively (Scheme 1). The thermal cleavage of the furoxan in the presence of an alkene as a dipolarophile generates isoxazoline at the temperature over 200 °C.<sup>10</sup> This reaction was proved by <sup>13</sup>C nmr to be proceeded via nitrile oxide in the flash vacuum pyrolysis (FVP, 500 °C, 10<sup>-3</sup> mmHg).<sup>9</sup> The 3, 4-diphenyl furoxan in EI mass spectrometer underwent fragmentation at 70 eV to give the (M-60) and (M/2) peaks with the relative intensities 41 and 100, respectively.<sup>11,12</sup> DCF also fragmented into NO and bis(2-chlorophenyl) acetylene in mass spectrometer at 20 eV giving the same peaks with the relative intensities 100 and 2, respectively.<sup>4</sup> At this point, the guide line for the selection of a cleavage pathway is not clear. However, the different peak ratios of the fragments in mass spectra for DCF and other furoxan derivatives suggest that the cleavage pathways are dependent on the substituents at 3- and 4-positions. Therefore, the structural variation arising from bulky substituents could

be a route to the stimulation of NO generation by the relatively low energy.

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## References

<sup>†</sup>This paper is dedicated to the 60th birthday of Professor Sang Chul Shim at KAIST

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