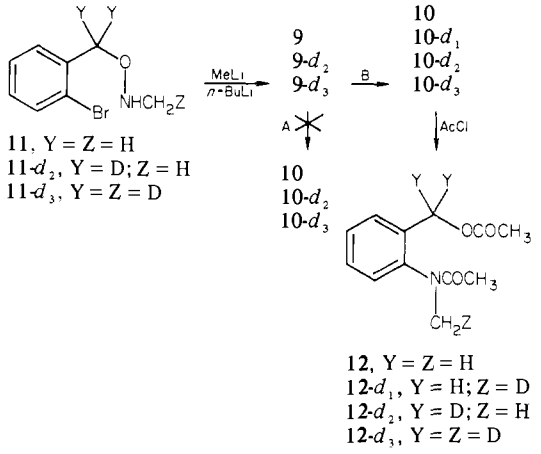
Scheme III



11, Y = Z = H
11-d_2, Y = D; Z = H
11-d_3, Y = Z = D

9
9-d_2
9-d_3

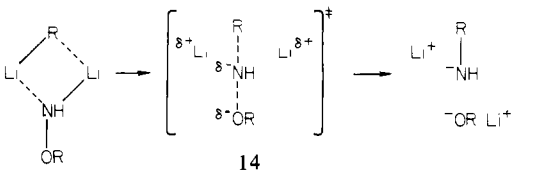
10
10-d_1
10-d_2
10-d_3

12, Y = Z = H
12-d_1, Y = H; Z = D
12-d_2, Y = D; Z = H
12-d_3, Y = Z = D

A distinction between possibilities A and B in Scheme I may be made on the basis of differences expected for each path in the conversion of **9** to **10** in Scheme II. The nitrenoid reaction of A would be expected to proceed without rigid geometrical requirement and should occur intramolecularly. Our earlier work on the conversion of *N*-(2-(2-bromophenyl)ethyl)methoxyamine to *N*-acetylindoline shows that intramolecular reaction is possible in an exocyclic mode.[2b,8] If the conversion of **9** to **10** proceeds by the direct displacement of path B a transition state in which the entering and leaving groups would be at 180° would be expected. That reaction would be of prohibitively high energy in the endocyclic mode in a five-membered ring, and an intermolecular reaction would be observed.[4-6]

The reaction of **11** to give **12** proceeds in 13% yield presumably via **9** and **10**.[9] The distinction between the intramolecular and intermolecular possibilities can be made by the double-labeling experiment shown in Scheme III. Thus a 51:18:31 mixture of **9**, **9**-d_2, and **9**-d_3 was generated from a 51:18:31 mixture of **11**, **11**-d_2, and **11**-d_3.[9] An intramolecular reaction would give **10**, **10**-d_2, and **10**-d_3 and subsequently **12**, **12**-d_2, and **12**-d_3 in a 51:18:31 ratio. Intermolecular reaction would give **10**, **10**-d_1, **10**-d_2, and **10**-d_3 and subsequently **12**, **12**-d_1, **12**-d_2, and 12-d_3 in a 35:16:33:15 ratio. The ratio of **12**, **12**-d_1, **12**-d_2, and **12**-d_3 obtained is 35 (±5):18 (±5):30 (±5):17 (±5) in accord with path B.[9] These observations may be taken to suggest that displacement of the alkoxy group requires bond angles that are characteristic of a concerted bimolecular substitution on a first-row element.[4-6,10]

Formally the displacement process of path B involves reaction of two anionic species, an interaction that should be repulsive.[11] However, organolithiums are generally aggregated, and a reasonable pathway involving associated species can be envisioned. In the simplest case, a dimer **13** in which the entering carbon is disposed on the back side of the nitrogen and the nitrogen oxygen bond is polarized, leading to transition state **14**, can be suggested.



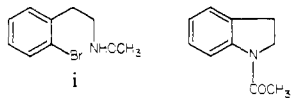
13 14

This appears to be another case in which a proximity effect operating in a lithium complex provides access to a novel reaction pathway.[12] The implication of these results, that other nucleophilic reactions may take place via formal dianions and that the geometry of nucleophilic substitutions at heteroatoms can be established by this approach, are under study.

Acknowledgment. We are grateful to the National Science Foundation and the National Institute of Health for support of this work.

Registry No. 11, 88703-76-8; **12**, 88703-77-9.

(8) The yield of ii from i for material that is spectroscopically uncontaminated is 78%, but losses on purification provide 42% of analytically pure



i ii

ii. The expected products of intermolecular reaction of i are not observed.

(9) The alkoxyamine **11** was prepared from *o*-bromobenzyl alcohol by the sequence of (1) hydroxyphthalamide, triphenylphosphine, and diethylazidodicarboxylete (65%), (2) hydrazine (98%), and (3) formaldehyde and pyridine–borane (66%). The structure of **12** was verified by independent synthesis from *o*-aminobenzyl alcohol by treatment with (1) acetyl chloride (56%) and (2) methyl iodide (35%). The intermediates were characterized by ^{1}H NMR, IR, and analysis, and **11** and **12** were characterized also by mass spectrometry. Deutrated **11** was prepared by reduction of *o*-bromobenzoic acid with lithium aluminum deuteride and by the use of pyridine–borane-d_3 in the third step of the synthesis of **11**. The deuterium composition of labeled reactants and products were determined by mass spectrometry. Details are available: Kokko, B. J. Ph. D. Thesis, University of Illinois, 1983, University Microfilms, Ann Arbor, Michigan.

(10) In the reaction via path B the loss of $LiNCH_3$ presumably occurs to provide **10**. The low yield of **12**, which may reflect the difficulty of amination ortho to a bulky group on an aromatic ring as well as the incursion of side reactions, does not compromise the mechanistic conclusions. Reaction via path A might be expected to produce methylnitrene, which would rearrange to methylene imine. Reactions of *N*-methylmethoxyamine give only methylamine products.[2b]

(11) It should be noted however, that M. Anbar and G. Yagel (Anbar, M.; Yagel, G. *J. Am. Chem. Soc.* **1982**, *84*, 1790) have reported a direct nucleophilic displacement on the chloramine anion.

(12) For diverse examples, see: Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350. Meyers, A. I.; Pansgrau, P. D. *Tetrahedron Lett.* **1983**, 4935. Comins, D.; Brown, J. D. *Ibid.* **1983**, 5465. Richey, H. G.; Heyn, A. S.; Erickson, W. F. *J. Org. Chem.* **1983**, *48*, 3821 and references cited therein.

Homo-Diels–Alder Reaction of Tricyclo[5.3.1.0^{4,9}]undeca-2,5-diene: A Molecule with Unusually Strong Through-Space Interaction in a 1,4-Cyclooctadiene System

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The [2 + 2 + 2] cycloaddition of a 1,4-diene with a dienophile is a symmetry-allowed reaction[2] and has been known as the homo-Diels–Alder reaction for 25 years.[3] In contrast with the Diels–Alder reaction where a large variety of 1,3-diene systems

(1) Hokkaido University Postdoctoral Fellow.

(2) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, 1970; pp 101.

(3) Recent leading references on this subject: (a) Fickes, G. N.; Metz, T. E. *J. Org. Chem.* **1978**, *43*, 4057–4061 and references cited therein. (b) Jenner, G.; Papadopoulos, M. *Tetrahedron Lett.* **1982**, *23*, 4333–4336.

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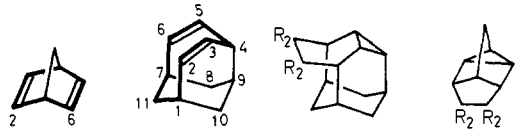
Table I. Kinetic Data for the Reactions 1 + TCNE and 2 + TCNE[a]

temp, °C	10^3k_2, L mol^{-1} s^{-1} [b]	
	1 + TCNE	2 + TCNE
90.0	2.24 ± 0.19	3.17 ± 0.12
80.0	1.57 ± 0.05	2.71 ± 0.06
70.0	0.58 ± 0.04	2.35 ± 0.06
40.0[c]	0.056[c] (lit.[d] 0.089)	
$\Delta H^{\ddagger}$, kcal mol^{-1}	16.6 ± 1.5	3.0 ± 0.2
$\Delta S^{\ddagger}$, eu	−24.9 ± 0.3	−62.1 ± 0.1

[a] Determined with ^{1}H NMR in C_6D_6. [b] Average of two or three separate runs. [c] Extrapolated from higher temperatures. [d] Reference 3b.

have been available, 1,4-dienes that undergo the homo-Diels–Alder reaction require the strict geometrical arrangement of the two double bonds, the through-space interaction between the two double bonds being primarily responsible for the homo-Diels–Alder reactivity.[3] As a matter of fact, the use of 1,4-dienes has been limited to mainly bridged 1,4-cyclohexadiene derivatives.[3,4] Among them, norbornadiene (**1**) has been the most reactive and almost exclusive 1,4-diene system used in this reaction and, therefore, the two *parallel* double bonds of **1** have been considered to adopt the optimum geometry for the through-space interaction.[3-6] We wish to report here that tricyclo[5.3.1.0^{4,9}]undeca-2,5-diene (**2**),[7] which contains a partial *1,4-cyclooctadiene* moiety



1 **2** **3** **4**

constrained in the cage system, undergoes homo-Diels–Alder reaction with tetracyanoethene (TCNE) faster than **1**. To our knowledge, **2** is the first example of a 1,4-cyclooctadiene as the homo-Diels–Alder partner.

When a 2:1 mixture of **2** and TCNE in benzene was heated to reflux for 1 h, a homo-Diels–Alder adduct (**3a**, R = CN, 6,6,7,7-tetracyanopentacyclo[7.3.1.0^{2,4}.0^{3,8}.0^{5,11}]tridecane, mp 254–256 °C) was obtained *in quantitative yield*.[8,9] The structure of **3a** was determined by the use of spectroscopic as well as elemental analysis. The ^{1}H NMR showed no olefinic proton, and the ^{13}C NMR [113.4 (s), 111.6 (s), 41.9 (s), 40.9 (d), 31.6 (t), 29.4 (t), 27.3 (d), 19.7 (d), 17.3 (d), 6.8 (d) ppm] was especially informative on the C_s symmetry and the presence of a cyclopropane ring.

The unexpectedly facile homo-Diels–Alder reaction of **2** with TCNE prompted us to compare the second-order rate constant (k_2) and kinetic parameters of **2** with those of **1** (Table I). The rate constants for **2** are always larger than those for **1** for the temperature range studied.[10] The activation enthalpy for **2** (3 kcal/mol) is much smaller than that for **1** (17 kcal/mol). This very low activation enthalpy for **2** is partly compensated by the extremely large negative activation entropy (-62 eu), indicating a tighter transition-state structure for this reaction than that for **1**.[11,12]

As mentioned above, the optimum geometry for the through-space interaction is suggested to be realized in **1**, where the two double bonds are *parallel* to each other. In contrast with **1**, the two double bonds of **2** are *not parallel*. While the molecular structure of **2** has not been determined experimentally, we resorted to two computational methods, MM2[13] and ab initio STO-3G[14] calculations. In the optimized geometry of **2**, the C3--C5 distance is 2.40 (STO-3G) and 2.32 (MM2) Å. For **1**, the C2--C6 distance is 2.47 (STO-3G), 2.40 (MM2), and 2.46 (electron diffraction)[15] Å. Hence both computational methods estimate the C3--C5 distance of **2** to be shorter by 0.07 Å than the C2--C6 distance of **1**. This estimation was supported by a large separation of 1.05 eV between the first (8.40 eV) and second (9.45 eV) ionization potentials in the photoelectron spectrum of **2**. The corresponding separation in **1** is 0.85 eV.[16]

The distance between the other ends of double bonds in **2** (C2--C6) was calculated to be 3.54 (STO-3G) and 3.38 (MM2) Å. Such a large distance may appear disadvantageous in view of Scharf's "1,4-distance" theory, which states that the most important factor in the Diels–Alder reaction of s-cis fixed 1,3-dienes is the shortest possible 1,4-distance.[17] However, the double-bond planes in **2** are not parallel, and the actual "end-to-end distance" between the endo lobes of p orbitals at C2 and C6 should be smaller than the internuclear distance. Further inspection of the optimized geometry suggests that endo p-orbital lobes at C2 and C6 of **2** are significantly inclined toward each other, and hence their interactions with the incoming dienophile starts at an early point along the reaction coordinate.[18]

In summary, we have demonstrated the first example of the homo-Diels–Alder reaction of a 1,4-cyclooctadiene system. Experimental and computational results suggest that the high reactivity of **2** is to be attributed to the strong through-space interaction of the p orbitals at the closer ends (C3 and C5) as well as the very favorable overlap of those at the wider ends (C2 and C6) with the dienophile. This suggestion implies that the close proximity at the *both* ends of the two double bonds in **1** is not necessarily required for a 1,4-diene to undergo the homo-Diels–Alder reaction efficiently. Thus, the present results appear to expand the scope of the homo-Diels–Alder reaction.[3a]

Acknowledgment. This work is supported in part by a Grant-in-Aid for Scientific Research (No. 58470073 to M.K. and No. 58045001 to E.Ō.). E.Ō. also thanks Kureha Chemical Ind. Co. for partial financial support. Calculations have been carried

(4) Recently, bicyclo[3.2.1]octa-2,6-diene has been reported to undergo competitive dipolar and homo-Diels–Alder cycloaddition. (a) Adam, W.; De Lucchi, O.; Peters, K.; Peters, E.; Schnering, H. G. *J. Am. Chem. Soc.* **1982**, *104*, 161–166. (b) Erden, I. *Tetrahedron Lett.* **1983**, *24*, 2047–2050.

(5) Goldstein, M. J.; Natowsky, S.; Heilbronner, E.; Hornung, V. *Helv. Chim. Acta* **1973**, *56*, 294–301.

(6) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1–9.

(7) (a) Katsushima, T.; Yamaguchi, R.; Kawanisi, M. *J. Chem. Soc., Chem. Commun.* **1975**, 692–693; (b) *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3245–3247. (c) Katsushima, T.; Maki, K.; Yamaguchi, R.; Kawanisi, M. *Ibid.* **1980**, *53*, 2031–2035.

(8) Maleic anhydride and dimethyl acetylenedicarboxylate gave the corresponding 1:1 homo-Diels–Alder adducts (**3b** and **3c**) with **2** in 81% and 22% yields, respectively.

(9) The reaction of **2** with TCNE in benzene and acetonitrile at 40 °C for 0.5 h gave **3** in 63% and 64% yields, respectively, indicating no influence of the solvent polarity on the cycloaddition.

(10) A competitive reaction of **1** and **2** with TCNE (**1**:**2**:TCNE = 1:1:1) at 50 °C for 1h gave **3** (R = CN) and **4** (R = CN) in a ratio of 85:15, showing qualitatively the faster reaction of **2** than that of **1** with TCNE.

(11) One of the referees suggested a possibility of electron-transfer mechanism for the reaction of **2** with TCNE because of the very low $\Delta H^{\ddagger}$ value and the very large negative $\Delta S^{\ddagger}$ value. While at the present time we have no other experimental evidence to indicate this mechanism, further investigation on this point seems worthwhile to be pursured (cf.: Hall, J. H.; Jones, M. L. *J. Org. Chem.* **1983**, *48*, 822–826).

(12) According to MM2 calculations,[13] the increase in strain in going from **1** to the corresponding adduct (**4**, R = H) is 20 .4 kcal/mol, whereas that between **2** and **3** (R = H) is 31.2 kcal/mol. Hence the latter reaction is less favorable than the former in terms of the strain change.

(13) (a) Allinger, N. L.; Yuh, Y. H. *QCPE* **1981**, *13*, 395. (b) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.

(14) (a) IMSPAK by K. Morokuma, S. Kato, K. Kitaura, I. Omine, S. Sasaki, and S. Obara. (b) GAUSSIAN80 (IBM version): Altona, C. *QCPE* **1980**, *15*, 437.

(15) Calculated on the basis of the structure of **1** given by electron diffraction: Yokozeki, A.; Kuchitsu, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2356–2363.

(16) Bischof, P.; Hashmall, J. A.; Heilbronner, E.; Hornung, V. *Helv. Chim. Acta* **1969**, *52*, 1745–1749.

(17) Scharf, H.-D.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* **1979**, *112*, 862–882.

(18) Both MM2 and STO-3G calculations agree that the double bonds of **2** are twisted and further deformed out-of-plane albeit to a small extent. According to perturbational molecular orbital calculations (Wipff, G.; Morokuma, K. *Tetrahedron Lett.* **1980**, *21*, 4445–4448), a small out-of-plane deformation greatly affects the reactivity of the double bond.

out at the Computing Centers of Hokkaido University and the Institute for Molecular Science. Thanks are also due to Dr. S. Kozima for his suggestion in the rate measurement.

Registry No. 1, 121-46-0; **2**, 58008-61-0; **3a**, 88686-24-2; **3b**, 88686-25-3; **3c**, 88686-26-4; TCNE, 670-54-2.

Supplementary Material Available: Physical and spectral data of the adducts (**3a**, **3b**, and **3c**) and photoelectron spectrum of **2** (2 pages). Ordering information is given on any current masthead page.

Demethylation of *N*,*N*-Dimethylaniline and *p*-Cyano-*N*,*N*-dimethylaniline and Their *N*-Oxides by Cytochromes $P450_{LM2}$ and $P450_{CAM}$

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Cytochrome P450 catalyzes the efficient oxidation of secondary and tertiary amines, providing an important pathway of xenobiotic metabolism. The chemical mechanism of oxidative amine dealkylation has been biomimetically studied by using (*meso*-tetraphenylporphinato)iron(III) chloride ((TPP)$Fe^{III}Cl$) and the exogenous oxidants *N*,*N*-dimethylaniline *N*-oxide (DMANO)[1] and *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide (*p*-CNDMANO).[2] To help clarify the enzymatic mechanism of cytochrome P450 dependent amine dealkylation reactions, we have tested amine *N*-oxides as oxygen donors to purified rabbit liver cytochrome $P450_{LM2}$[3] and bacterial cytochrome $P450_{CAM}$.[4] Intra- and intermolecular isotope effects on amine dealkylation were used to compare the mechanism of these exogenous oxidant supported reactions with that of the pyridine nucleotide/O_2 dependent ones.

Several conceptual pathways for enzymatic dealkylation of amines should be considered; direct hydroxylation of the methyl carbon, with or without formation of an intermediate *N*-oxide, or electron-transfer oxidation of the nitrogen is the most probable of the proposed mechanisms.[5] To distinguish between these various reaction pathways we have synthesized *N*,*N*-dimethylaniline (DMA) and *p*-cyano-*N*,*N*-dimethylaniline (*p*-CNDMA) with specific deuterium contents: *N*-methyl-*N*-(trideuteriomethyl)aniline (DMA-D_3); *p*-cyano-*N*-methyl-*N*(trideuteriomethyl)aniline (*p*-CNDMA-d_3); and their corresponding *N*,*N*-bis(trideuteriomethyl) compounds (DMA-d_6 and *p*-CNDMA-d_6). The deuterated dimethylaniline *N*-oxides DMANO-d_3, *p*-CNDMANO-d_3, DMANO-d_6, and *p*-CNDMANO-d_6 were synthesized from the corresponding dimethylanilines by oxidation with *m*-chloroperoxybenzoic acid.[7]

Table I. Isotope Effects on Oxidative Demethylation by Cytochrome P450

	exogenous oxidant		$NAD(P)H + O_2$	
	p-CNDMANO	DMANO	*p*-CNDMA	DMA
$P450_{LM2}$				
intermolecular (d_0 vs. d_6)	1.1	1.0	1.0	1.0
intramolecular (d_3)	2.0	3.0	3.9	2.6
$P450_{CAM}$				
intermolecular (d_0 vs. d_6)	1.7	1.4	*a*	*a*
intramolecular (d_3)	2.5	4.3	*a*	*a*

[a] Due to the extreme substrate specificity of this enzyme, $P450_{CAM}$ will not catalyze the demethylation of dimethylaniline. Statistical errors on all isotope effects average ±8%.

Purified rabbit liver cytochrome $P450_{LM2}$ was found to efficiently utilize the exogenous oxidant DMANO, generating *N*-methylaniline (NMA) and formaldehyde in a second-order reaction with a velocity of 0.0231 turnovers min^{-1} mM^{-1}. Negligible amounts of heme oxidation were observed in contrast to results obtained with peroxides, peroxy acids, and iodosylbenzene. No saturation of the *N*-demethylation reaction was observed over the concentration range 0.2–50 mM. At very high concentrations of *N*-oxide, a significant autocatalytic effect was observed with the reaction velocity increasing with time.[8] Cytochrome $P450_{CAM}$ was also observed to efficiently catalyze the demethylation of DMANO and *p*-CNDMANO. Presumably due to its substrate specificity, cytochrome $P450_{CAM}$ has not been shown to oxidatively dealkylate tertiary amines. On mixing DMANO with $P450_{CAM}$, linear production of NMA and formaldehyde was observed over a wide range of concentrations, from 0.2 to 50 mM. No aniline or dimethylaniline was produced in the reactions with either $P450_{LM2}$ or $P450_{CAM}$ suggesting that the N-demethylation reaction occurs very rapidly after the generation of the active oxygen intermediate, in contrast to results obtained in similar experiments with (TPP)$Fe^{III}Cl$.[1,2] This hypothesis is supported by the observation that the normal substrate of $P450_{CAM}$, camphor, is not hydroxylated when the *N*-oxides are used as exogeneous oxidants. The addition of the electron-withdrawing *p*-cyano group would be expected to increase the oxygen-transfer potential of the aniline *N*-oxide and also to deactivate the nitrogen to electron-abstraction reactions.[2] Substitution of *p*-CNDMANO for DMANO, however, did not significantly alter the kinetics of the demethylation reaction or allow the hydroxylation of camphor, suggesting that the resulting *p*-CNDMA did not have time to leave the cage following the transfer of the oxygen of *p*-CNDMANO to iron.

To further probe the mechanisms of oxygen atom transfer by this oxidant, intra- and intermolecular isotope effects were quantified using DMANO-d_3 [$C_6H_5N(CH_3)(CD_3)O$] and a mixture of DMANO-d_6/DMANO-d_0 (1:1). In addition, the $NADPH/O_2$ dependent demethylations of DMA-d_3 and of a mixture of DMA-d_0/DMA-d_6 (1:1) were determined for cytochrome $P450_{LM2}$ (Table I). In these experiments an intramo-

(1) Shannon, P.; Bruice, T. C. *J. Am. Chem. Soc.* **1981**, *103*, 4580–4582.
(2) Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 6123–6125.
(3) Hepatic cytochrome $P450_{LM2}$ was purified essentially as described by: Coon, M. J.; Van der Hoever, T. A.; Dahl, S. B.; Haugen, D. A. *Methods Enzymol.* **1978**, *52*, 109–123.
(4) Bacterial $P450_{CAM}$ was purified essentially as described by Gunsalus, I. C.; Wagner, G. C. *Methods Enzymol.* **1978**, *52*, 166–188.
(5) Gorrod, J. W. "Biological Oxidation of Nitrogen"; Elsevier/North Holland Biomedical Press: New York, 1978.
(6) The deuterated DMA compounds were synthesized by $LiAlD_4$ reduction of the ethyl carbamate of the appropriate aniline. Deuterated *p*-CNDMA compounds were synthesized by alkylation of the appropriate *p*-cyanoaniline with either dimethyl sulfate-d_6 or methyl iodide-d_3. All compounds were characterized by ^1H NMR and mass spectrometry.
(7) Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721–1722.
(8) The increase in reaction velocity was observed by monitoring production of DMA via HPLC, GC, and UV spectrophotometry and by monitoring production of formaldehyde via the Nash reaction.[11] Detailed studies were performed to determine the source and mechanism of this autocatalytic effect. These studies included measuring the effects of *N*-methylaniline, lipid, oxygen, and buffer composition on the catalysis. Anaerobisis or changes in buffer composition had no effect on reaction velocity or autocatalysis. Reactions performed in buffer containg the product of the reaction, *N*-methylaniline, showed a small increase in the initial velocity of the reaction, but this increase was not significant enough to explain the observed autocatalysis. Lipid concentration effects were measured and showed the expected dependence with maximal reaction velocities obtained at 30 μg DLPC per mL. Higher or lower concentrations did not eliminate autocatalysis. The origin of this effect at very high *N*-oxide concentrations is unclear, and all reported velocities are derived from the initial slope of product formation, which was linear for over 4 h.

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