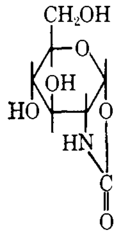
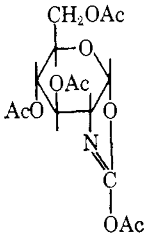

III

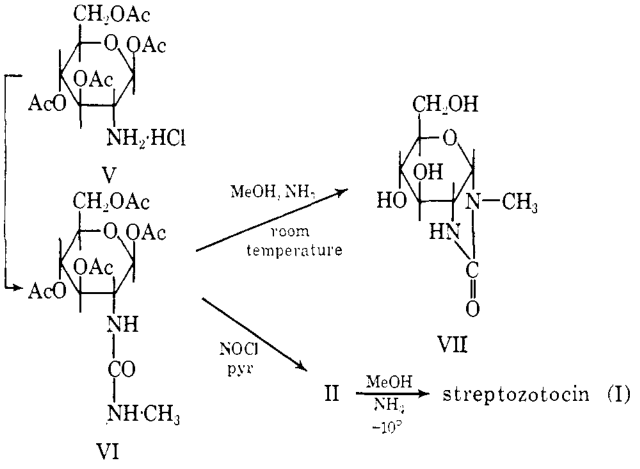

IV, Ac = $COCH_3$

2.48; three singlets, 3 H each, at δ 1.97, 2.03, and 2.07) of the tetraacetate IV are consistent with the postulation of the presence of an enol acetate grouping in IV.

The formation of diazomethane and a positive Liebermann nitroso test[9] suggested the presence of an N-nitrosomethylamide group in streptozotocin. The absence of a free amino group in streptozotocin, together with the isolation of carbon dioxide and D-glucosamine from acid hydrolysis of III or IV, indicate the nitrosoamide to be present as a urea derivative involving the nitrogen of the glucosamine. This conclusion is consistent with both the ultraviolet [λ_{max} 228 mμ (ε 6360)][10] and the infrared spectra (carbonyl absorption at 1700 cm^{-1},[11,12] -NN=O at 1530 cm^{-1} [13]) of streptozotocin. These data establish the structure of streptozotocin as I.

Various lots of crystalline streptozotocin as isolated, identical in all other respects, have shown wide variations in optical rotation ($[\alpha]^{25}D$ +15 to 68°). However, aqueous solutions of these samples rapidly undergo mutarotation to an equilibrium value of $[\alpha]^{25}D$ 39°. This indicates that streptozotocin is a mixture of α and β anomers with the C_1-hydroxyl unsubstituted.

The structure of streptozotocin was confirmed by its synthesis. Tetra-O-acetylglucosamine hydrochloride[14] (V) treated with methyl isocyanate[15] gave VI, $C_{16}H_{24}N_2O_{10}$, mp 142–144°, $[\alpha]^{25}D$ +18° (*c* 0.9, 95% ethanol). Attempts to deacetylate VI prior to nitrosation, using ammonia in methanol (room temperature), afforded only the cyclic product VII, $C_8H_{14}N_2O_5$,[16] mp 177–178°, $[\alpha]^{25}D$ −21° (*c* 0.77, water). VII, which shows no reducing properties, has also been obtained from streptozotocin by treatment with 0.1 *N* aqueous sulfamic acid; 1 mole of N_2/mole of I is evolved during this reaction. Treatment of VI with nitrosyl chloride in pyridine[17] afforded tetraacetylstreptozotocin (II) identical with an authentic sample. Ammonolysis of II in methanol (−10°) afforded streptozotocin identical in all respects with that obtained from fermentations.



In addition to streptozotocin, *S. achromogenes* produces enteromycin[18,19] and U-15,774,[19] both compounds containing unusual nitrogen functions.

Acknowledgments. The authors are grateful to members of the Physical and Analytical Chemistry Department for microanalytical and spectral data.

---

[9] W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd ed, Longmans, Green and Co., Ltd., London, 1948, p 358.

[10] A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The MacMillan Co., New York, N. Y., 1964, p 41.

[11] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 2nd ed, 1958, p 223.

[12] The reported value for amide carbonyl absorption in substituted ureas is 1660 cm^{-1}.[11] However, the presence of the electronegative N-nitroso group is expected to reduce the contribution of the ionic form of the amide and as a result the carbonyl frequency is raised. A similar effect may account for the high frequencies of N-nitrosoamides which absorb near 1740 cm^{-1} in solution.[13]

[13] E. H. White, *J. Am. Chem. Soc.*, 77, 6008 (1955).

[14] M. Bergmann and L. Zervas, *Ber.*, **64B**, 975 (1931).

[15] F. Micheel and W. Lengsfeld, *ibid.*, **89**, 1246 (1956).

[16] This cyclization of the methyl ureido compound is contrary to the results reported by C. J. Morel, *Helv. Chim. Acta*, **44**, 403 (1961), who did not obtain the cyclic product during ammonolysis of several other alkyl derivatives, but is analogous to the results reported by both Morel and Micheel[15] with aryl derivatives.

[17] M. S. Newman and A. Kutner, *J. Am. Chem. Soc.*, 73, 4199 (1951).

[18] K. Mizuno, *Bull. Chem. Soc. Japan*, 34, 1419, 1425, 1631, 1633 (1961).

[19] P. F. Wiley, R. R. Herr, F. MacKellar, and A. D. Argoudelis, *J. Org. Chem.*, 30, 2330 (1965).

R. R. Herr, H. K. Jahnke, A. D. Argoudelis
Research Laboratories, The Upjohn Co.
Kalamazoo, Michigan
Received June 9, 1967

Metal Ion Facilitation of Atom-Transfer Oxidation–Reduction Reactions[1]

Sir:

Reactions of transition metal compounds can often be classified in analogous patterns, from which new reactions can be deduced. The efficacy of this approach is illustrated by the oxidative addition reactions of d^8 [2,3] and d^{10} [4] systems. Herein we propose another class of transition metal reactions: metal ion promoted atom-transfer oxidation–reduction reactions.

Consider a molecule or ion X–Y reacting with a molecule or ion Z to form products X–Z and Y such that atom (or group) transfer takes place, X–Y being reduced and Z being oxidized (eq 1).

$$X\text{-}Y + Z \longrightarrow X\text{-}Z + Y \qquad (1)$$

A partial list of potential oxidizing agents X–Y includes RN_3, N_3^-, $RCHN_2$, RNCNR, RNO_2, NO_2, NO_2^-, NO, NO^+, ArN_2^+, N_2O, SeO_2, O_3, O_2, H_2O_2, ROOR, and ROOH.[5] Reducing agents Z might include H^-, R^-, $RC{\equiv}C{:}^-$, RC≡CR, RCH=CHR, R_3P, CO, RNC, CN^-, N_3^-, SO_2, and $SnCl_2$.[6] Most of the possible permutations afford thermodynamically allowed reactions; however, many combinations lack a low-energy

---

[1] This research was supported by the National Science Foundation and the Advanced Research Projects Agency, Contract SD 100.

[2] (a) L. Vaska and S. S. Bath, *J. Am. Chem. Soc.*, **88**, 1333 (1966); (b) P. B. Chock and J. Halpern, *ibid.*, **88**, 3511 (1966).

[3] J. P. Collman and W. R. Roper, *ibid.*, **87**, 4008 (1965); **88**, 3504 (1966).

[4] C. D. Cook and G. S. Jauhal, *Can. J. Chem.*, **45**, 301 (1967).

[5] In a few instances atom transfer takes place from the reducing agent to the oxidizing agent rather than the converse which is shown in eq 1.

[6] Ligands are written in their uncoordinated state.

pathway to allow the reaction to occur under moderate conditions. It is our hypothesis that incorporation of both reactants (X–Y and Z) into *cis* positions of the coordination sphere of a metal complex might provide a mechanism to facilitate such atom-transfer redox reactions. In cases where reactants X–Y and Z replace products X–Z and Y in the coordination sphere, the over-all process would be homogeneously catalyzed by a metal complex. Such reactions may also be heterogeneously catalyzed by chemisorption.

Our first encounter with such a process was the reaction of acyl or aryl azides with iridium(I) or rhodium(I) carbonyl complexes (**1**) to form organic isocyanate or

$$\begin{gathered}\mathrm{MCl(CO)L_2}\\ \mathbf{1a},\ \mathrm{M = Rh}\\ \mathbf{b},\ \mathrm{M = Ir}\\ \mathrm{L = triphenylphosphine}\end{gathered}$$

nitrogen complexes (only the iridium nitrogen complex is stable enough to be isolated).[7] Addition of CO regenerates the original carbonyl complex (**1**) which can then react with more organic azide so that the over-all process is catalytic (eq 2). The activation energies are

$$\mathrm{ArN_3 + CO \xrightarrow[\mathrm{MCl(CO)L_2\ (1)}]{} ArNCO + N_2} \qquad (2)$$

small and these reactions are rapid at low temperatures. Coordinatively saturated iridium carbonyl complexes do not react with organic azides under these mild conditions, illustrating the requirement of incorporating both oxidizing and reducing agent in the metal coordination sphere. In the absence of a metal complex, CO and organic azides do not react at a measurable rate.

A related process is the stoichiometric reaction of the *iridium(I)* and *rhodium(I)* carbonyl azides (**2**) with CO to yield the corresponding isocyanates (**3**)[5] (eq 3). The bisazido complexes of palladium and platinum (**4**) undergo a similar transformation (eq 4).[9] The parallel

$$\mathrm{MN_3(CO)L_2 + CO \longrightarrow \underset{\mathbf{3}}{MNCO(CO)L_2} + N_2} \qquad (3)$$

$$\mathbf{2a},\ \mathrm{M = Rh};\quad \mathbf{b},\ \mathrm{M = Ir}$$

$$\mathrm{M(N_3)_2L_2 + CO \longrightarrow \underset{\mathbf{5}}{M(NCO)_2L_2} + 2N_2} \qquad (4)$$

$$\mathbf{4a},\ \mathrm{M = Pd};\quad \mathbf{b},\ \mathrm{M = Pt}$$

$$\mathrm{NaN_3 + Pd\text{–}C + CO \xrightarrow{H_2O} NaOCN + N_2} \qquad (5)$$

between homogeneous and heterogeneous catalysis is demonstrated by the reaction of sodium azide, carbon monoxide, and palladium on charcoal to form the sodium cyanate (eq 5).

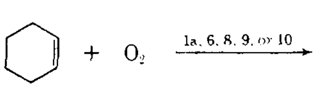
Incorporation of azide and CO into *cis* positions or within close proximity in the coordination sphere is insufficient to cause the reaction to occur (at least at ambient temperatures). Thus the hydrogen, oxygen, and diethyl acetylenedicarboxylate adducts[8] derived from the iridium carbonyl azide **2** are stable and do not undergo spontaneous atom-transfer redox reactions.

Among examples of metal ion promoted atom-transfer redox reactions from the recent literature, carbon monoxide is the reducing reagent in several instances. Aryl nitro compounds oxidize CO to CO_2 and form isocyanates in the presence of rhodium(I) complexes[10] and palladium or rhodium metal.[11] Nitrobenzene reacts with iron pentacarbonyl to form carbon dioxide and azo and nitroso compounds.[12] In the latter case thermal or photochemical activation is required to produce a coordinatively unsaturated metal complex. The reaction of water with carbon monoxide in the presence of $PdBr_3^-$ has been recently reported.[13] Nitrite ion also reacts with coordinated CO to form CO_2 (as complexed carbonate) and coordinated NO.[14]

Among potential oxidizing agents perhaps the most intriguing is molecular oxygen. It has been proposed that coordinated oxygen is peroxidic on the basis of increased oxygen–oxygen bond length[15] and on the formation of hydrogen peroxide upon protonation.[16,17] Catalytic oxidation of tertiary phosphines[17,18] and isonitriles[18] by O_2 using complexes derived from d^{10} systems have been described. Similarly, oxidation of SO_2 to coordinated SO_4^{2-} and NO_2 to coordinated NO_3^- has been recently reported.[19,20] We have found that NO reacts with the platinum(II)–oxygen complex **6**[17,21] to form the bisnitro complex **7** (eq 6).

$$\mathrm{\underset{\mathbf{6}}{PtO_2L_2} + NO \longrightarrow \underset{\mathbf{7}}{Pt(NO_2)_2L_2}} \qquad (6)$$

Olefins are significant reducing agents in the above list. We report here the catalysis of autoxidation of cyclohexene and cyclopentene by complexes of d^8 metals (eq 7). Using oxygen pressures of 14–36 psi at 25–60° and catalyst concentrations of 10^{-2} *M* in benzene or methylene chloride, oxidation of 20 to 50% of 2–5 g of cycloolefin was observed in 24 hr. Cyclohexen-3-one[22a,b] and water[22a] were identified as major products of the autoxidation of cyclohexene; cyclohexene oxide[22a,b] and other as yet unidentified compounds were minor products. Cyclopentene oxide[22a] was also identified as a minor product in the oxidation of cyclopentene. It is likely that 3-cyclohexene hydroperoxide is an intermediate in the above reaction, but this has not



(7)

$$\underset{\mathbf{8}}{\mathrm{IrI(CO)L_2}}\quad \underset{\mathbf{9}}{\mathrm{IrCl(N_2)L_2}}\quad \underset{\mathbf{10}}{\mathrm{RhClL_3}}$$

---

[7] J. P. Collman, M. Kubota, J.-Y. Sun, and F. Vastine, *J. Am. Chem. Soc.*, **89**, 169 (1967).

[8] Satisfactory elemental analyses and infrared spectra have been obtained for these compounds.

[9] After completion of our study of reactions 4, similar results were reported by W. Beck and W. P. Fehlhammer, *Angew. Chem. Intern. Ed. Engl.*, **6**, 169 (1967).

[10] British Patent 993,704 (June 2, 1965); Dutch Patent 6,502,601 (Nov 25, 1965). We are indebted to R. P. Bennett, American Cyanamid Co., for calling our attention to these references.

[11] W. B. Hardy and R. P. Bennett, *Tetrahedron Letters*, 961 (1967).

[12] (a) E. A. Koerner von Gustorf, Abstracts, 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, p L43; (b) J. E. Kimlick, *J. Org. Chem.*, **30**, 2014 (1965).

[13] G. G. Kutyokov, A. B. Fasman, A. E. Lyuts, Yu. A. Kushnikov, V. F. Vozdvizhenskii, and V. A. Golodov, *Russ. J. Phys. Chem.*, **40**, 798 (1966).

[14] W. Hieber and K. Beutner, *Z. Naturforsch.*, **15b**, 323 (1960).

[15] J. A. McGinnety, R. J. Doedens, and J. A. Ibers, *Science*, **145**, 709 (1967).

[16] L. Vaska, *ibid.*, **140**, 809 (1963).

[17] G. Wilke, H. Schott, and P. Heimbach, *Angew. Chem. Intern. Ed. Engl.*, **6**, 92 (1967).

[18] S. Takahashi, K. Sonogashira, and N. Hagihara, *J. Chem. Soc. Japan*, **87**, 610 (1966).

[19] J. J. Levison and S. D. Robinson, *Chem. Commun.*, 198 (1967).

[20] C. D. Cook and G. S. Jauhal, *J. Am. Chem. Soc.*, **89**, 3066 (1967).

[21] C. D. Cook and G. S. Jauhal, *Inorg. Nucl. Chem. Letters*, **3**, 31 (1967).

[22] (a) Identified by comparison of their glpc retention time with that of authentic samples; (b) identified by comparison of their mass spectra with those of authentic samples.

been verified.[23] With the exception of the rhodium complex **1a**, the other active catalysts[15,24] are known to form complexes with molecular oxygen. It is significant that the iridium chloride complex **1b** is a poor catalyst for the autoxidation in benzene solution, but the analogous iodide complex **8** is an effective catalyst. Apparently, olefins such as cyclohexene displace oxygen from the coordination sphere in **1b**, and the resulting olefin complex is less likely to coordinate with oxygen. It is probable that a prerequisite for this oxidation is prior coordination of molecular oxygen. The iodide **8** is known to form a much more stable oxygen adduct than the chloride **1b**.[2b,15]

---

(23) Such an intermediate has been suggested in the autoxidation of olefins catalyzed by iron phthalocyanine: A. H. Cook, *J. Chem. Soc.*, 1774 (1938).

(24) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc., Sect. A*, 1711 (1966).

(25) Author to whom inquiries should be addressed: Department of Chemistry, Stanford University, Stanford, Calif. 94305.

(26) National Science Foundation Science Faculty Postdoctoral Fellow, 1966–1967.

James P. Collman,[25] Mitsuru Kubota,[26] John W. Hosking
Venable Laboratory, University of North Carolina
Chapel Hill, North Carolina
Received June 19, 1967

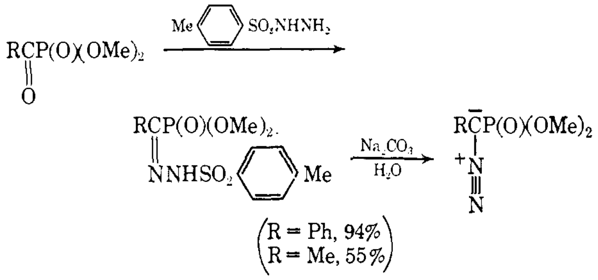
Novel Diazoalkanes and the First Carbene Containing the $(MeO)_2P(O)$ Group

Sir:

The preparation of diazoalkanes containing heteroatom substituents, *e.g.*, $(RS)_2CN_2$,[1] $(PhSO_2)_2CN_2$,[2] $ROCH_2CHN_2$,[3] and RSO_2CHN_2,[4] their preparative utilization, and their decomposition to carbenes have been of current interest. Diazoalkanes containing phosphorus substituents, $Ph_2P(O)C(Ph)N_2$[5] and $R_2P(O)CHN_2$ (R = Ph, $PhCH_2$),[6] have been reported also.

We have prepared $(MeO)_2P(O)C(Ph)N_2$ (I) and $(MeO)_2P(O)C(Me)N_2$ (II) because we felt that they would serve excellently, *via* the great variety of reactions diazoalkanes and the carbenes (or carbenoids) derived from them are capable of undergoing, in the introduction of organophosphorus functionality into diverse organic and inorganic compounds. We felt that I and II would be more useful than the $Ph_2P(O)$-substituted diazoalkanes since their methoxy groups represent reactive phosphorus functionality which would be useful in further synthetic steps.

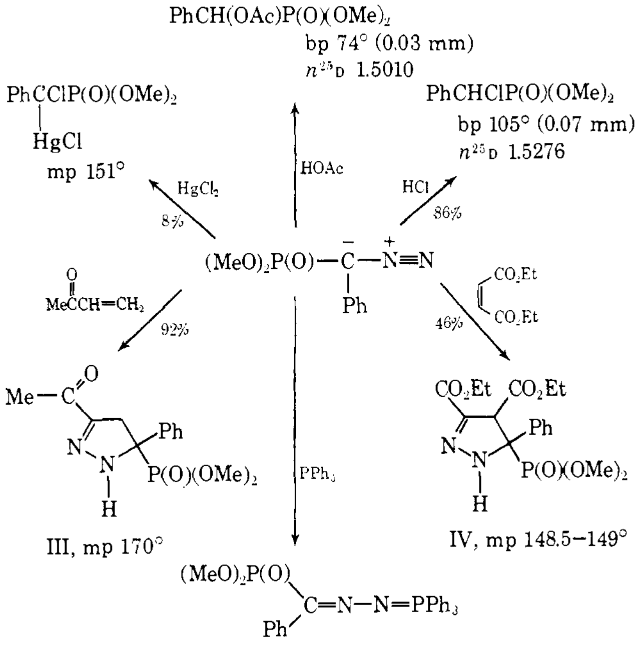
Compounds I and II were synthesized as shown in eq 1. Compound I is an orange-red, crystalline solid, mp 44–44.5°, which could be distilled at reduced pressure and which appears to be stable indefinitely at room temperature. Compound II is a yellow, distillable liquid, bp 37–38° (0.13 mm), $n^{25}D$ 1.4583, which decomposes slowly at room temperature but is quite stable on storage at 0°. Both compounds show infrared bands characteristic of the diazo group, I at 2080 and II at 2075 cm^{-1}, as well as P–O absorption at 1260 cm^{-1}.



(1)

The unusually high stability of $Ph_2P(O)$- and $(MeO)_2P(O)$-substituted diazoalkanes is noteworthy and may be a consequence of C → P π bonding. Compounds I and II have proved to be versatile reagents, undergoing the usual diazoalkane reactions and also showing carbenoid reactivity on treatment with copper powder. Scheme I summarizes reactions of I, Scheme II reactions of II. The products of 1,3-dipolar addition of I and II to activated vinyl compounds appear to be 2-pyrazolines as shown; where two modes of addition are possible, the isomer involving Michael addition of the diazo carbon is favored. All 1,3-dipolar adducts showed strong N–H infrared absorption at ~3200 cm^{-1} and a broad downfield singlet in the nmr spectrum, which was assignable to the N–*H* proton. Adducts to methyl vinyl ketone and ethyl acrylate showed carbonyl absorption corresponding to α,β unsaturation: $\nu_{C=O}$ (cm^{-1}): III, 1660; V, 1655; VI, 1725. The diethyl maleate adduct IV showed two distinct C=O peaks at 1725 and 1735 cm^{-1}, demonstrating the presence of conjugated and unconjugated carbonyl groups.[7] Of special interest in Scheme II is the reaction of II with phenyl(bromodichloromethyl)mercury in refluxing ben-

Scheme I. Reactions of $(MeO)_2P(O)C^{-}(Ph)N_2^{+}$



---

(1) U. Schöllkopf and U. Wiskott, *Ann. Chem.*, **694**, 44 (1966).

(2) J. Dieckmann, *J. Org. Chem.*, 28, 2933 (1963).

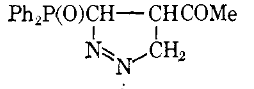
(3) C. Grot, E. Pfeil, E. Weinrich, and O. Weissel, *Ann. Chem.*, **679**, 42 (1964).

(4) A. M. Van Leusen, R. J. Mulder, and J. Strating, *Rec. Trav. Chim.*, **86**, 225 (1967), and earlier publications of this research group.

(5) L. Horner, H. Hoffmann, H. Ertel, and G. Klahre, *Tetrahedron Letters*, 9 (1961).

(6) N. Kreutzkamp, E. Schmidt-Samoa, and A. K. Herberg, *Angew. Chem.*, 77, 1138 (1965).

(7) Kreutzkamp, *et al.*,[6] reported that additions of $Ph_2P(O)CHN_2$ to methyl vinyl ketone and dimethyl maleate give 1-pyrazolines, *e.g.*, i,



i

but unfortunately provided no spectroscopic evidence in support of their structural assignments, so that their correctness cannot be assessed.