are identical to Fiberfrax (long-staple fines) (Carborundum Co.). Also found were fibers of almost pure silica, likely diatom spicules, irregular silica (diatom) fragments, and irregular fragments high in calcium (calcium oxalate phases from the natural tobacco leaf).

The temperatures at which cigars burn during smoking were measured to determine the degree of opal devitrification and particle size reduction in the cigar flame. A Chromel-Alumel thermocouple was inserted 1.5 cm from the end of the cigar, and the signal obtained during burning was fed into the X-input (temperature) axis of the XY recorder of a differential thermal analyzer system. Volunteers puffed cigars, reproducing "normal" smoking conditions. The cigars burned at high temperatures,  $690^{\circ} \pm 30^{\circ}$ C, and two cigars were observed to burn at 800°C. Compared with the published data (1), these values are low, but the nature of the thermocouple design and the recording instrument suggests that they are reasonably accurate. Examination by light and electron microscopy of ash obtained at the same temperatures by muffle furnace heating shows that the ceramic fibers tend to fracture into shorter fibers and that most diatoms fragmentize into fine, mottled particles. Electron diffraction study of the latter fragments indicates that high (beta) cristobalite is the predominant crystalline phase, associated with minor tridymite. Whole diatoms have not been observed to survive the burn intact. We have examined ash residues of tobacco sheets by x-ray diffractometry and have observed a discernible high cristobalite peak at 4.2 Å. It is likely that the cristobalite phase is naturally present but is enhanced by cigar burning.

Cigar smoke was also examined for disintegrated crystalline particles. Several representative cigars were "smoked" through a Casella air sampler and the smoke trapped on Millipore AA membrane filters. We also drew cigar smoke into an electrostatic precipitator and collected particles on an electron microscope grid. The membrane filters were prepared for electron microscopy by dissolving with acetone vapor. Examination of the membrane filters by light microscopy demonstrated the presence of fibrous particles that were optically isotropic and were either diatom spicules or broken ceramic fibers. Electron microscopic examination showed particles of disintegrated diatoms to be present (Fig. 3). They

5 NOVEMBER 1971

appeared to be identical with the mottled diatom fragments observed after high-temperature ashing. Electron diffraction patterns obtained from these fragments indicate that they are, in part, high cristobalite (Fig. 3, insert). Although quantitation was not attempted, the number of these particles observed in the smoke appears to be small. The biological effects that might be associated with the inhalation of these particles has not been studied.

ARTHUR M. LANGER ANNE D. MACKLER, IVAN RUBIN E. CUYLER HAMMOND **IRVING J. SELIKOFF** 

Environmental Sciences Laboratory, Mount Sinai School of Medicine of the City University of New York, New York 10029

## **References and Notes**

- 1. E. Wynder and D. Hoffmann, Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis (Academic Press, New York, 1968).
- Tobacco Products and Processes Thereof, U.S. Patent 2 592 553, 15 April 1952; Water Soluble Cellulose Derivatives in Smoking Products, U.S. Patent 2706 695, 19 April 1955; Tobacco Processing and Resultant Products, U.S. Patent 3 076 729, 5 February 1963. Resilient Tobacco Product and Method o 3. Resilient
- Making the Same, U.S. Patent 2 592 554, 15 April 1952.4. E. J. King and G. Nagelschmidt, *Proceedings of*
- the Pneumoconiosis Conjerence, A. J. Oren-stein, Ed. (Little, Brown, Boston, 1959), p. 78; F. Holt, Pneumoconiosis (Arnold, London,
- P. F. Holt, Pneumoconiosis (Arnold, London, 1957), p. 268.
  S. F. L. Kadey, Jr., Abstr. Soc. Min. Eng. Meeting AIME, Los Angeles (1967).
  D. Hunter, Diseases of Occupations (English Universities Press, London, 1969), p. 991.
  We thank Dr. Albert J. Fritsch of the Center for Responsive Law for providing us with the tobacco patents. One of us (A.M.L) wishes to acknowledge support under PHS career
- to acknowledge support under PHS career award ES 44812 from the National Institute of Environmental Health Sciences.
- 29 April 1971; revised 16 July 1971

## **Oxygen-Carrying Iridium Complexes:** Kinetics, Mechanism, and Thermodynamics

Abstract. The rates of oxygenation and deoxygenation of a series of iridium complexes increase and decrease, respectively, with increasing electron-releasing tendency of the anionic ligands (A) attached to the metal atom in the oxygencarrying compounds,  $[IrA(CO)(Ph_3P)_2]$ . Calculated heats of oxygenation  $(-\Delta H_2^{0})$ , related to  $Ir-O_2$  bond energies, are proportional to the previously reported O-Obond lengths in the oxygen adducts,  $[O_2IrA(CO)(Ph_3P)_2]$ .

We report some dynamic data for the reversible uptake of molecular oxygen by a group of isoelectronic and isostructural metal complexes in solution (Eqs. 1-3 and Table 1), and a correlation of these results with the electronic and structural properties of the oxygen-carrying compounds (Figs. 1 and 2). While the rates of oxygenation of a number of transition metal complexes have been widely studied in recent years (1-4), direct measurements of deoxygenation  $(k_{-1} \text{ in Eqs. } 1)$ and 2 and Table 1) of monomeric M-O<sub>2</sub> species, and the resulting thermodynamic parameters, do not seem to have been reported previously.

$$trans - [IrA(CO)(Ph_3P)_2] + O_2 \underset{k_{-1}}{\underset{k_{-1}}}{\underset{k_{-1}}{$$

A is a univalent anionic ligand (Table 1);  $Ph_3P$  is  $(C_6H_5)_3P$  (triphenylphosphine)

$$d[O_{2}IrCl(CO)(Ph_{3}P)_{2}]/dt = k_{2}[IrCl(CO)(Ph_{3}P)_{2}][O_{2}] - k_{-1}[O_{2}IrCl(CO)(Ph_{3}P)_{2}]$$
(2)  
$$K_{2} = \frac{k_{2}}{k_{-1}} = \frac{[O_{2}IrA(CO)(Ph_{3}P)_{2}]}{[IrA(CO)(Ph_{3}P)_{2}][O_{2}]}$$
(3)

Our work is based on a simple oxygen-carrying synthetic system [(5), ligand A is Cl in Eq. 1] which has reawakened interest in this class of compounds and led to widespread current research in the field. Significant



Fig. 1. Free energy of activation ( $\Delta G_2^* =$  $\Delta H_2^* - T \Delta S_2^*$ ) for the oxygenation of  $[IrA(CO)(Ph_3P)_2]$  (Eq. 1; Table 1) as a function of the electronic excitation energy  $(E_1)$  corresponding to an absorption band in the visible spectrum of [IrA(CO)  $(Ph_3P_2)$ ] (11) in benzene solution; ligands are F, Cl, Br, and I.

587

Table 1. Kinetic  $(k_2 \text{ and } k_{-1} \text{ in Eqs. 1 and 2})$ , equilibrium  $(K_2 \text{ in Eq. 3})$ , and activation enthalpy  $(\Delta H_2^*, \Delta H_{-1}^*)$  and entropy  $(\Delta S_2^*, \Delta S_{-1}^*)$  data for the reversible oxygenation of some iridium complexes in chlorobenzene solution at 40°C as a function of the anionic ligand A in the oxygen-carrying complexes [IrA(CO)(Ph<sub>3</sub>P)<sub>2</sub>]. Subscript 2 refers to the second-order oxygenation reaction, subscript -1 to the first-order deoxygenation reaction (Eq. 1) (24, 25).

Complex A	$10^2 k_2$ (sec <sup>-1</sup> $M^{-1}$ )	$10^{6} k_{-1}$ (sec <sup>-1</sup> )	$10^{-3} K_2 \ (M^{-1})$	$\Delta H_2^*$ (kcal)	$\Delta H_{-1}^*$ (kcal)	$\Delta S_2^*$ (eu)	$\Delta S_{-1}^{*}$ (eu)
F†	1.48	50.9	0.291	13.6	23.7	- 24	- 0.5
NCO	2.99	90.2	0.331	11.1	21.0	- 30	- 10
OClO <sub>a</sub> †	6.96	,-		4.01		- 50	
Na	7.33	13.1	5.60	9.57	26.2	- 33	. 3
CI	10.1	13.8	7.32	9.50	26.5	- 33	4
Br	20.6	3.32	62.0	8.42	28.8	- 35	8
ONO <sub>2</sub> †	36.3			5.50		- 43	
I	72.3	0.84	857	5.76	29.0	- 41	6
$NO_2^{\dagger}$	172			3.48		- 46	

<sup>†</sup> Data for reactions carried out in benzene (F, and apparently OClO<sub>8</sub>, ONO<sub>2</sub>, and NO<sub>2</sub>, react with chlorobenzene). Because of the relatively high vapor pressure of benzene, the results of the deoxygenation reactions (24) are of uncertain significance and are given only for F, for comparison. The data for OClO<sub>3</sub> and NO<sub>2</sub> represent preliminary results.

recent advances include the structural studies by Ibers et al. (6-8) of some of the oxygenated complexes cited here (Fig. 2), and new investigations of numerous oxygen complexes of cobalt [reviewed by Wilkins (2)] and some of iron (3, 9).

The reactions (Eq. 1) reported here obey the simple rate law given in Eq. 2. The velocity of oxygen uptake  $(k_2,$ Table 1) is strongly dependent on the anionic ligand A, in agreement with earlier data for Cl, Br, and I (4) and with observations on related addition reactions; that is, the reaction rate is proportional to the basicity of the metal complex, which is a function of the electron-donating properties of the ligands (10). A new correlation, given in Fig. 1, shows that the free energy of activation ( $\Delta G_2^*$ ) for oxygenation increases with increasing energy of electronic transitions in the four halogeno complexes (11, 12). The latter may be related to the ligand field stabilization energy of these planar  $d^8$  species. The

(A) (B) ΟI 1.5 4.0 п m 0-0 Distance (Å ectronegativity, x, NCO 🗖 N<sub>3</sub> 1.4 3.5 B 1.3 3.0 C  $(0_{2})$ 2.5 C1.2 ΠГ 0 10 20 Enthalpy, - △ H<sub>2</sub>° (kcal) 588

rates of deoxygenation  $(k_{-1})$  are also strongly dependent on the halide or pseudo-halide ligand, but in the reverse order, with the result that the calculated stability constants ( $K_2$ , Eq. 3) for the six oxygen adducts span more than three orders of magnitude.

As is expected for simple addition reactions, the entropy changes for oxygenation,  $\Delta S_2^0$  (13), are highly negative (for example, -37 eu for Cl). The entropies of activation ( $\Delta S_2^*$ ) are also negative [see (4)] and their magnitudes are close to those of  $\Delta S_2^0$ , which implies that the transition state configurations resemble the structures of the oxygen adducts (5-7).

The oxygenation reactions are exothermic  $[\Delta H_2^{0}$ 's are negative (13)] (14), and the calculated enthalpy changes, ranging from -10 for F to -23 kcal mole<sup>-1</sup> for I, are relatively close to those found for the oxygenation of myoglobin (16) and other hemoproteins (17). It should be pointed out, however, that although the

> Fig. 2. A correlation between the enthalpy,  $\Delta H_2^{0}$ (Cl,  $\pm$  0.2; Br,  $\pm$  0.8; I,  $\pm$ 2.8) (13), for the oxygenation of  $[IrA(CO)(Ph_3P)_2]$ (Eq. 1; Table 1) and (A) electronegativity the  $[x_A]$ (20)] of the anionic ligand A in the oxygen-carrying complexes,  $-\Box$ -; ligands F, NCO, N<sub>3</sub>, Cl, Br, and I; and (B) the O-O distance  $[O_2 Ir A(CO)(Ph_3P)_2],$ in ligands Cl [1.30 Å -0 (6)], Br [1.36 Å (23)], and I [1.51 Å (7)]. The point corresponds to the  $(\mathbf{0}_{*})$ O-O distance (1.21 Å in molecular oxygen and  $\Delta H_2^{\circ}$ = 0.

stability constants for some of our oxygen adducts (for example, Br) are also in the same range as those for the biological oxygen carriers, the kinetics of the two systems are vastly different (17).

The enthalpy values  $(\Delta H_2^0)$ , in conjunction with the reported O-O bond lengths in  $[O_2IrA(CO)(Ph_3P)_2]$  (6, 7), may be used to roughly estimate the Ir– $O_2$  dissociation energies in the chloro and iodo compounds (18, 19). The results are about 80 for Cl and 97 kcal  $mole^{-1}$  for I, or one-half of these values for each Ir-O "single" bond (15). Figure 2 shows a correlation between the heats of formation of the oxygen adducts and (A) the electronegativity,  $x_A$  (20), of the anionic ligand A, and (B) the O-O distance in the coordinated O<sub>2</sub> moiety. The latter curve (B) appears to demonstrate that integral oxidation states of the metal in  $[O_2IrA(CO)(Ph_3P)_2]$ , or a classification of these complexes as superoxo (Cl), peroxo (I), and so on, species may not represent the best description of the electronic interactions involved, but that there seems to be a gradual electron transfer from the metal to  $O_2$ , proportional to the basicity of the complex (21). Curve A illustrates that the reversible oxygenation of these synthetic complexes can best be regarded as acid  $(O_2)$ -base (metal complex) interactions (21, 22).

> L. VASKA LOOMIS S. CHEN C. V. SENOFF

Department of Chemistry, Clarkson College of Technology, Potsdam, New York 13676

## **References and Notes**

- 1. S. Fallab, Angew. Chem. Int. Ed. Engl. 6, Anaco, Angew. Chem. Int. Ed. Engl. 6, 496 (1967); E. Bayer and P. Schretzmann, Struct. Bonding (Berlin) 2, 181 (1967); J. P. Franck, C. Bocard, I. Séréé de Roch, L. Sajus, Rev. Inst. Fr. Petrole 14, 710 (1969).
- 2. R. G. Wilkins, Bioinorganic Chemistry (American Chemical Society, Washington, D.C., 1971), pp. 111-13
- 3. I. A. Cohen and W. S. Caughey, *Biochemistry* 7, 636 (1968).
- 4. P. B. Chock and J. Halpern, J. Amer. Chem. Soc. 88, 3511 (1966).
- 5. L. Vaska, Science 140, 809 (1963).
- S. J. La Placa and J. A. Ibers, J. Amer. Chem. Soc. 87, 2581 (1965). 6. S.
- J. A. McGinnety R. J. Docdens, J. A. Ibers, Inorg. Chem. 6, 2243 (1967).
- Inorg. Chem. 6, 2243 (1967).
  8. J. A. McGinnety, N. C. Payne, J. A. Ibers, J. Amer. Chem. Soc. 91, 6301 (1969).
  9. J. O. Alben, W. H. Fuchsman, C. A. Beaudreau, W. S. Caughey, Biochemistry 7, 624 (1968); E. B. Fleischer and T. S. Srivastava, J. Amer. Chem. Soc. 91, 2403 (1969).
  10. L. Vaska and M. F. Werneke, Trans. N.Y. Acad. Sci. Ser. 2 33, 70 (1971).
  11. The visible spectra of [IrA(CO(Ph<sub>2</sub>P)<sub>2</sub>] show three absorption bands [427 to 451 (E<sub>1</sub>), 378 to 398 (E<sub>2</sub>), and 328 to 356 nm (E<sub>2</sub>)].
- 398  $(E_2)$ , and 328 to 356 nm  $(E_3)$ ], assignable to d-d transitions in the  $d^8$  planar complexes (12). In Fig. 1, the lowest energy transition  $(E_1, d_{xy} \rightarrow d_{x^2-y^2})$  is used. 12. H. B. Gray and C. J. Ballhausen, J. Amer.
- Chem. Soc. 85, 260 (1963).

SCIENCE, VOL. 174

- 13. The values for thermodynamic parameters are readily evident from the activation data given
- readily evident from the activation data given in Table 1. Thus, for oxygenation : enthalpy, ΔH<sub>2</sub>° = ΔH<sub>2</sub>\* ΔH<sub>-1</sub>\*; entropy, ΔS<sub>2</sub>° = ΔS<sub>2</sub>\* ΔS<sub>-1</sub>\*; free energy, ΔG<sub>2</sub>° = ΔH<sub>2</sub>° T ΔS<sub>2</sub>°.
  14. A recent note (15) reports a calorimetric enthalpy for the reaction, [O<sub>2</sub>IrCl(CO)(Ph<sub>3</sub>P)<sub>2</sub>] (crystals) → [IrCl(CO)(Ph<sub>3</sub>P)<sub>2</sub>] (crystals) + Õ<sub>2</sub> (gas), as 22 kcal mole<sup>-1</sup> at 25°C; according to this result, the oxygenation of the crystals by the gas is endothermic. Because of the low by the gas is endothermic. Because of the low rates of the reversible oxygenations (Table 1), calorimetric measurements on our systems are infeasible (courtesy of Dr. W. Partenheimer). We have, however, determined the temperature dependence of the equilibrium constants for Cl, Br, and I directly from spectral data. The  $K_2$  decrease with increasing temperature, in
- K<sub>2</sub> decrease with increasing temperature, in agreement with the kinetic data (Eq. 3).
  15. S. J. Aschcroft and C. T. Mortimer, J. Organometal. Chem. 24, 783 (1970).
  16. M. H. Keyes, M. Falley, R. Lumry, J. Amer. Chem. Soc. 93, 2035 (1971).
  17. E. Antonini and M. Brunori, Annu. Rev. Biochem. 39, 977 (1970).
  18. Proceeding outlined for the estimation
- 18. By a procedure outlined for the estimation of the Ir-H bond strengths in  $[H_2IrA(CO)$  $(Ph_3P)_2]$  (10). The basic assumptions in the present case are that the O-O bond energy decreases on coordination from 118 kcal (free  $O_2$  to 63 kcal in  $[O_2IrCl(CO)(Ph_3P)_2]$  and 49 kcal in [O<sub>2</sub>IrI(CO)(Ph<sub>3</sub>P)<sub>2</sub>] (19).
- B. deB. Darwent, Bond Dissociation Energies in Simple Molecules (U.S. Department of Commerce, National Bureau of Standards, NSRDS-NSB 31, Washington, D.C., 1970).
   J. K. Willmhurst, J. Chem. Phys. 28, 733 (1969)
- (1958).
- 21, L. Vaska, Accounts Chem. Res. 1, 335 (1968).
- 22. D. F. Shriver, ibid. 3, 231 (1970).

- 23. E. L. Amma, private communication.
  24. The rate data (k<sub>2</sub> and k<sub>1</sub>) have been obtained by monitoring the intensity of an absorption band (378 to 397 nm) in the electronic spectrum of [IrA(CO)(Ph<sub>3</sub>P)<sub>2</sub>] under the followed ing conditions (i) Ovvenantion was followed. ing conditions. (i) Oxygenation was followed under a constant pressure (150 to 750 mm-Hg) of O., depending on the complex and the of  $O_{22}$  depending on the complex and the temperature. The starting concentration of the complex was about  $10^{-4}M$ ; in solution the ratio  $O_{2}$ : Ir ranged from 4 to 50 in differ-ent experiments. The disappearance of [IrA- $(CO)(Ph_3P)_2$ ] was first order in the complex  $(K_{obs})$ ; separate experiments showed that the reaction was also first order in O<sub>2</sub>. Thus,  $k_2 = k_{obs}/[O_2]$ . Note that these reactions go essentially to completion; the reverse reactions is negligible under the conditions cited. (ii) Deoxygenation was followed in deoxygenated solutions of  $10^{-4}M$  [O<sub>2</sub>IrA(CO)(Ph<sub>3</sub>P)<sub>2</sub>] (constant  $Po_2 \sim 0$  mm Hg). The reaction  $(k_{-1})$  was first order in the complex. The activation parameters have been calculated from the kinetic constants determined at 15° to 60°C. Maxi rows that is deviations are, for  $k_2$ ,  $k_{-1}$ , and  $K_2$ ,  $\pm 2$  percent; for  $\Delta H_2^*$  and  $\Delta H_{-1}^*$ ,  $\pm 1$  kcal (except  $\Delta H_{-1}^*$ ,  $\pm 2.6$  kcal for I); for  $\Delta S_2^*$ ,  $\pm 4$  eu; for  $\Delta S_{-1}^*$ ,  $\pm 1.5$  eu.
- 25. Some of these reactions (Cl, Br, I) have also been studied by infrared spectrophotometric (26) and volumetric [(4), oxygenation only] methods. The results for oxygenation (4, 26)agree, in general, with those given here, but the data for deoxygenation (26) differ from and appear to be less reliable than the present results.
- 26. L. Vaska and C. V. Senoff, unpublished re-
- 27. Supported by NIH grant HE-09678.

1 July 1971

## Marihuana: Standardized Smoke Administration and **Dose Effect Curves on Heart Rate in Humans**

Abstract. A spirometer was used to deliver marihuana and placebo smoke to human subjects. This procedure produced linear dose-effect curves on heart rate and replicable dose effects in individual subjects. No differences were observed between experienced and inexperienced smokers in responsiveness to heart rate increases produced by marihuana.

Marihuana research in humans has been difficult to evaluate because of conflicting results (1). A major problem complicating the comparability and replicability of studies has been the lack of a standard way of administering doses of marihuana (2, 3). Smoking marihuana cigarettes introduces at least two major sources of error: first, considerable and indeterminable amounts of smoke are lost to the air, and second, there is no way of determining the actual amount of smoke inhaled by the subject. Giving marihuana orally carries no assurance that the same substances pharmacologically active in smoke are being administered (2).

In an effort to overcome these problems, we have developed a system to deliver a measured quantity of smoke to a subject. Using change in heart rate as the measured effect, we investigated various dosages of marihuana to determine the efficiency of this delivery system.

5 NOVEMBER 1971

Ten subjects were used, four inexperienced with marihuana, and six experienced smokers. An experienced smoker is defined as one who is currently engaged in smoking marihuana at least once a week. Three of the inexperienced subjects had never had any contact with marihuana before, and one had smoked marihuana three times 6 months before. All subjects were experienced tobacco smokers.

The subjects were all males. Nine were between 24 and 30 years of age, and one inexperienced smoker was 45. They were all judged to be in good health on the basis of routine medical history, physical examination, complete blood count, urinalysis, chest x-ray, and psychiatric examination.

All subjects were advised of the nature of the experiment and that both marihuana and placebo would be administered to them. They were also advised of the possible dangers of marihuana before they signed forms consenting to be subjects (4).

The marihuana and placebo were obtained from the National Institute of Mental Health. The marihuana was assayed to contain 1.5 percent  $\Delta$ -9-tetrahydrocannabinol. Placebo had been commercially prepared by multiple extractions with alcohol to remove most of the  $\Delta$ -9-tetrahydrocannabinol. Dosages of marihuana administered were the smoke from the total combustion of 62.5 mg, 125 mg, 250 mg and 435 mg of marihuana. The doses of placebo were equivalent to those of marihuana, but since all produced similar reactions, they were combined for purposes of our analysis.

The basic apparatus consists of a 12liter spirometer and a machined aluminum crucible or pipe attached to the tubing so that as the inside bell of the spirometer is raised, air is drawn through the crucible into the spirometer. When marihuana, suitably chopped for burning, is placed in the crucible and ignited while air is being drawn through it, all of the smoke produced is drawn into the apparatus. Since the spirometer collapses to only half its size, the smoke is diluted by one-half with air. Once combustion is complete, the aluminum crucible is quickly disconnected, and the subject, with respiratory mask in place, is connected to the spirometer and inhales the smoke from it. Essentially, this is a closed, partially collapsible system which contains a fixed amount of smoke, and from which no smoke is lost into the atmosphere. The subject receives the same amount of smoke each time he empties the spirometer. The dose can easily be changed by varying the amount of marihuana burned, resulting in different concentrations of the smoke. Placebo can be administered in the same fashion, insuring the possibility of a double blind for any given dose.

Other variables in administering smoke are the duration of inhalation and the interval between inhalations. These variables were brought under stimulus control by instructing the subject to breathe according to a series of four lights. (i) A "ready" light signals the approaching cycle for 5 seconds. (ii) An "inhale" light comes on for 5 seconds, during which the subject inhales continuously. (iii) This is followed by the "hold" light, during which the subject holds the smoke in his lungs. This has a 15-second duration, and, during the breath-holding, the technician turns a valve closing the spirometer connection and opening the