be the consequence of the load imposed by the subsynaptic membrane, which is highly conducting, upon the spike generator. This conclusion implies that membrane resistance remains appreciable during spike activity, at least for the spikes in the vicinity of the peak of the strychnine wave.

The height of the strychnine slow wave increases rapidly as the strength of a stimulus to a dorsal root is increased. If supramaximal stimuli are repeated at a frequency of about 5 to 8 per second, the late component may disappear in an all-or-none manner (Fig. 2). This behavior suggests that the activity of interneurons becomes abnormally homogeneous under the influence of strychnine, as may happen with more effective coupling among the different units.

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14 March 1963

Preference Aversion in Mice to Bitter Substance

Abstract. *Preference-aversion functions demonstrable for sweet and salty stimuli have been found for a "bitter" substance, sucrose octaacetate, at individually specific concentrations for mice. The data support Schneirla's views correlating stimulus magnitudes and approach-withdrawal. The positive reinforcing value of this bitter substance as a weak stimulus is diminished with continuous exposure and no secondary reinforcement. Avoidance is related to intensity of stimulation rather than modality or postingestion effects.*

Avoidance of bitter flavored aqueous solutions is considered to be biologically determined and of evolutionary significance, since many of the toxins found in poisonous plants are alkaloids, which are intensely bitter. Moreover, the bitter modality is the most sensitive of the tastes, responding to the lowest concentrations of naturally occurring compounds (*1*).

The typical preference-aversion curve, dependent on concentration, which has been derived for sweet and salty solutions has not been reported for bitter solutions. In studies with the two-bottle choice situation (the substance to be studied dissolved in water is offered simultaneously and continuously with unflavored water), solutions of bitter substances in low concentration may be accepted equally with water. With increasing concentrations, however, there is a marked reduction in the amount of bitter solution drunk compared with water, but no preference point has been reported.

In the course of drinking experiments five of ten NIH/N albino male mice withdrew from water flavored with $10^{-3}M$ sucrose octaacetate (SOA) after 16 hours of water deprivation when no other source of fluid was available. This synthetic substance is intensely bitter to man and is rejected by guinea pigs, rats, hamsters, and great tits at this concentration (*2*). All of the fluid-deprived mice began to drink SOA at once. Half of them stopped after their initial laps, while the other five continued to drink at the same rate as controls drinking only water. Since need should be similar in all animals, it was expected that a striking difference might exist in the sensitivity of the animals to the bitter substance. To investigate the problem the behavior toward SOA under conditions of ad libitum food and fluid was measured.

Another group of ten mice was given a two-bottle choice, $10^{-5}M$ SOA or water. The two bottles were presented for 8 days. Solutions were changed daily and sides of presentation were alternated to eliminate the effect of side preferences. The results are summarized in Fig. 1. Under these conditions, and with animals that had not previously tasted the bitter solution, half showed almost complete rejection at this weaker concentration. Of the remaining five, three drank more test substance (in excess of 55 percent) than water at least for several successive days. The two mice which showed neither preference nor rejection (they drank 55 and 46.4 percent respectively in 48 hours), drank whichever was on the preferred side. However, the animals that started out initially preferring SOA to water tended, after 5 days, to

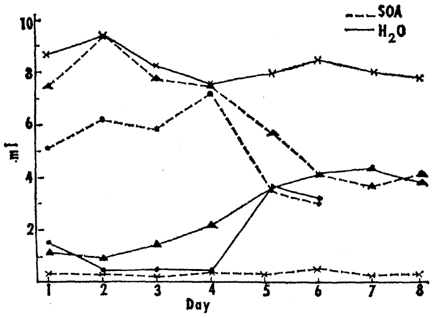

Fig. 1. Mean daily fluid intake. (Cross) Mice that rejected SOA at $10^{-5}M$. (Triangle and circle) Mice that preferred SOA at $10^{-5}M$ and $5 \times 10^{-7}M$, respectively.

a more equal daily intake regardless of prior preference for a particular side. This may be due to habituation, for there is apparently no secondary reinforcing value of the stimulus (*3*).

Since at least half of the animals did not reject the test solution at $10^{-5}M$ and some actually preferred it, a search for preference concentrations was instituted for the five animals which showed almost complete rejection. Presenting animals with rejected concentrations may affect subsequent behavior to less concentrated solutions. Nevertheless, four of the five animals drank more of the test substance at individually specific concentrations when a series of lower concentrations was presented randomly, each for 48 hours or longer.

Two of these showed a peak preference at $5 \times 10^{-7}M$ and were maintained on this concentration to determine if they also showed the apparent habituation decrease. After 4 days of high intake, these also began a daily consumption more equal to that of water (Fig. 1). The other two mice preferred SOA at $10^{-6}M$. Increasing the concentration above the preferred one resulted first in equal intake with water; only side preference was evident. With greater concentrations, the bitter substance was avoided. Two of the three mice which preferred it at $10^{-5}M$ continued their preference at $10^{-3}M$, which is near the limit of its solubility. The remaining animal drank more of it than water only when it was on the preferred side, so that a 48-hour total indicated neither preference nor rejection.

Of the two mice that originally did not prefer or reject sufficiently to overcome side preference at $10^{-5}M$, one rejected and one showed preference at $10^{-3}M$. Thus, for one animal at least, the preference point was at saturation.

Such variability in behavior from animal to animal is not uncommon. Kare has reported (*4*) that some chicks showed preferences for sapid substances at concentrations which most chicks rejected. Thus when animals are treated as groups, the net result with increasing concentrations may be behavior varying from indifference to avoidance, such that any preferential trend for substances usually considered aversive might be obscured. With attention to individual differences however, preference concentrations were established for eight out of ten mice, avoidance concentrations for six, and for four, both preference and avoidance concentrations.

The evidence puts in question a generally accepted view that specific gustatory stimuli, by virtue of their primary positive or negative reinforcing values, elicit an innate consummatory or avoidance response (*5*). First, we have a bitter stimulus which is acceptable in specific concentrations in preference to water. Second, the relative acceptability is a function of concentration rather than the qualitative nature of the stimulus. And finally, maintenance of preference appears to be dependent on prior experience with the stimulus.

Since in the concentrations tested, SOA is not nutritive and has a negligible effect on osmotic pressure, the preference-avoidance function cannot be directly compared to that obtained for sugars and NaCl. However, the preference for the bitter substance as well as for sugar and salt at low concentrations may be comparable, in that all are acting as weak stimuli capable of eliciting preferential behavior. Certainly, at high concentrations detrimental osmotic effects come into play for both sugar and salt, but for SOA, even at the limit of solubility, the osmotic effects are still negligible.

The biphasic response towards the bitter substance exemplifies Schneirla's concept of orientation based on the quantitative nature of the stimulus (*6*). Accordingly, it is the degree of stimulation which determines behavior that precedes learning; a weak stimulus elicits approach, a strong stimulus withdrawal. The fact that preference or differential intake diminishes for the bitter test substance after the continuous experience of several days suggests that lack of secondary reinforcement and decrease in novelty (habituation) are responsible (*7*).

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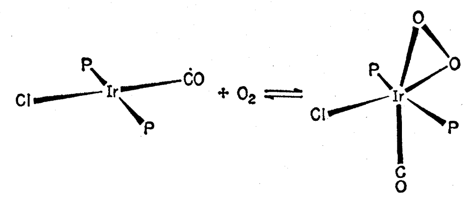
22 March 1963

Oxygen-Carrying Properties of a Simple Synthetic System

Abstract. *An iridium compound, chloro-carbonyl-*bis*(triphenylphosphine)-iridium, in solution, takes up molecular oxygen—one molecule per metal atom —which is subsequently recovered by reducing the pressure. The adduct is photosensitive but otherwise stable at ambient temperatures. It is a monomeric molecular complex and probably contains a peroxo group with both oxygens bonded to the same metal atom.*

I wish to report an oxygen-carrying synthetic system which stands out in its simplicity and exposes new paths toward explaining and understanding the activation of molecular oxygen by metal complexes (synthetic or natural) or metals.

The oxygen carrier is a coordination compound of iridium, chloro-carbonyl-*bis*(triphenylphosphine)iridium (I), $[IrCl(CO)(Ph_3P)_2]$ (*1, 2*), with a probable molecular structure as shown in Fig. 1*A* (*1, 3*). The compound is insoluble in water and most other polar media (such as alcohols); it is soluble and stable in benzene, in which the reaction cycles have been studied. The oxygenation-deoxygenation equations are formulated in Fig. 2; conditions for the reactions, and stabilities of the reactants are summarized in Table 1.



(A) (B)

Fig. 1. Diagrams of probable molecular configurations of $[IrCl(CO)(Ph_3P)_2]$ and $[O_2\ IrCl(CO)(Ph_3P)_2]$.

The yellow crystals of the starting complex, $[IrCl(CO)(Ph_3P)_2]$, do not react with oxygen under normal conditions (I→IV). In solution, the compound takes up one molecule of oxygen for each atom of iridium, with a color change from yellow to orange (II→III). The rates of oxygenation are moderate, that is they are considerably slower than those reported for oxygen carriers based on cobalt (*4*). The oxygen uptake has been followed volumetrically and by observing the infrared-spectral shift of the carbonyl group (*1, 5*) (Table 2).

When the oxygen pressure above the solution is reduced, the adduct reverts to the starting material (III→II). Its reappearance has been followed by infrared spectra; simultaneous evolution of molecular oxygen has been verified by gas-chromatographic analysis. Deoxygenation is fairly rapid in boiling benzene, but it is also observed at 25°C (III→II).

The oxygen adduct, $[O_2IrCl(CO)$-

Table 1. Conditions for oxygenation-deoxygenation reactions, and stabilities of the reactants. Roman numerals refer to compounds formulated in the oxygenation-deoxygenation equations.

Reaction	Ir (mole/lit.)	P_{O_2} (mm-Hg)	T (°C)	Time (hr)	Conversion (%)
		Oxygenation			
Crystals (I → IV)		150	25	$>10^4$	0
Crystals (I → IV)		740	25	120	0
Solution (II → III)	10^{-2}	130	25	25	70
Solution (II → III)	10^{-2}	670	27	4	100
(In toluene) (II → III)	6×10^{-3}	740	-78	120	25
		Deoxygenation			
Solution (III → II)	2×10^{-3}	$10^{-4} \rightarrow 5$	25	<65	20
Solution (III → II)	3×10^{-3}	($\sim$0)	80	1	100
Crystals (IV → I)		10^{-5}	25	16	0
Crystals (IV → I)		$10^{-4} \rightarrow 20$	25	240	50
Crystals (IV → I)		10^{-4}	$25 \rightarrow 200$	<1	100