764. *The Catalytic Toxicity of Nitrogen Compounds Part I. Toxicity of Ammonia and of Amines.*

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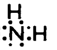
The toxicity of ammonia towards platinum in the catalytic hydrogenation of *cyclo*hexene, and the suppression of this toxicity by small concentrations of water, have been studied; this toxicity has been compared with that of the cyanide ion, which forms a convenient standard for poisons containing nitrogen. The toxicity of dry ammonia is about 40 per cent. of that of the cyanide ion. The toxicity of some typical saturated amines, and the detoxication of these amines by acetic acid, has also been studied.

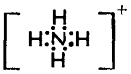
Although the toxicity of compounds of phosphorus, arsenic, and antimony towards catalysts has been studied extensively, less is known of the corresponding toxicity of compounds of nitrogen, which forms the first member of this potentially toxic fifth-group series. The subject is interesting because of the close parallelism between enzymic and catalyst poisoning, in that many classes of nitrogen compounds including the alkaloids, are strong physiological poisons. Isolated instances of catalytically toxic nitrogen compounds have long been known, for example the cyanides.

Carefully dried ammonia, dissolved in a water-free non-ionising solvent such as *cyclo*hexane, poisons a platinum catalyst in the liquid-phase hydrogenation of *cyclo*hexene,[1] the ammonium ion being non-toxic; but only a single observation was made of this, and a poisoning curve for ammonia was not determined. This difference in toxicity of ammonia and of the ammonium ion would be expected from the general rule developed for the catalytic toxicity of compounds of the non-metallic fifth- and sixth-group elements,[2] and especially for sulphur, according to which the formation of the strong poison-to-catalyst bond the strength of which is typical of toxicity, depends on the presence in the valency shells of the potentially toxic element of free electron pairs which are used to form this bond.



$$\mathrm{H{:}\overset{H}{\underset{\cdot\cdot}{N}}{:}H}$$

Toxic, non-shielded structure



$$\left[\mathrm{H{:}\overset{H}{\underset{H}{N}}{:}H}\right]^+$$

Non-toxic, shielded structure

The toxicity of ammonia towards platinum and its suppression by water have now been studied in greater detail. Dry ammonia is about 40 per cent. as toxic as the cyanide ion, which is a convenient standard for poisons containing nitrogen. This similarity, at any rate in the order of magnitude, of the catalytic toxicity of ammonia with that of the cyanides is of considerable interest. The cyanide ion, which can be written $(\mathrm{{:}C{\equiv}N{:}})^-$ in addition to other resonance components, is on grounds of its greater size and consequently greater coverage of catalyst surface, as well as the presence of two separated free electron

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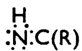
[1] Maxted and Walker, *J.*, 1948, 1093.
[2] Maxted and Morrish, *J.*, 1940, 252.

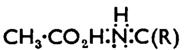
pairs, expected to be more toxic than ammonia, it being known that the effective toxicity of a poison increases with its size: further, the unsaturated internal bonding in the cyanide ion also probably contributes to the toxicity since the cyanides, in addition to containing a potentially toxic fifth-group element, also fall into the class of unsaturated poisons typified by carbon monoxide. This agreement in the order of magnitude of the toxicities, and the effect of water in the case of ammonia, have also an interest from the standpoint of the parallelism between physiological and metallic catalyst poisoning, since the low physiological toxicity of ammonia is probably due to the fact that such poisoning occurs in the presence of water: otherwise ammonia might well be as physiologically toxic as the cyanides, which are not affected by water.

This work on ammonia was supplemented by the measurement of the toxicity of typical amines. Saturated amines were chosen in order to avoid the complication of the saturation, during the hydrogenation tests used for the assessment of the toxicity, not only of the main unsaturated substrate (*cyclo*hexene) but also of the poison, with a corresponding change in its form. Such amines should give non-toxic derivatives also on addition of acids, this being so in both ionising and non-ionising solvents:



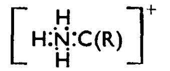
$\overset{\text{H}}{\underset{\text{H}}{\text{:N:}}}\text{C(R)}$

Free amine (unshielded, toxic type)



$\text{CH}_3\text{·CO}_2\text{H:}\overset{\text{H}}{\underset{\text{H}}{\text{N}}}\text{:C(R)}$

Undissociated acetate (shielded, non-toxic type)



$\left[\text{H:}\overset{\text{H}}{\underset{\text{H}}{\text{N}}}\text{:C(R)}\right]^+$

Corresponding substituted ammonium ion (shielded, non-toxic structure)

The course of the detoxication of butylamine by acetic acid as an alternative to water, as had been done with ammonia, was therefore studied.

EXPERIMENTAL

Toxicity of Dry Ammonia.—The hydrogenation tests, by means of which the toxic effect of progressively increased small concentrations of dry ammonia was measured, were carried out at 30° in a mechanically driven hydrogenation shaker operating under standardised conditions, the normal charge (9 c.c. of dry *cyclo*hexane containing ammonia, 1 c.c. of dry *cyclo*hexene, and 0·025 g. of stock platinum black) being contained in a hydrogenation pipette previously dried by hot air.

In order to prepare a stock solution of dry ammonia in *cyclo*hexane, a stream of ammonia from a cylinder of already substantially dry liquid ammonia was further dried by passage through carefully dried soda-lime and finally over phosphoric oxide, and passed into *cyclo*hexane previously dried with sodium. The stock solution, thus prepared, was kept dry in a doubly sealed bottle; its ammonia concentration was determined periodically by conductimetry. From this stock solution, the dilute solutions used in the tests were made by dilution with dry *cyclo*hexane. Traces of oxygen in the electrolytic hydrogen used can produce water by hydrogenation, and were eliminated by passing the hydrogen over a heated platinum filament, any water formed, together with water vapour from the hydrogenation burettes, being frozen out by passage through a capillary copper coil at −180° before the hydrogen was admitted to the hydrogenation pipette.

The toxic effect of small additions of rigorously dried ammonia on the hydrogenation rate of *cyclo*hexene is shown in curve I of Fig. 1, where curves for diethyl sulphide in *cyclo*hexane and for potassium cyanide in aqueous alcohol are shown for comparison, all the measurements being made with the same stock of platinum catalyst. The activity of the catalyst is expressed as a percentage of its unpoisoned activity. Aqueous alcohol was used for the cyanide, as potassium cyanide is insoluble in *cyclo*hexane. Under the conditions of extreme dilution used the potassium cyanide is almost completely dissociated; curve (III) can accordingly be regarded as being given by the cyanide ion, the potassium ion being non-toxic.

All these toxicity curves are of the continuously curved type rather than of the flexed, initially linear form, the occurrence of the one or of the other of these types of toxicity graph having been shown by Schwab and Waldschmidt [3] to depend on the degree of subdivision of the

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[3] Schwab and Waldschmidt, *J. Chim. phys.*, 1954, **51**, 461.

catalyst; but, if the respective concentrations of ammonia, cyanide, and ethyl sulphide necessary to depress the activity of the constant amount of catalyst to one half of its unpoisoned value are taken as a convenient (reciprocal) approximate measure of their relative toxicity, ethyl sulphide is considerably more toxic than the cyanide, and the latter than ammonia. From the curves, these half-activity values are about $2{\cdot}3 \times 10^{-6}$ mole for ammonia, $0{\cdot}85 \times 10^{-6}$ for the cyanide, and $0{\cdot}18 \times 10^{-6}$ for ethyl sulphide, giving relative toxicities approximately 0·38, 1, and 4·9 respectively.

FIG. 1. *Poisoning by* (I) *ammonia,* (II) *diethyl sulphide, and* (III) *cyanide ion.*

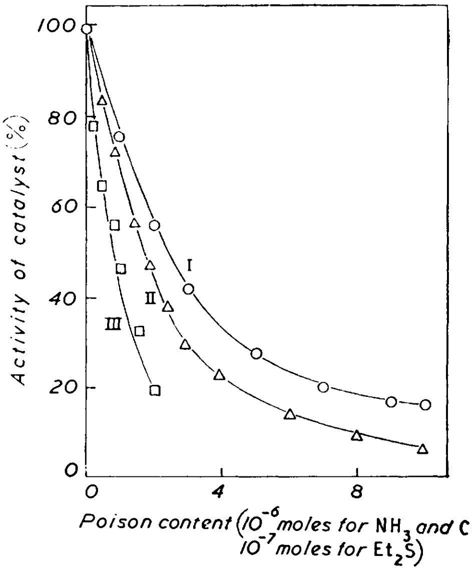


FIG. 2. *Poisoning by* (I) n-*butylamine,* (II) cyclo*hexylamine, and* (III) *dicyclohexylamine.*

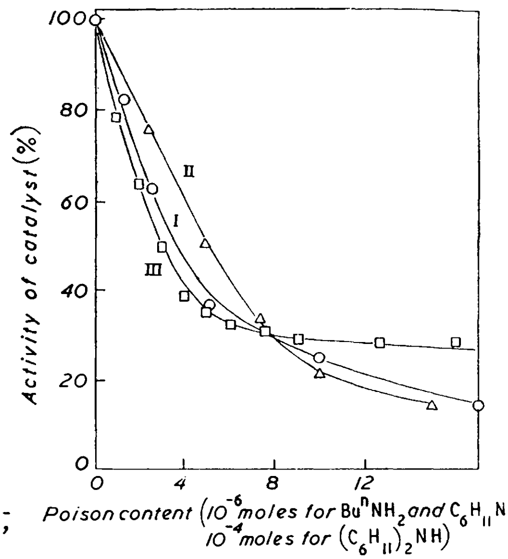
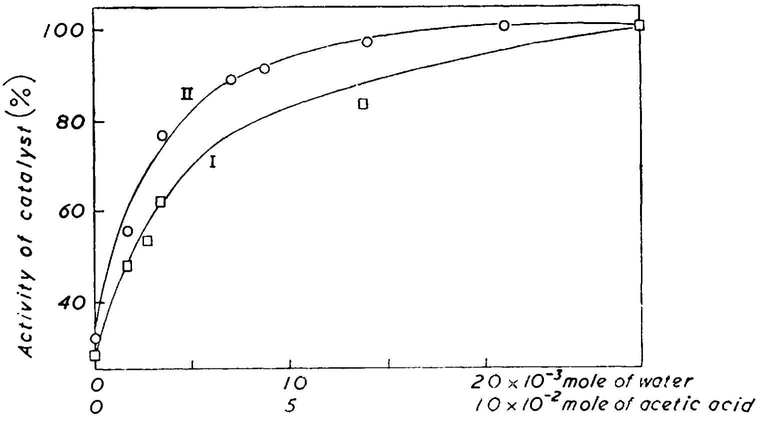


FIG. 3. *Effect of* (I) *acetic acid on poisoning by* n-*butylamine and* (II) *water on poisoning by ammonia.*



Influence of Water on the Toxicity of Ammonia.—The catalyst was poisoned by a constant amount of dry ammonia throughout, the suppression of the toxicity of the ammonia, shown by the rise in the activity of the catalyst caused by addition of a progressively increased amount of water, being measured. Although the toxicity of ammonia is very sensitive to water, the amounts of water required were too large to give a homogeneous liquid phase with the *cyclo*hexane used as solvent, and this water was accordingly added as a dilute solution in sufficient dry dioxan to give a clear solution in the hydrogenation pipette. The rest of the hydrogenation charge consisted of 0·025 g. of stock platinum, 1 c.c. of *cyclo*hexene, and 10 c.c. of solvent containing in each case 5×10^{-6} mole of dry ammonia, added in *cyclo*hexane. Accordingly, since the additions of ammonia and of water were conveniently made from standard solutions, the ratio of *cyclo*hexane to dioxan in the solvent phase varied. Since the unpoisoned hydrogenation rate varies with the composition of the solvent, blank runs without ammonia were made to eliminate this factor.

The effect on the toxicity of the constant amount of ammonia of the water content is shown in curve I of Fig. 3.

Toxicity of Amines.—*n*-Butylamine, *cyclo*hexylamine, and di*cyclo*hexylamine were studied, these being two primary amines differing largely in molecular size, and one still larger secondary amine. The last two were dried by distillation and collection of the middle fraction. *n*-Butylamine, in view of its lower b. p. (77·8°), was re-distilled over sodium wire in nitrogen. Solutions in dry *cyclo*hexane were made and tested as before. Toxicity curves are given in Fig. 2. Di*cyclo*hexylamine is only about one-hundredth as toxic as the two primary amines, which are only slightly less toxic than ammonia. Half-activity values and relative toxicites, as before, are as follows:

Poison	*M*	Half-activity value	Relative molecular toxicity
CN^-	26	$0{\cdot}85 \times 10^{-6}$	1
Ammonia	17	$2{\cdot}3 \times 10^{-6}$	0·38
n-Butylamine	73	$3{\cdot}7 \times 10^{-6}$	0·23
*cyclo*Hexylamine	99	$5{\cdot}0 \times 10^{-6}$	0·17
Di*cyclo*hexylamine	181	$3{\cdot}0 \times 10^{-4}$	0·0028

In order to discuss the factors which may contribute to this observed sequence, more systematic work, including a study of primary, secondary and tertiary amines of equal size, is being carried out.

Influence of Acetic Acid on the Toxicity of n-*Butylamine.*—Increasing amounts of acetic acid were added to a hydrogenation system containing a constant amount (5×10^{-6} mole) of butylamine, analogously to the ammonia–water series. Although a second solvent was not needed the composition of the liquid phase was altered by the addition of acetic acid. Since large amounts of it were eventually added, blank runs were again necessary.

Results are shown in curve II of Fig. 3. The detoxicating effect of this acid on butylamine is less pronounced than that of water on the toxicity of ammonia.

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