Catalytic Hydration of Nitriles to Amides

PLATINUM-CONTAINING CATALYST OFFERS NEW OPPORTUNITY

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The hydration of nitriles to amides is one of the basic transformations in organic chemistry. However, it is not generally appreciated how difficult this transformation is to carry out efficiently, since amides themselves undergo further hydrolysis to the acid. While nicotinamide and acrylamide are usually manufactured from the corresponding nitriles using metallic copper heterogeneous catalysts, applications in the fine chemicals industry are rare. Now, the use of a new platinum-containing homogeneous catalyst applicable to complex organic nitriles containing sensitive functional groups will create an opportunity for nitrile hydration in the fine chemical and pharmaceutical industries.

The hydration of nitriles to amides and the subsequent conversion to the carboxylic acid is taught at an early stage in organic chemistry courses, see Equation (i).

$$R\text{-}C\equiv N \rightarrow R\text{-}CONH_2 \rightarrow RCO_2H \qquad (i)$$

The textbooks tell us that the reaction is catalysed by acid or alkali, but often do not comment on the relative rates of the two reactions. Broadly speaking, the second step – the conversion of an amide to an acid (or a carboxylate ion) – is faster than the conversion of a nitrile to an amide, so that the isolation of the amide uncontaminated by acid is difficult. This generalisation requires some qualification, as the situation is more complicated in acidic than in basic solution (1). ("Hydrolysis" here means reaction with water, "hydration" is the result).

An alternative reagent for nitrile hydrolysis is the peroxide ion, reported over a hundred years ago (2). The kinetics of the reaction have been studied by Wiberg (3) and this approach is occasionally used today (4); however, it is not catalytic and, of course, cannot be employed where the compound might be oxidised by the peroxide.

Homogeneous Metal Ion Catalysis

It is well known that when organic molecules are co-ordinated to metal cations in organo-metallic or co-ordination compounds, they become susceptible to nucleophilic attack. A useful and well known (if slightly controversial) example is the attack of hydroxide on co-ordinated ethene in the Wacker process. In the case of nitriles, which are co-ordinated to a metal ion through the nitrogen atom, nucleophilic attack occurs at the carbon atom. Very recently Suh and colleagues working with a nickel complex of a tetradentate ligand were able to isolate an intermediate containing a hydroxy-imine unit, (I) (5).

I
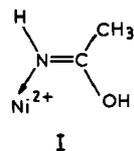
The enhancement of the rate of nucleophilic attack on nitriles co-ordinated to a metal ion is generally in the range 10^6 to 10^8 (6). However, in order to make a catalytic system, the amide needs to be expelled from the co-ordination sphere and be replaced by a new nitrile molecule. This has been accomplished by Taube and co-workers with a redox process using Ru(II)/Ru(III) (7).

Another approach which can cause large enhancements in the rate of nucleophilic attack on nitriles is to arrange for the nitrile to be attacked intramolecularly. An example of this is shown in Scheme I, in which the nitrile group of cyanomethylamine is activated by

Scheme I
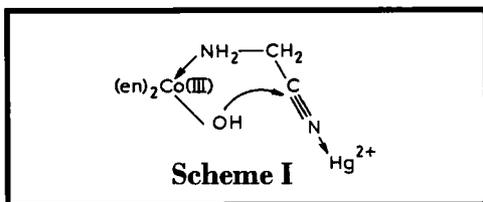
co-ordination to Hg^{2+} and undergoes intramolecular nucleophilic attack by an adjacent hydroxygroup (8). It has been estimated that in this case the combination of the intramolecular process and activation by co-ordination to Hg^{2+} accelerates the rate of hydrolysis by a factor of 10^{18}, compared with the unco-ordinated nitrile. However, the reaction is not catalytic as the amide remains in the co-ordination sphere of the cobalt.

Another system which involves intramolecular attack has been reported by Chin and coworkers using the macrocyclic tetradentate nitrogen ligand, cyclen (9). The rate enhancement due to the intramolecular attack is thought to be about 10^4, and the overall rate enhancement of nucleophilic attack on acetonitrile co-ordinated to cyclen Co(III), compared with free acetonitrile, is about 10^{10}. Sadly, however, the catalytic activity is low and the turnover number is only about 10; this is because Co(III) complexes are generally inert to substitution, although the cyclen complex is slightly less inert than most.

One of the more active catalysts so far reported
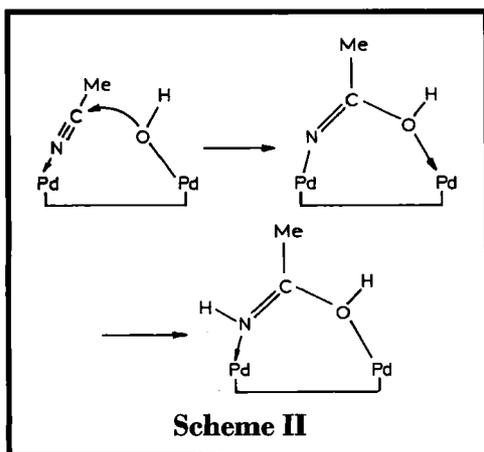
Scheme II

for nitrile hydration is a dinuclear palladium complex constructed by use of a multidentate ligand by McKenzie and Robson (10), which probably owes its high turnover number to an intramolecular nucleophilic attack (Scheme II). The catalyst does not appear to have been widely adopted by the chemical industry, possibly because of the difficulty of the ligand synthesis.

One ion which does appear able to activate a co-ordinated nitrile to nucleophilic attack, and for which the displacement of the resultant amide by a new nitrile molecule is possible, is platinum(II). Several catalysts involving platinum(II) have been reported, see Table I, but until recently none combined the advantages of metal ion activation with intramolecular attack. It appears that a good catalyst for nitrile hydration would be a platinum complex which could, in some way, promote intramolecular attack on a co-ordinated nitrile. The answer was found in secondary phosphine oxide complexes.

Secondary phosphine oxides react with nitriles at the phosphorus atom to give α-iminophosphine oxides (11), Equation (ii).

$$R_2P(O){-}H \quad + \quad R'{-}C{\equiv}N \quad \longrightarrow \quad R_2P(O){-}C(=NH){-}R' \qquad (ii)$$

α-iminophosphine oxide
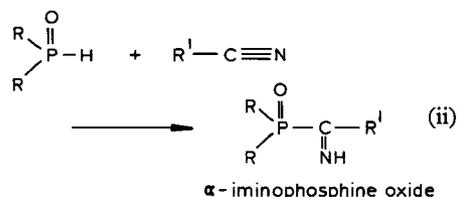
However, on co-ordination to metal ions secondary phosphine oxides become hydroxyphosphines, see Equation (iii), and so can carry out the necessary intramolecular nucleophilic attack on a co-ordinated nitrile.

$$R_2P(O){-}H \quad + \quad M^{n+} \quad + \quad R'{-}C{\equiv}N \quad \longrightarrow \qquad (iii)$$
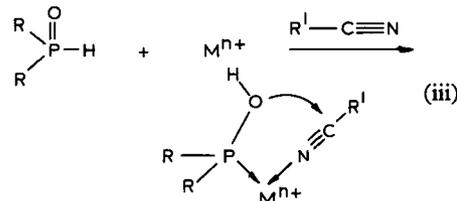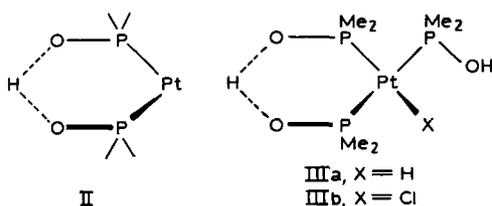
Catalysis by Phosphinito Complexes

The catalytic activity of phosphinito complexes in the hydrolysis of nitriles was discovered while studying the reactions of secondary phosphines

Table I
Comparison of Catalytic Activities for the Hydration of Acetonitrile to Acetamide

Catalyst	Temperature, °C	Turnover frequency, mol/(mol of cat.h)	Turnover number, mol/(mol of cat.)	Reference
[PtH(PMe₂OH)(PMe₂O)₂H]	90	380	5,700	12
[PtH(H₂O)(PMe₃)₂][OH]	78	178	5,000–6,000	16
[PtH(H₂O)(PEt₃)₂][OH]	78	70	not reported	16
[PdCl(OH)(bipy)(H₂O)]	76	29	not reported	17
Pt[P(cC₆H₁₁)₃]₂	80	27	405	18
Pt(PEt₃)₃	80	3	54	18
C₂₃H₂₉N₄O₂SPd₂	80	not reported	4,000	10
NaOH	78	0.4		16

in the co-ordination sphere of metals (12). It was found that under some conditions involving air or hydroxylic solvents, secondary phosphines form a six membered hydrogen bonded chelate of the type shown in II.

II

IIIa, X = H
IIIb, X = Cl

Compounds of this type have been known for many years (earlier work has been reviewed by Roundhill and colleagues (13)) and their use as hydroformylation catalysts has been investigated by van Leeuwen and co-workers (14).

The phosphinito complex IIIa catalyses the hydration of nitriles to amides, with no detectable further hydrolysis to the acid. This selective hydrolysis is very useful synthetically because, as mentioned above, the rates of hydrolysis of amides to the carboxylic acid are usually greater than the rates of hydrolysis of nitriles to amides. The catalytic hydration of nitriles using IIIa is carried out by boiling the nitrile with water under reflux, or, if the nitrile is not soluble in water, in aqueous tetrahydrofuran or ethanol.

The most active catalyst that has been found so far is derived from dimethylphosphine oxide, although complexes made from other secondary phosphine oxides are also active. Generally, an amount of 0.01 to 0.1 mole per cent of IIIa is sufficient to carry out the hydrolysis, which suggests there could be possible industrial applications (15).

A comparison of the effectiveness of the new catalyst for acetonitrile hydration, relative to some reported catalysts, is given in Table I.

The catalyst is effective with a wide range of nitriles, some of which are listed in Table II.

Interestingly, although the catalyst is a co-ordination compound of platinum, the catalysis is not inhibited by co-ordination of the pyridine nitrogen in 3-cyanopyridine. The catalyst is especially active for acrylonitrile hydrolysis: 0.004 mol per cent of catalyst is sufficient, and the turnover number exceeds 50,000.

The hydrolysis of acetonitrile also provides a test of selectivity, as usually hydration of the carbon-carbon double bond competes with amide formation (16). GLC (gas liquid chromatographic) analysis of the reaction mixture from acrylonitrile hydrolysis, using IIIa as catalyst, shows a selectivity to acrylamide of over 99 per cent.

Mechanism of Hydrolysis by Phosphinito Complexes

The most convenient catalyst precursor is the hydride complex IIIa, however, since it is insoluble, its solution NMR spectra could not

Table II
Yields and Turnover Frequencies Using Phosphinito Complex IIIa

| Nitrile	Reaction medium at reflux temperature	Isolated yield of amide, per cent	Turnover frequency, mol/(mol of cat.h)
Acetonitrile	Water	91	380
Acrylonitrile	Aqueous ethanol	93	1485
Benzonitrile	Aqueous ethanol	86	518
2,6-Difluorobenzonitrile	Aqueous tetrahydrofuran	78	220
3-Cyanopyridine	Water	91	450

be measured. Solid state NMR studies have confirmed the structure of IIIa, and have shown that the method of preparation also gives a small amount of the bis-chelate compound, IV (19). The active catalyst appears to be cationic as, although IIIb is not active, it becomes so on reaction with Ag⁺. The cationic nature of the catalytic species is also demonstrated by the fact that the catalysis can be stopped by adding halide ion.

IV

V
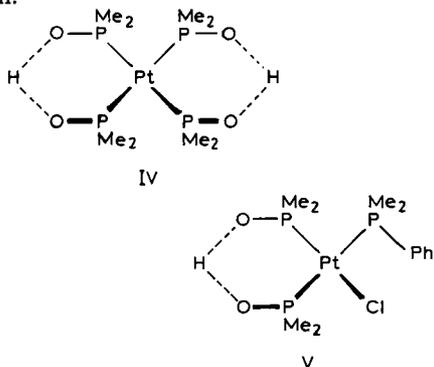
In this system we find that the catalytic activity is lowered when one of the phosphorus donors does not have a hydroxy substituent. Thus the catalyst derived from V and AgBF₄ has less than half the turnover rate of the catalyst derived from IIIb and AgBF₄. This leads us to suggest that there is an intramolecular attack by the hydroxyphosphine on the co-ordinated nitrile, as displayed by the catalytic cycle shown in Figure 1.

A related reaction has been reported by Thorn and Calabrese in which an iridium nitrile com-

plex undergoes intramolecular nucleophilic attack producing a metallocycle, however, in this case the five-membered ring is stable and no catalysis occurs (20), see Equation (iv).
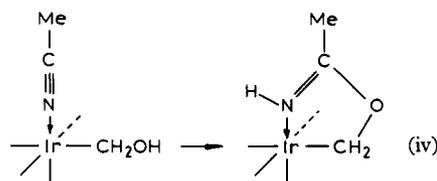

So far no conditions have been found under which free phosphine oxides catalyse the hydration of nitriles, although triphenylarsine oxide has been reported as a reagent for the hydrolysis of activated nitriles (21). Substantial increases in the rates of reaction, on comparing intramolecular and intermolecular reactions, are well known, and intramolecular reactions are important in enzyme mimics (22).
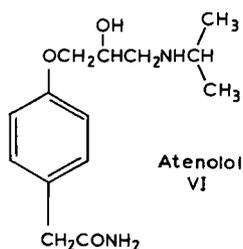
Platinum Phosphinito Catalysts in Synthesis

Two amides are now manufactured on a large scale by the hydrolysis of a nitrile to an amide; the processes being the hydrolysis of 3-cyanopyridine to nicotinamide and of acrylonitrile to acrylamide. Both these reactions can be carried out in excellent yield using the platinum phosphinito catalyst.

Another possible application for which the phosphinito catalyst has been shown to be extremely effective is in the synthesis of a β-blocker which has annual sales greater than
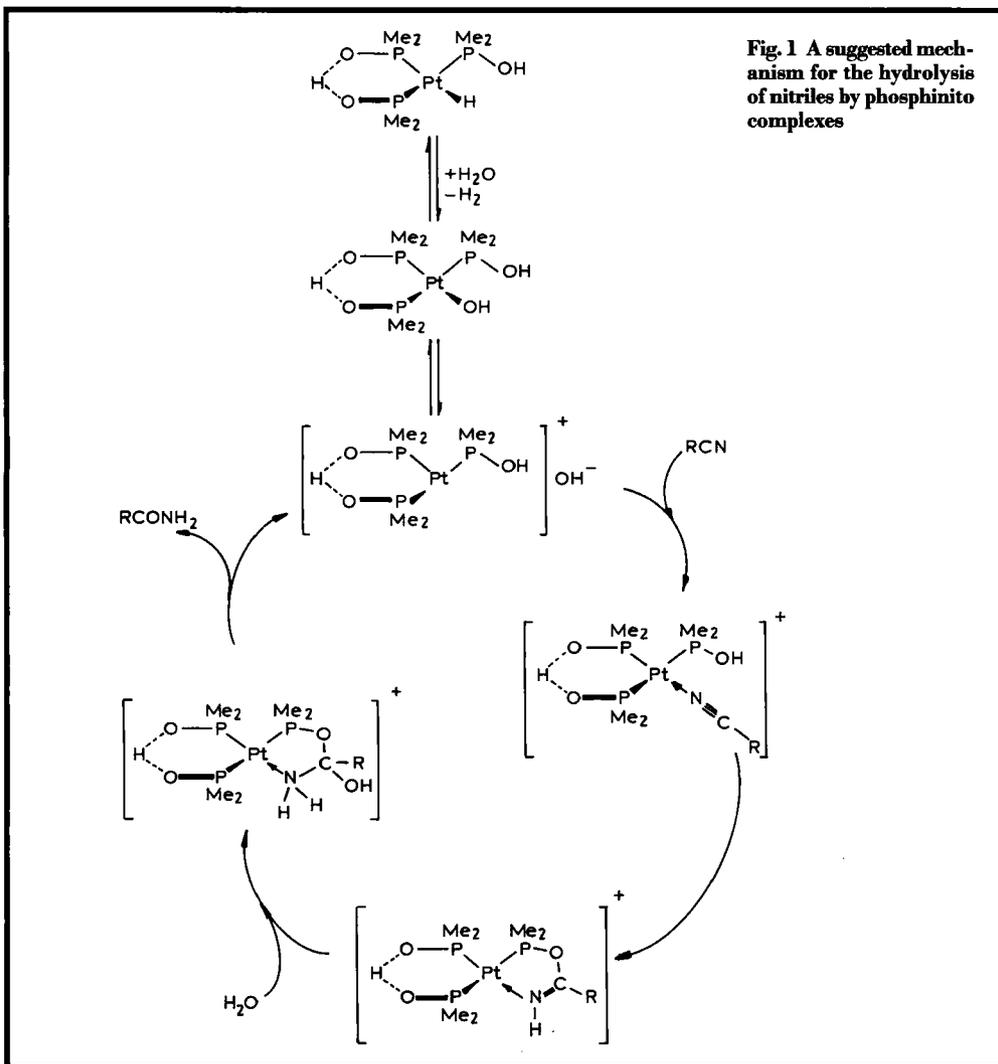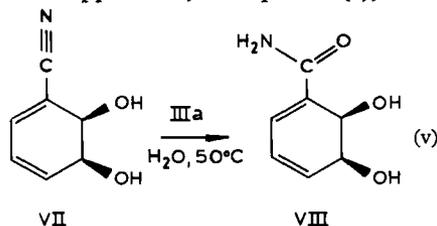
U.S.$500M: atenolol, VI. Here, the catalyst can introduce the amide group by hydrolysis of the corresponding nitrile, as the final step in the synthesis, or it can be used to convert p-hydroxyphenylacetonitrile into p-hydroxyphenylacetamide,

Atenolol
VI

which is used in the existing synthesis (23).

Another application, see Equation (v), which

$$(v)$$

VII   **VIII**

shows the compatibility of the catalyst with functional groups, is the hydrolysis of the nitrile VII to the amide VIII (24). In this case, despite the danger of aromatisation, the conversion was

essentially quantitative, with an 88 per cent yield after recrystallisation.

Other work on nitrile hydration, not involving the platinum group metals, has been undertaken, but is not discussed here.

Conclusion

The hydration of nitriles, while being one of the classic reactions of organic chemistry, is, at present, used comparatively little in the fine chemicals industry. The discovery of extremely active platinum-containing homogeneous catalysts, in particular one derived from dimethylphosphine oxide, which can hydrate several nitriles in aqueous media and in particular, can hydrate acetonitrile with a turnover number of over 50,000, suggests that the fine chemical and pharmaceutical industries will in future be able to make use of this reaction much more widely.

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The Fourth Edition of the recently published Volume 19 of the Kirk-Othmer "Encyclopedia of Chemical Technology" contains sections covering the platinum group metals and their compounds. The first section overviews sources, mineralogy, recovery, refining and economic aspects, uses and physical properties, and is well illustrated by Tables.

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