Nickel(II) Bis(phosphine) Complexes

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The synthesis, characterization, disproportionation, and dynamic ligand-exchange reactions of the complexes [Ni(dppe)X2], where X = dpp, dpp = 1,2-bis(diphenylphosphino)ethane, and dppe complexes, where X = Cl or NO2, are reported. For [Ni(dppe)X2], the halide affinity in chloroform was determined to be Cl > Br > I by 31P NMR spectroscopy, and dppe complexes were more stable than dppe complexes. Chloride and bromide ions place the P-P bonds in closer contact than in the dppe complex, which is consistent with the formation of more stable complexes. The latter cross-links intrastrand guanine bases on DNA, whereas the tetrahedral gold(I) dppe complex cross-links towards thiols and also exhibits a broad spectrum of antitumor activity. The mechanism of action appears to differ from that of cisplatin. The latter cross-links intrastrand guanine bases on DNA, whereas the tetrahedral gold(I) dppe complex cross-links proteins to DNA. Although auranofin is potentially cytotoxic to tumor cells in culture, it is active only against one tumor model in vivo. The bis(phosphine) complexes such as XAu(dppe)AuX (X = dpp) containing linearly coordinated gold(I) exhibit a wider spectrum of activity but are readily converted into four-coordinate tetrahedral gold(I) complexes by thiols and in blood plasma. Tetrahedral complexes such as [Au(dppe)Cl] are reactive toward thiols and also exhibit a broad spectrum of antitumor activity.

Introduction

Current medical interest in metal phosphine complexes ranges from the clinical use of a triethylgold(I) complex, auranofin ("Ridaura"), as an antiarthritic agent, through the investigation of positively charged technetium complexes as heart-imaging agents, to the anticancer activity of certain phosphine complexes.

Although auranofin is potentially cytotoxic to tumor cells in culture, it is active only against one tumor model in vivo. Bridged bis(phosphine) complexes such as XAu(dppe)AuX (X = dpp) containing linearly coordinated gold(I) exhibit a wider spectrum of activity but are readily converted into four-coordinate tetrahedral gold(I) complexes by thiols and in blood plasma. Tetrahedral complexes such as [Au(dppe)Cl] are reactive toward thiols and also exhibit a broad spectrum of antitumor activity. The mechanism of action appears to differ from that of cisplatin. The latter cross-links intrastrand guanine bases on DNA, whereas the tetrahedral gold(I) dppe complex cross-links proteins to DNA. The complex [Au(dppe)Cl] does not lose activity against a subline of P388 leukemia, which is resistant to cisplatin, and moreover, [Au(dppe)Cl] and cisplatin can be administered concurrently at their respective maximum-tolerated doses to tumor-bearing mice with no lethality. The combination is more effective against moderately advanced P388 leukemia than cisplatin alone. These results indicate that the mechanism or site of action of the bis(phosphine) complex is different from that of cisplatin.

The recent work of Kish et al. suggests that the lipophilic cation [Au(dppe)]2+ and related complexes belong to a novel class of inhibitors of mitochondrial function. The complex causes a rapid, dose-related collapse of the inner mitochondrial membrane potential accompanied by an efflux of calcium. It is very effective in depleting cellular ATP levels. These reactions may give rise to some of the toxic side effects of the complex.

In our attempts to design more effective bis(diphosphine) complexes we have assumed that Au(I) acts as a carrier for the reactive bis(diphosphine) ligand and therefore some kinetic lability in the metal–phosphine bonds is required for activity. Thus, tetrahedral bis(phosphine) complexes of Cu(I) and Ag(I) are also active antitumor agents. In contrast, the complexes [M(dppe)Cl2] of the group 10 metal ions M = Pd(II) and Pt(II) are inactive. However, Ni(II) complexes are known to be more kineticlally labile and therefore it seemed likely that Ni(II) bis(phosphine) complexes might exhibit antitumor activity. Although the synthesis of several mono- and bischelated complexes has been reported there seems to be few data on their stability and ligand-exchange rates in solution. As necessary preliminary work prior to antitumor testing, which will be reported elsewhere, we have therefore studied the solid-state and solution chemistry of Ni(II) bis(phosphine) complexes by conductivity, magnetic susceptibility, infrared spectroscopy, electronic ab

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[1] Abbreviations: CPMAS, cross polarization magic angle spinning; dppe, 1,2-bis(diethylphosphino)ethane (Et2PCH2CH2P(=O)Et); dpp, 1,2-bis(diphenylphosphino)ethane (Ph2PCH2CH2P(=O)Ph); dppe, 1,2-bis(diphenylphosphino)ethane (Ph2PCH2CH2P(=O)Ph); dppe, 1,2-bis(diphenylphosphino)ethane (Ph2PCH2CH2P(=O)Ph).


sorption, and NMR spectroscopic measurements.

Experimental Section

Solid-State NMR Spectroscopy. Solid-state $^{31}P$ NMR spectra were recorded by Dr. Groomebridge of the University of London Intercollege Research Service on a Bruker MSL-300 at 121.5 MHz with high-power proton-decoupling, cross polarization from protons and magic angle spinning (CPMAS). Samples (0.1-0.3 g) were packed into an aluminum oxide double air-bearing rotor (6.95 mm o.d.) for spinning at 4.4-4.6 kHz. Contact times were 10 ms, except for that of [Ni- (dppe)$_2$X$_2$], which was 1 ms, pulse cycle repetition times were 10-30 s, and receiver dead times were 10-25 μs. The reference was H$_3$PO$_4$ (external).

Spectra were analyzed by the primary components of the shielding tensors by using the theory of Maricq and Waugh. The components were calculated from the measured peak intensities by using the program TENSOR written by Dr. C. Groomebridge. Estimates of errors were obtained by varying the intensity values by amounts equal to the baseline noise.

Solution NMR Spectroscopy. $^1$H NMR spectra were recorded on a JEOL FX200 spectrometer at 199.5 MHz using 5-mm tubes, 2-kHz frequency width, 60-65° pulses, 4-s acquisition time, 2-s pulse delay, and 16k data points. The internal reference was TMS. $^{31}$P [$^1$H] NMR spectra were recorded on either JEOL FX60, Bruker WM202, or Bruker AM500 instruments at 24.15, 81.00, or 202.4 MHz, in 8 or 10.15, or 5-mm tubes, respectively. Typically, pulse widths were 45-90°, pulse delays 2.2-2.5 s, sweep widths 4-50 kHz, and acquisition times 0.02-1.6 s, and there were 8-16k data points. The shift reference was 85% H$_3$PO$_4$ (external, with a CDC$_1$Cl or D$_2$O lock as appropriate for the compounds).

$^3$J(P-H) values were measured by using the inversion-recovery method with $^1$H decoupling. The samples were not degassed, and Teflon plugs were used to limit vortexing. Peak heights were used for the logarithmic plots.

Magnetization Transfer. Measurements of exchange rates by magnetization transfer were carried out on a Bruker WM202 at 81 MHz. A typical sample contained [Ni(dppe)$_2$Br$_2$] (12.3 mg, 20 μmol) and dppe (80 μg, 0.20 μmol) in ca. 5 mL of CHCl$_3$-CDC$_3$ (1:1 v/v). Exact volumes were determined by weighing, and the NMR tube was sealed by plastic film to minimize evaporation losses.

Selective peak excitation was achieved by using a DANTE sequence:

$$D_1-(P_1-D_1)^2, \text{ with the transmitter offset set to the frequency of the resonance to be inverted. The parameters were chosen, and the selectivity was checked by using D_1-(P_1-D_1)_2-Acq with P_1 adjusted such that (P_1-D_1)_2, resulted in a 90° pulse. This was increased to 180° and a hard pulse added to give D_1-(P_1-D_1)_2-VD-90°-Acq. The time interval D_1 was chosen to allow complete recovery of all magnetization, and D_2 was sufficiently short that transmitter sidebands at 1/2D_2 lay outside the spectral window of the variable delay or mixing time. Typical values used for [Ni(dppe)$_2$Br$_2$]-dppe were as follows: D_1, 8 s; P_1, 2.2 μs; D_2, 100 μs; VD, 1-5 ms and 8 s. The approximate selectivity of the DANTE sequence was therefore $[n(P_1 + D_1)^2]^{-1} = 466$. For [Ni(dppe)-dppe], the relaxation delay was 14 s and the mixing times were extended up to 0.5 s. Integrations or peak weights of peaks enabled the equilibrium proportions of each species to be calculated and hence the equilibrium constants. The absolute quantities and the peak heights in the fully relaxed spectra were used to scale the other spectra in the set, and the magnetizations were expressed in micromole equivalents. From plots of magnetization against VD, the rates of change of magnetization were obtained for substitution into eqs 12-14 in the Appendix.

UV–Visible and IR Spectroscopy. UV–visible absorption spectra were recorded on a Perkin-Elmer 544 or Lambda 3 instrument using 1 cm path-length cells at ambient temperature. IR spectra were recorded on a Perkin-Elmer 597 instrument. Samples were in Nujol and placed in path-length cells at ambient temperature.

Conductivity. Conductivities on 1 mM solutions at 25°C were measured using a Griffin bridge with Cadmium electrodes. Known salts and bis(phosphine) ligands were measured as references.

Magnetic Susceptibilities. These were measured by using a JME magnetic susceptibility balance and Hg[Co(SCN)$_4$] as calibrant. Diamagnetic corrections for the phosphine ligands were measured, and those for Ni(II) and halides were taken from Figgis and Lewis.

Syntheses. The complexes [Ni(P-P)$_2$X$_2$] and [Ni(P-P)$_3$]X$_2$ were prepared by using published procedures except that an N$_2$ atmosphere was not used for dppe and dppey, which are both released in air. Previous reports have rarely included mp’s. The complexes are all soluble in polar solvents such as chloroform and acetone, dimethylacetamide, and acetonitrile, slightly soluble in methanol and ethanol, but insoluble in water and nonpolar organic solvents (e.g., toluene, cyclohexane). A table of elemental analyses, yields, colors, and melting points has been deposited as supplementary material (Table D1).

[Ni(dppe)$_2$X$_2$] (X = Cl, Br, I). These were made by the method of both Booth and Chatt and recrystallized from CHCl$_3$ or alcholic CHCl$_3$.

[Ni(dppe)$_2$X$_2$] (X = Br, I, NO$_3$). These were made by a method similar to that of Chatt et al., except that dppe was dissolved in EtOH prior to the addition of the dissolved metal salt. For X = Br a better yield was obtained with dppe in excess. The complexes were recrystallized from EtOH-H$_2$O.

[([Ni(dppe)$_2$X$_2$] ] (X = Cl, Br). These were made by the method of McAlulife and Meek except that the reactions were stirred for only 10 min and hydrated metal salts were used. The complexes were recrystallized from EtOH-CHCl$_3$.

[([Ni(dppe)$_2$X$_2$] ] (X = Cl, Br) and [Ni(dppe)$_2$Br$_2$]. The metal salts were dissolved in EtOH, and after N$_2$ bubbling (>15 min), the liquid phosphine was added either by direct methods (eppe) or in solution with CHCl$_3$ (dppe). The color formed immediately, and after stirring for ca. 10 min under N$_2$, the solution was concentrated under reduced pressure and the precipitate collected by filtration.

Oxidized Phosphines. Dppe and dppey were oxidized by the method of Slinkard and Meek. DpeO$_2$ and eppeO$_2$ were prepared by dissolving the liquid phosphines in toluene and heating at 80°C with a slight excess of H$_2$O. The aqueous layer was separated and freeze-dried to give viscous products.

Results

Syntheses. The monoatomic complexes [Ni(P-P)$_2$X$_2$] (P-P = dppe, dppey = X = Cl, Br, I) were easily made. [Ni(dppe)(NO$_3$)$_2$] could not be prepared, and the bis complex was isolated instead. Of the bis complexes, the nitrate formed the most readily, indicative of the weakness of NO$_3$- coordination compared with the halides. [Ni(dppe)$_2$Cl$_2$] could not be isolated, as has been found previously, suggesting that Cl$^-$ displaces bound phosphine.

Solid-State Studies. Magnetic Measurements. The magnetic moments of the complexes [Ni(dppe)$_2$X$_2$] (X = Cl, Br, I), [Ni(dppe)$_2$X$_2$] (X = Br, I, NO$_3$), and [Ni(dppe)$'$(dppe)$_2$X$_2$] (X = Cl, Br) (Table D2, supplementary material) were within the range 0.35-0.83 μμ$_B$ (lit. 0.3-0.6 μμ$_B$) ascribable to temperature-independent paramagnetism in predominantly square-planar complexes.

Infrared Spectroscopy. The spectra of [Ni(dppe)$_2$X$_2$] (X = Cl, Br, I) contained many bands in the region 250-400 cm$^{-1}$ and were very similar to each other and also to dppe. The positions of the bands in the region 250-400 cm$^{-1}$ are listed in the supplementary material, Table D3. The spectra of [Ni(dppe)$_2$X$_2$]...
The other spectra), perhaps because the proton dppeO, was detected in the spectrum of \([\text{Ni(dppe)}]_2(\text{NO}_3)_2\), which complexes have been assigned a planar structure and the band the order CI

\[
\text{CI} > \text{Br} > \text{I},
\]

were line widths. The 3p FT Data for Bis(phosphines), Bis(phosphine) Oxides, and Ni(II) Bis(phosphine) Complexes at 81 MHz, 300 ± 2 K, in CDCl_3–CHC1, 1:1

\[
\begin{array}{cccc}
\text{compd} & \text{conc/mM} & T_1/\text{s} & \text{compd} & \text{conc/mM} & T_1/\text{s} \\
\hline
\text{dppe} & 9.7 & 8.6 & \text{dppey} & 5.2 & 20 \\
\text{dppeO}_2 & 10.0 & 9.2 & \text{dppeO}_2 & 10.6 & 17 \\
[\text{Ni(dppe)Cl}]_2 & 10.0 & 0.51 & [\text{Ni(dppe)Cl}]_2 & 2.1 & 2.8 \\
[\text{Ni(dppe)Br}]_2 & 1.0 & 0.49 & [\text{Ni(dppe)Br}]_2 & 2.1 & 2.9 \\
[\text{Ni(dppe)I}]_2 & 6.6 & 0.21 & [\text{Ni(dppe)I}]_2 & 0.5 & 1.3 \\
[\text{Ni(dppe)}_2(\text{NO}_3)_2 & 8.7 & 0.15 & [\text{Ni(dppe)}_2(\text{NO}_3)_2 & 1.1 & 1.7 \\
\text{Ni(dppe)}_2(\text{NO}_3)_2 & 1.1 & 1.5 & [\text{Ni(dppe)}_2(\text{NO}_3)_2 & 0.96 & 1.5 \\
\end{array}
\]

appeared colorless within 24 h at ambient temperature. The shoulder at ca. 415 nm may be the \(3\Delta_{1g} \rightarrow T_{2g}(P)\) transition of dppm or methanol-coordinated Ni(II). The spectra of free ligands and their oxides were not easily distinguished, so the spectra after 24 h cannot be unambiguously assigned.

**Conductivity.** Conductivities in acetonitrile solutions are given in the supplementary material, Table D6. [Ni(dppe)Cl]_2 is a nonconductor, as was shown previously for [Ni(dppe)]_2X (X = Cl, Br, I) in nitrobenzene; in contrast, the dibromo and diiodo complexes show much greater dissociation in acetonitrile, the latter approaching a 1:1 electrolyte after 1 day. [Ni(dppe)I]_2 is a 1:1 electrolyte in acetonitrile. The conductivities of the complexes [Ni(dppe)]_2X (X = Br, I) have been reported to be less than for 1:1 electrolytes in nitrobenzene and nitroethane; in nitromethane, they are 1:1 electrolytes. Simple dissociation of one dppe ligand from the bischelated complex did not account for the observed conductivities although formation of a five-coordinate complex would. However, McAuliffe and Meek failed to isolate [Ni(dppe)]_2X' from a variety of solvents, and there was no evidence for such species in their 31P NMR spectra. [Ni(dppe)]_2(\text{NO}_3)_2 behaved as a 1:2 electrolyte in acetonitrile as it does in nitroethane. Conductivities of both dppe and dppm complexes increased in the order CI > Br > I, the order of the rates of dissociation. The low conductivities of [Ni(dppe)]_2X (X = Cl, Br, I) in acetonitrile agree with earlier measurements in nitromethane. In methanol, [Ni(dppe)]_2Cl was a 1:2 electrolyte consistent with the formation of [Ni(dppe)]_2Cl, and NiCl_2.

**NMR Spectroscopy.** The range of 1H chemical shifts showed that all the complexes were diamagnetic in chloroform. 3p FT Data for Bis(phosphines), Bis(phosphine) Oxides, and Ni(II) Bis(phosphine) Complexes at 81 MHz, 300 ± 2 K, in CDCl_3–CHC1, 1:1

\[
\begin{array}{cccc}
\text{compd} & \text{conc/mM} & T_1/\text{s} & \text{compd} & \text{conc/mM} & T_1/\text{s} \\
\hline
\text{dppe} & 9.7 & 8.6 & \text{dppey} & 5.2 & 20 \\
\text{dppeO}_2 & 10.0 & 9.2 & \text{dppeO}_2 & 10.6 & 17 \\
[\text{Ni(dppe)Cl}]_2 & 10.0 & 0.51 & [\text{Ni(dppe)Cl}]_2 & 2.1 & 2.8 \\
[\text{Ni(dppe)Br}]_2 & 1.0 & 0.49 & [\text{Ni(dppe)Br}]_2 & 2.1 & 2.9 \\
[\text{Ni(dppe)I}]_2 & 6.6 & 0.21 & [\text{Ni(dppe)I}]_2 & 0.5 & 1.3 \\
[\text{Ni(dppe)}_2(\text{NO}_3)_2 & 8.7 & 0.15 & [\text{Ni(dppe)}_2(\text{NO}_3)_2 & 1.1 & 1.7 \\
\text{Ni(dppe)}_2(\text{NO}_3)_2 & 1.1 & 1.5 & [\text{Ni(dppe)}_2(\text{NO}_3)_2 & 0.96 & 1.5 \\
\end{array}
\]

appeared colorless within 24 h at ambient temperature. The shoulder at ca. 415 nm may be the \(3\Delta_{1g} \rightarrow T_{2g}(P)\) transition of aquea- or methanol-coordinated Ni(II). The spectra of free ligands and their oxides were not easily distinguished, so the spectra after 24 h cannot be unambiguously assigned.
Nickel(II) Bis(phosphine) Complexes

Table III. $^{31}$P($^1$H) NMR Chemical Shifts ($\delta$) and Coupling Constants ($J$) of Species Observed in Titrations and Mixed Solutions of Ni(II) Bis(phosphines)

<table>
<thead>
<tr>
<th>compd</th>
<th>$\delta$</th>
<th>$J_{PP}/$Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ni(dppe)ClBr]</td>
<td>63.1</td>
<td>64</td>
</tr>
<tr>
<td>[Ni(dppe)BrI]</td>
<td>61.1</td>
<td></td>
</tr>
<tr>
<td>[Ni(dppe)ClI]</td>
<td>72.4</td>
<td>48</td>
</tr>
<tr>
<td>[Ni(dppe)ClBr]</td>
<td>71.6</td>
<td></td>
</tr>
<tr>
<td>[Ni(dppe)BrI]</td>
<td>67.3</td>
<td>60</td>
</tr>
<tr>
<td>[Ni(dppe)ClBr]</td>
<td>66.7</td>
<td></td>
</tr>
<tr>
<td>[Ni(dppe)BrI]</td>
<td>71.1</td>
<td>50</td>
</tr>
<tr>
<td>[Ni(dppe)ClI]</td>
<td>68.0</td>
<td></td>
</tr>
<tr>
<td>[Ni(dppe)ClBr]</td>
<td>80.8</td>
<td>36</td>
</tr>
<tr>
<td>[Ni(dppe)ClI]</td>
<td>80.3</td>
<td></td>
</tr>
<tr>
<td>[Ni(dppe)BrI]</td>
<td>77.3</td>
<td>41</td>
</tr>
<tr>
<td>[Ni(dppe)ClI]</td>
<td>73.6</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Tentative assignment.

presumably by exchange, but were well resolved at 202 MHz. New species were identified by their $^{31}$P chemical shifts and, in the case of mixed halide complexes, their $^{31}$P-$^{31}$P coupling constants, which are listed in Table III. ($J_{PP}$-$^{31}$P can be seen to be smaller in the dppe complexes than in the dppe complexes. Approximate equilibrium constants were calculated from peak areas, and the values are listed in Table IV. The order of halide affinities for Ni(P-P) is Cl > Br > I.

Phosphine Exchange. [Ni(dppe)X] + dppe. Addition of dppe to a solution of [Ni(dppe)Cl] caused a new peak to appear in the 202-MHz $^{31}$P($^1$H) NMR spectrum at 49.3 ppm, identified as [Ni(dppe)Cl] (Table V). Addition of a second equivalent of dppe caused this resonance to increase in intensity. At 24 MHz, peaks were broadened and overlapped (Figure 2). From this coalescence behavior, an approximate exchange rate for dppe between mono- and bischelated species was calculated to be 460 s$^{-1}$. With the assumption of a second-order reaction (association of dppe with the mono chelate), this gives a second-order rate constant of ca. 5 x 10$^4$ M$^{-1}$ s$^{-1}$. In contrast to [Ni(dppe)Cl], for which a peak persisted even after the addition of 2 mol equiv of dppe, addition of 1 mol equiv of dppe to the iodide complex produced wholly the bischelated species [Ni(dppe)$_2$] and further addition of dppe led to the appearance of a peak for free dppe (slow exchange). Intermediate behavior was observed for the bromide complex.

[Ni(dppe)X] + dppe. Titrations of dppe into [Ni(dppe)X] gave sharp peaks in the region 45-57 ppm even at 24 MHz, suggesting a slower rate of exchange compared to dppe. As with dppe, 3 mol equiv of dppe did not displace all the bound chloride, whereas [Ni(dppe)$_2$] formed stoichiometrically for the iodide complex.

Mixed Titrations. Careful consideration of relative peak heights, concentrations, and $T_a$ values allowed assignment of resonances to mixed bis chelates, as shown in Table III.

Phosphine-Exchange Rates by Magnetization Transfer. Since many of the systems above exhibit separate NMR resonances from magnetically distinct species (i.e., slow exchange), exchange rates were studied by magnetization transfer with the equations described in the Appendix. A set of spectra from a typical magnetization-transfer experiment is shown in Figure 3, together with magnetization against time plots.

The equilibrium constant ($K$) for the reaction of [Ni(dppe)Br] with dppe

$$[\text{Ni(dppe)Br}] + \text{dppe} = [\text{Ni(dppe)}]^{2+} + 2\text{Br}^{-}$$

was calculated to be 0.05 ± 0.02 M. Six inversion experiments were carried out and sixteen values of $k_a$ calculated. The mean and standard deviation ($\sigma_{k_a}$) were (5.2 ± 3.2) x 10$^4$ M$^{-2}$ s$^{-1}$, yielding $k_a = (4.1 ± 1.6) x 10^6$ M$^{-1}$ s$^{-1}$.

For the dppe complex, the equilibrium constant for the reaction

$$[\text{Ni(dppe)Br}] + \text{dppe} = [\text{Ni(dppe)}]^{2+} + \text{Br}^{-}$$

was about 6.0, and the exchange rate was much less favorable for magnetization-transfer experiments. From two experiments, $k_a$ appeared to be ca. 10$^8$ M$^{-1}$ s$^{-1}$ and $k_b$ 10-10$^8$ M$^{-2}$ s$^{-1}$.

Discussion

Nickel(II) Bis(phosphine) Complexes in the Solid State. Very few solid-state $^{31}$P NMR studies of phosphines coordinated

Table IV. Successive Stability Constants for Ni(II) Bis(phosphine) Halides Calculated from $^{31}$P($^1$H) NMR Spectra at 81 MHz

<table>
<thead>
<tr>
<th>(P-P)</th>
<th>X</th>
<th>Y</th>
<th>$K_1^a$</th>
<th>$K_2^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>dppe</td>
<td>I</td>
<td>Br</td>
<td>11.6</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>Cl</td>
<td>3.6</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>Cl</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>dppe</td>
<td>I</td>
<td>Br</td>
<td>8.9</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>Cl</td>
<td>9.4</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>Cl</td>
<td>7.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

$^a$ $K_1 = [\text{Ni(P-P)XY}] [\text{X}]/[\text{Ni(P-P)X}_2] [\text{Y}]$; $K_2 = [\text{Ni(P-P)Y}_2] [\text{X}] / [\text{Ni(P-P)XY}]$.

Figure 2. 24-MHz $^{31}$P($^1$H) NMR spectra of [Ni(dppe)Cl] (10 mM) in CDC$_2$ in the presence of various amounts of added dppe (mol equv).

Table V. $^{31}$P($^1$H) NMR Data at 81 MHz for Ni(II) Bis(phosphine) Complexes in CDC$_2$-CHC$_2$ (1:1)

<table>
<thead>
<tr>
<th>complex</th>
<th>$\delta$</th>
<th>$\Delta_{obs}$</th>
<th>complex</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ni(dppe)Cl]</td>
<td>58.2</td>
<td>70.0</td>
<td>[Ni(dppe)Cl]</td>
<td>64.9</td>
</tr>
<tr>
<td>[Ni(dppe)Br]</td>
<td>66.4</td>
<td>78.2</td>
<td>[Ni(dppe)Br]</td>
<td>74.0</td>
</tr>
<tr>
<td>[Ni(dppe)I]</td>
<td>78.2</td>
<td>90.0</td>
<td>[Ni(dppe)I]</td>
<td>87.5</td>
</tr>
<tr>
<td>[Ni(dppe)Br]</td>
<td>49.6</td>
<td>61.4</td>
<td>[Ni(dppe)Cl]</td>
<td>74.4</td>
</tr>
<tr>
<td>[Ni(dppe)I]</td>
<td>49.3</td>
<td>61.1</td>
<td>[Ni(dppe)Br]</td>
<td>60.7</td>
</tr>
<tr>
<td>[Ni(dppe)I]</td>
<td>55.7</td>
<td>67.5</td>
<td>[Ni(dppe)Br]</td>
<td>67.8</td>
</tr>
</tbody>
</table>

$^a$ Coordination chemical shift $\Delta_{obs} = \delta(\text{complex}) - \delta(\text{ligand})$. $^b$ Not resolved. 24.25 MHz in CHC$_2$.
phosphines\textsuperscript{38-40} have been reported, although extensive use is made of solution \textsuperscript{31}P NMR chemical shifts, \( \delta \), to characterize such compounds. Solution chemical shifts are averages, corresponding to \( \sigma_{90} \) in the solid state, and it might be expected that the principal components of the shift tensor, \( \sigma_{11}, \sigma_{22}, \) and \( \sigma_{33} \), would show better correlations with structural parameters than would \( \sigma_{90} \) or \( \delta \). This has been shown to be the case for a series of phosphido-bridged diron complexes.\textsuperscript{39} The data in the Table I appear to be the first reported for a series of mononuclear phosphine complexes. It is apparent that relatively small changes in \( \sigma_{90} \) mask larger changes in the components, especially \( \sigma_{22} \) and \( \sigma_{33} \). The chemical shift anisotropy, \( \Delta \sigma \), for dppe was much less for the free ligand than for the complexes. Several phosphines PR\(_1\)R\(_2\)R\(_3\) have been shown to be the case for a series of phosphido-bridged diron complexes.\textsuperscript{39} Our measurements on free and complexed dppe show that the dipolar mechanism probably does not dominate the spin-lattice relaxation of these complexes either. The decrease in \( T_1 \) upon coordination of monodentate arylphosphines\textsuperscript{46} has been attributed to increased shielding anisotropy.\textsuperscript{45} Measurements show that \( \Delta \sigma \) for triphenylphosphine increases from 50 ppm when free\textsuperscript{45} to 121-222 ppm when complexed.\textsuperscript{35,48} Our measurements on free and complexed dppe show this also to be the case for the bidentate phosphine, so the decreased \( T_1 \) of the complexes (Table II) is probably a consequence of increased shielding anisotropy.

The \( T_1 \) values of the compounds studied cover 2 orders of magnitude. This would be expected to lead to problems in choice of a pulse delay time. However, it was found that in solutions of Ni(II), dppe, and halides, where comparisons of peak intensities were required to estimate relative concentrations, the ligands were exchanging at a rate fast relative to \( T_1^{-1} \). Thus determinations of \( T_1 \) for a mixture of dppe-Ni(dppe)Br\(_2\) (1:1 mol/mol) in chloroform returned averaged values of 0.8 s (±0.1 s), and the peak heights at any pulse delay were proportional to concentration. The only exception was oxidized dppe, i.e. dppeO\(_2\). This did not exchange, and its \( T_1 \) remained long. In contrast, measurements of \( T_1 \) in a chloroform solution of dppe-Ni(dppe)Br\(_2\) (1:1 mol/mol) gave values very close to those for the isolated species, and the rate of exchange must have been slower than the shortest \( T_1 \) observed (1.4 s), which put an approximate upper limit of 0.7 s\textsuperscript{-1} on the rate, and gives a second-order rate constant of \(<350 \text{ M}^{-1} \text{ s}^{-1})\). Bearing in mind the above results, it was possible to interpret and assign the spectra from the competition and exchange experiments. The order of halide affinities for Ni(P-P) was Cl > Br > I, and the tendency for bis chelation


\textit{Figure 3.} (A) 81-MHz \textsuperscript{31}P/\textsuperscript{1}H NMR spectra of [Ni(dppe)Br\(_2\)] in the presence of added dppe (1 mol equiv) in chloroform solution. The magnetization of [Ni(dppe)\(_2\)]\textsuperscript{2+} was inverted, and spectra were acquired after a delay of \( \tau \). Assignments: (a) [Ni(dppe)Br\(_2\)]; (b) [Ni(dppe)J\(_2\)]\textsuperscript{2+}; (c) dppeO\(_2\); (d) dppe. (BC) Changes in magnetization (M/\mu mol equiv) of [Ni(dppe)\(_2\)]\textsuperscript{2+} and [Ni(dppe)Br\(_2\)], respectively, at times \( t \) following inversion of the magnetization of [Ni(dppe)\(_2\)]\textsuperscript{2+}. Solid lines are best fits, weighted toward earlier points.
in the presence of halide or NO₃⁻ increased in the order Cl < Br < I < NO₃⁻. This behavior is typical of a class "a" metal ion and contrasts with the usual behavior of Pd(I) and Pt(I) which are class "b" ions. Both the mono- and bischelated dppey complexes contrasts with the usual behavior of Pd(I) and Pt(I) which are of complexes as the halide was changed Cl⁻.

Consistent with the increasing conductivities of the monochelated compounds in polar, nonprotic solvents and not simple measurements which appear to have been previously reported are for similar rates for the bromide and chloride complexes, although very notable biological systems there are many potential ligands for Ni(II), where L, ML, and ML₂ denote nuclei in the free ligand, mono-resonances. The rate constants determined here for bischelating phosphines correspond to slow exchange on the NMR time scale: sharp resonances were observed for individual species, and magnetization-transfer experiments were possible. However, they are fast on the preparative time scale in that even for dppey millimolar concentrations of Ni(II)-bis(phosphine) complexes come into equilibrium with ligands such as halides within a few seconds. In biological systems there are many potential ligands for Ni(II), notably H₂O, Cl⁻, and N-containing bases. Thus it must be expected that a Ni(II)-bis(phosphine) complex introduced into a biological milieu would rapidly come into equilibrium with the available ligands, giving rise to a number of species which might or might not include the original species.

Some work was also carried out on methanol solutions of the complexes, since it is a protic solvent and therefore a better model for parts of biological systems. The solubilities in methanol were very low, so it was difficult to obtain NMR spectra and long accumulation times were required. However, the results may be interpreted in conjunction with the electronic absorption spectra as showing the rapid formation of [Ni(dppe)]⁺ in solutions of all the dppe complexes followed by slow oxidation of the ligand to dppeO₂ over several hours or days. It would seem therefore that equilibrium (1) is shifted wholly to the right-hand side in methanol, presumably due to better solvation of the ions by methanol compared to chloroform. Resonances due to semioxidized ligands (dppeO₀, dppeO⁻) and completely oxidized ligands (dppeO₂, dppeO₃) were also observed in spectra of the phosphine-exchange experiments. They were not present in spectra of pure compounds in chloroform and were not a simple consequence of the presence of free bis(phosphine) in solution since autoxidation of such compounds in chloroform takes place over several days. Rather the oxidation seems to be related to ligand exchange on Ni(II). PPh₃ is known to be oxidized in the presence of [Pd(PPh₃)₂], and a mechanism analogous to that proposed for the latter reaction can be considered in the present case, although this would require the involvement of Ni(0) intermediates, which may be unlikely.

Conclusions

³¹P NMR spectroscopy in particular has provided a deeper insight into the structures and reactivity of Ni(II) bis(phosphine) complexes in solution and the solid state. Ni(II) in solution exchanges rapidly with bis(phosphine) and halide ligands and can promote catalytic oxidation of the bis(phosphine). Since dppeO₂ is not cytotoxic, Ni(II) bis(phosphines) must be stabilized if they are to be of biological use.

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Appendix

Magnetization loss from a particular site is due to spin–lattice relaxation at that site and to chemical exchange with other sites as described by the Bloch equations modified by McConnell and generalized for N equivalent sites by Forsén and Hoffman. The generalization is

\[ \frac{dM_A}{dt} = -\rho_A + \lambda_A M_A + \rho_M M^0_A + \sum \lambda_M M \]

where \( \rho_M \) is the instantaneous z magnetization of nucleus Y at site A, \( \lambda_A \) is the equilibrium z magnetization of nucleus Y at site A, \( \lambda_M \) is the probability per unit time for a nucleus Y at site A to be transferred to site B, \( \rho_A = 1/T_{1A} \) is the spin–lattice relaxation time of nucleus Y at site A. The lifetime of Y at site A is \( \tau_A \) with \( 1/\tau_A = \sum \lambda_M \). This assumes no dipolar coupling between the sites, which is true in the present case since they are on different molecules.

The following equilibrium was assumed for the Ni(II)-dppe system:

\[ [\text{Ni(dppe)}] + \text{dppe} \rightarrow \text{Ni(dppe)}_2 \]

From eq 1, it follows that

\[ \frac{dM_L}{dt} = -\rho_L + \lambda_L M_L + \rho_M M^0_L + \lambda_M M_{ML} \]

where \( \lambda_A \) is the instantaneous z magnetization of nucleus Y at site A, \( \rho_M \) is the equilibrium z magnetization of nucleus Y at site A, \( \lambda_M \) is the probability per unit time for a nucleus Y at site A to be transferred to site B, \( \rho_A = 1/T_{1A} \) is the spin–lattice relaxation time of nucleus Y at site A. The lifetime of Y at site A is \( \tau_A \) with \( 1/\tau_A = \sum \lambda_M \). This assumes no dipolar coupling between the sites, which is true in the present case since they are on different molecules.

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Reactions of [Ni(1,4,7-triazacyclononane)2]^{3+}/^{2+} with the Components of Nitrous Acid

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The reactions of [Ni(tacn)X]^{3+} with some of the components of nitrous acid have been studied in aqueous solution at 25 °C. NO2- reacts to form [Ni(tacn)X]^{4+} and NO3-, and the rate law is \( \frac{d[MML]}{dt} = k[M]^{0.5} \) with \( k = 212 \pm 7 M^{-1} s^{-1} \) and \( K_0 = (9.6 \pm 1.1) \times 10^4 M^{-1} \) at \( \mu = 0.1 M (LiClO_4) \). Electron transfer from NO2- to [Ni(tacn)X]^{3+} is proposed as the rate-limiting step. In 0.79 mM NO, [Ni(tacn)X]^{3+} reacts with the rate law \( \frac{d[Ni(tacn)X]}{dt} = k[Ni(tacn)X]^{2+} + H^+ \) with \( k = 1.02 \pm 0.06 \times 10^6 M^{-1} s^{-1} \) and \( k'' = (3.6 \pm 0.07) \times 10^4 M^{-1} s^{-1} \) at \( \mu = 1.0 M (LiClO_4) \). The k' pathway leads to destruction of the complex, presumably through nitrosation of the N-deprotonated conjugate base form of the Ni(III) reactant. The k' pathway is interpreted as an outer-sphere electron-transfer reaction between NO and [Ni(tacn)X]^{3+}.

Introduction

Rapid acid/base equilibria cause solutions of nitrous acid to contain HNO3, NO2-, and NO3-, the relative concentrations depending on pH. Moreover, such solutions are unstable and contain significant quantities of NO, NO2, NO3-, and other species. Many of these components of nitrous acid are quite reactive, so that the study of nitrous acid chemistry remains a pending issue. Many of these components of nitrous acid react by an outer-sphere electron-transfer mechanism, specifically, reactions in which the NO2/NO3 and NO*/NO2 redox couples participate.

Electron-transfer reactions involving the NO2/NO3 couple have been investigated previously, and they serve as important examples of the class of triatomic redox couples. An effective self-exchange reaction constant of 2 \( \times 10^{-5} M^{-1} s^{-1} \) was derived by applying the cross relationship of Marcus' theory to a series of reactions with substitution-inert coordination compounds.1 Although there was good consistency between the results for the various metal complexes, there was some basis for concern that the reactions were not truly outer sphere in that all the complexes had exposed lone pairs or \( \pi \)-systems that might interact specifically with the NO2. More recently, a value of 580 M^{-1} s^{-1} was measured for the actual electron-transfer rate constant between NO2 and NO3-.3 The significant discrepancy between the effective and actual self-exchange rate constants, combined with the reservations expressed above regarding the nature of the cross-reactions, suggested the need for further study.

Chemists who have studied the NO*/NO2 couple agree that further investigation of the NO2/NO3 couple remains a pending issue. Many of these components of nitrous acid react by an outer-sphere electron-transfer mechanism, specifically, reactions in which the NO2/NO3 and NO*/NO2 redox couples participate.

Electron-transfer reactions involving the NO*/NO2 couple have not been studied as often as those of the NO2/NO3 couple. Potentially, the system is of great interest because of the substantial difference in bond length between NO* and NO and because of the high force constants of those bonds. These factors could lead to a high degree of nuclear tunneling in electron-transfer reactions. We reported that the reaction of NO* with [IrCl4]^{2-} was diffusion-controlled and that this high rate required an inner-sphere mechanism.4 In that paper, we reviewed the literature evidence for outer-sphere electron transfer involving the NO*/NO2 couple and concluded that it was lacking. To our knowledge, the only subsequent report pertains to the reaction of NO* with Re6(CO)10 in CH3CN, but this reaction is complicated by Re-Re bond cleavage.4 Thus there is considerable motivation for investigating reactions of the NO*/NO2 couple that are truly outer sphere.

To investigate genuine outer-sphere electron-transfer reactions of the NO2/NO3 and NO*/NO2 redox couples requires special properties of the redox partner. It must be substitution-inert, a strong oxidant, and a species with a strictly saturated ligand system. The [Ni(tacn)X]^{2+}/^{3+} system (tacn = 1,4,7-triazacyclononane) meets these requirements. An added benefit is its low self-exchange rate, which makes the cross-reaction rate constants quite sensitive to the intrinsic barriers of the NO2/NO3 and NO*/NO2 couples.

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