Rapid Formation of a Potent Nitrosating Agent by Solvolysis of Ionic Nitrite in Dichloromethane

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Bis(triphenylphosphine)nitrogen(1+) nitrite reacted extensively with dichloromethane at 25 °C to produce an intermediate that converted secondary amines also present in these solutions into carcinogenic nitrosamines in high yields.

Bis(triphenylphosphine)nitrogen(1+) nitrite,[1] $[N(PPh_3)_2][NO_2]$, is a commercially available, non-hygroscopic, easily purified reagent that has proven useful in numerous applications requiring high concentrations of reactive nitrite ion in non-aqueous media.[2] The literature to date has emphasized its many advantages, including its ability to dissolve in aprotic organic solvents, allowing a variety of intersolute reactions involving nitrite to proceed in high yields.[2]

We now report that $[N(PPh_3)_2][NO_2]$ can react extensively with at least one of the solvents employed in the prior studies, and that attack by this reagent's nucleophilic nitrite ion on dichloromethane and related solvents leads to an unstable intermediate capable of converting amines into their highly carcinogenic[3] *N*-nitroso derivatives in yields as high as 100% of theoretical.

Our first evidence indicating the reactivity of $[N(PPh_3)_2][NO_2]$ with dichloromethane was revealed by the electronic spectral data. An absorbance band due to the nitrite ion was found at $\lambda_{max.}$ 370 nm (ε 25 dm^3 mol^{-1} cm^{-1}) when $[N(PPh_3)_2][NO_2]$ was freshly dissolved in either acetonitrile or dichloromethane. In the former solvent, the spectrum was invariant over time, but in dichloromethane the intensity of this band increased 2- to 3-fold in the first 10 min after dissolution. The rate of increase could be slowed either by lowering the dichloromethane concentration through addition of acetonitrile or by decreasing the initial nitrite concentration. After reaching a maximum at about 1 h after the solution had been prepared, the absorbance at 370 nm began to decrease slightly with the simultaneous appearance of a second peak at 340 nm. The second peak increased in intensity at a slower rate than the 370 nm peak had, taking about 8 h to reach maximum absorbance. No differences were observed with time in the ^1H, ^{13}C, or ^{31}P n.m.r. spectra of $[N(PPh_3)_2][NO_2]$ in CD_2Cl_2 solution, indicating that the $[N(PPh_3)_2]^+$ ion underwent no significant change during the reaction. Involvement of the solvent in the reaction was directly indicated by precipitation of silver chloride when an aliquot of a dichloromethane solution that had been kept at room temperature for 16 h was mixed with aqueous silver nitrate. Evidence for formation of formaldehyde was also found when the aqueous extracts were treated with the Nash reagent.[4]

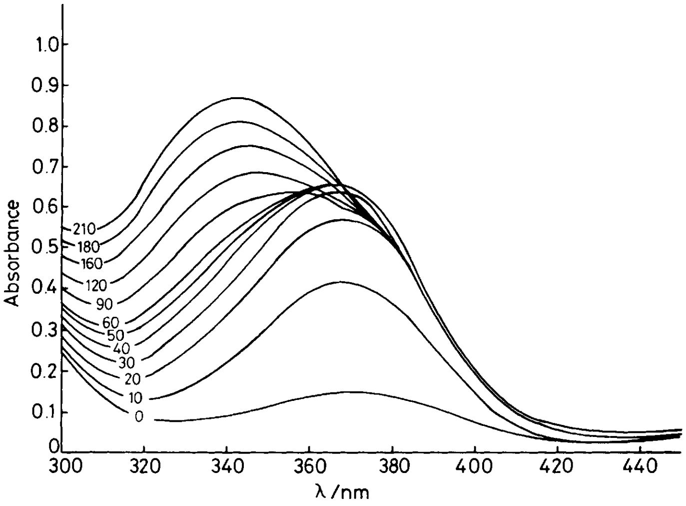

Figure 1. Changes in the electronic spectrum of a dichloromethane solution initially 4.8 mM in $[N(PPh_3)_2][NO_2]$ as a function of time at 25 °C. The number on each curve indicates the time it was recorded in minutes following dissolution of the $[N(PPh_3)_2][NO_2]$.

As to the nitrosamine-forming capability of these systems, dichloromethane solutions containing both $[N(PPh_3)_2][NO_2]$ and pyrrolidine showed a slow increase in absorbance at 358 nm ($\lambda_{max.}$ for *N*-nitrosopyrrolidine in dichloromethane 360 nm) that was essentially complete after 24 h. Yields of the nitrosamine as determined by gas chromatography were 60—100% of theoretical. In a typical reaction, a dichloromethane solution 20.0 mM in $[N(PPh_3)_2][NO_2]$ and 21.5 mM in pyrrolidine was kept at 25 °C for one day. An aliquot of the resulting intensely yellow solution was mixed with aqueous silver nitrate to produce an amount of silver chloride equivalent to 25.4 mM ionic (or labile covalent) chloride in the solution after 24 h. The *N*-nitrosopyrrolidine concentration was 12.4 mM, suggesting that one solvent molecule was consumed for each molecule of nitrosamine produced.

The results indicate that the nitrite ion can attack dichloromethane efficiently when $[N(PPh_3)_2][NO_2]$ is dissolved in this solvent. The first step presumably involves displacement of chloride in a reaction similar to those already noted between dichloromethane and such nucleophiles as azide ion[1] and piperidine.[5] We postulate that the nucleophilic attack occurs largely *via* the oxygen rather than the nitrogen of the ambident nitrite ion to yield α-chloromethyl nitrite. This nitrite ester might be expected to *N*-nitrosate amines with facility, as do the homologous β-substituted alkyl nitrites.[6] By-products of such a nitrosation step should include formaldehyde, previously shown to be capable of catalysing nitrosation of amines by nitrite ion,[7] and HCl; this or any other acid could induce further nitrosamine formation by protonating an unreacted nitrite even in the presence of excess of amine base.[8] Alternatively, the nitrile ester could undergo 1,2-elimination to form formaldehyde and nitrosyl chloride, also known to be capable of *N*-nitrosating amines.[9]

The nitrosation mechanism operative in the $[N(PPh_3)_2][NO_2]$ solutions seems to differ fundamentally from that of the superficially similar nitrosation of amines in dichloromethane solution by suspended sodium nitrite,[10] as the electrophilic attack by solvent that initiates the reaction in homogeneous medium appears to be on the nitrite ion while the first step occurring in the dichloromethane-mediated *N*-nitrosation of amines by $NaNO_2$ in the two-phase system[10] is postulated to be attack of solvent on the amine. Consistent with this conclusion, initial rates of nitrosamine formation were almost the same when the $[N(PPh_3)_2][NO_2]$ was added to a dichloromethane–pyrrolidine solution 1 h after it had been constituted as they were when all three components were mixed at once, but approached zero when the pyrrolidine was added to dichloromethane solutions 1 h after the $[N(PPh_3)_2][NO_2]$ had been dissolved.

Results analogous to those outlined above were found when $[N(PPh_3)_2][NO_2]$ was dissolved in 1,2-dichloroethane, and it is possible that any solvent that is sensitive to nucleophilic attack could react with the nitrite ion of $[N(PPh_3)_2][NO_2]$ to produce a potentially nitrosamine-forming intermediate. Similar caveats might also apply to solutions of other organic-soluble nitrite salts, such as tetraphenylphosphonium nitrite;[11] consistent with this possibility, potassium nitrite solubilized in dichloromethane–acetonitrile with 18-crown-6[12] behaved similarly to $[N(PPh_3)_2][NO_2]$ in its ability to induce spectral changes and nitrosate amines.

This investigation was supported in part by grant No. CA 35733 awarded by the National Cancer Institute.

Received, 29th January 1987; Com. 114

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