MECHANISM OF THE REACTION OF DIPHENYLPHOSPHINODITHIOIC ACID WITH NITRILES

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Summary: Kinetic studies of the reaction of diphenylphosphinodithioic acid with nitriles support a two step mechanism, the first step being an "ene" reaction.

In the preceeding communication we described the use of diphenylphosphino-dithioic acid (1) as a reagent for the rapid conversion of nitriles to thio-amides under mild conditions.[1] We have studied the kinetics of this process, and wish to report here evidence that the reaction proceeds via the reaction mechanism shown below. The first step is especially interesting, as it appears to be an "ene" reaction involving the participation of no fewer than four heteroatoms.
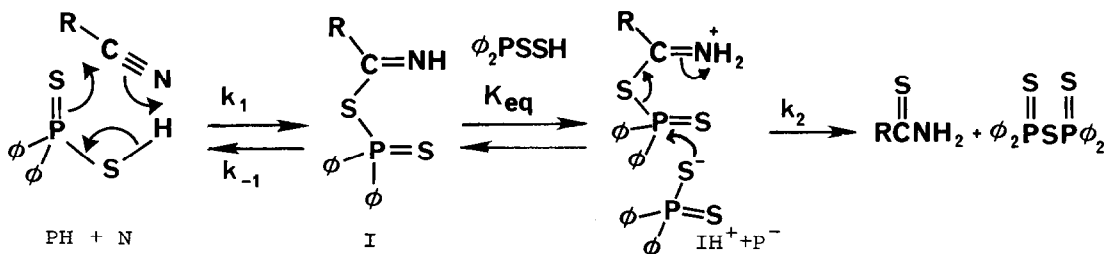
The reaction can be described by the following rate law:

$$v = \frac{k_1 k_2 K_{eq} [PH]^2 [N]}{k_2 K_{eq} [PH] + k_{-1}}$$

where v is the rate of the reaction, [PH] and [N] are the concentrations of 1 and nitrile respectively, and $K_{eq} = [\phi_2 PSS^-][IH^+]/[\phi_2 PSSH][I]$. This law can be derived by assuming rapid proton transfer between 1 and I, low, steady state concentrations of I and IH, and negligable dissociation of 1 into $\phi_2 PSS^-$ and H^+. Kinetic data were obtained on the reaction of 1 with p-chlorobenzo-nitrile in 2-propanol at 30 °C. The reaction was followed spectrophotometri-cally at 320 nm ($\Delta\varepsilon = 6100$ $M^{-1}cm^{-1}$). At low concentrations of 1, the reaction is second order in 1, while at high concentrations of 1, the reaction is first

order in $\underset{\sim}{1}$. The reaction is first order in nitrile at all concentrations of nitrile. Reciprocal plots (1/v vs. 1/N and P/v vs. 1/P) provided values for the rate constants $k_1 = 8.8 \times 10^{-3}$ $M^{-1}sec^{-1}$, $k_{-1}/K_{eq}k_2 = 5.6 \times 10^{-3}$ sec^{-1}, and $k_1 \ll k_{-1}$ and k_2.

The change over from first order to second order behavior provides the clearest evidence that the overall reaction proceeds in two discrete chemical steps. The dependence of the rate of this reaction on the dielectric constant of the solvent (Figure I) provides further evidence for a two step mechanism. Rates were measured in 2-propanol mixed with varying amounts of methanol (to obtain media with higher dielectrics) or benzene (for lower dielectrics). Upon moving into lower dielectrics, the rate of the reaction falls by over four orders of magnitude. However, in media having dielectric constants between that of 2-propanol and methanol, the rate falls by an order of magnitude. In poorer dielectrics than pure 2-propanol, the reaction is cleanly second-order in $\underset{\sim}{1}$. even at high concentrations of $\underset{\sim}{1}$, indicating that the second step (k_3) is rate limiting under these conditions. In solvent mixtures having high dielectric constants, the reaction is clearly first order in $\underset{\sim}{1}$, except at very low concentrations of $\underset{\sim}{1}$, indicating that the first step (k_1) is rate limiting under these conditions.
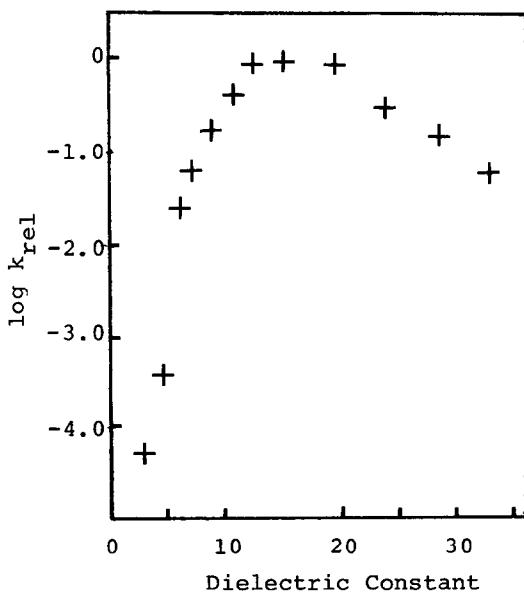

TABLE I: Effect of Substituents on the Rate of the Reaction of $\underset{\sim}{1}$ with p-substituted Benzonitriles.

Substituent	σ	$\log k/k_0$
NO_2	.78	.09
Cl	.23	-.10
H	0	.00
MeO	-.27	.01

Figure 1: Rate of the reaction of $\underset{\sim}{1}$ with p-chlorobenzonitrile vs. solvent dielectric constant.

While these kinetic studies establish that this reaction proceeds via two discrete steps, the kinetic behavior in solvents of varying dielectric constant provides clues as to what the chemistry in those steps might be. Thus, at low dielectrics, where the overall rate of the reaction is determined by the rate of the step which is second order in 1, the solvent dependence shows that poorer dielectrics destabilize the transition state of the second step with respect to the ground state. This suggests that the transition state is a more highly charged species than the ground state. While these data do not rule out any "concerted" transition states having significant charge separation, they can be understood as arising from an equilibrium proton transfer between 1 and I prior to the product forming step. This interpretation is especially plausible since the pK_a of 1 is ~ 2 (in water),[2] while the pK_a of the imine I is perhaps 6 or 7,[3] making the proton transfer entirely reasonable only in media with high dielectric constants; furthermore any "concerted" process would seem to require a geometrically unfavorable eight-center cyclic transition state.

At high dielectrics, where the overall rate of the reaction is determined by the step which is first order in 1, the solvent dependence shows that better dielectrics stabilize the ground state with respect to the transition state of the reaction, implying that the transition state has less charge separation than the ground state. If uncharged 1 and nitrile are assumed to be the ground state, this implication is not consistent with any transition state having significant charge separation, making plausible a single step addition of 1 and nitrile in a fashion analogous to an "ene" reaction. An alternative kinetically indistinguishable reaction between $\phi_2 PSS^-$ and $RCNH^+$ present at low equilibrium concentrations via a "late" transition state is implausible. The equilibrium constant between $\phi_2 PSSH + RCN$ and $\phi_2 PSS^- + RCNH^+$ is likely to be ~ 10^{-12} in water, and still lower in 2-propanol. Since $k_{1(obs)} \approx 1 \times 10^{-2}$ $M^{-1}sec^{-1}$, any reaction proceeding via the charge separated intermediates would require reaction of those intermediates at rates greater by several orders of magnitude than the maximum diffusion rate. Rather the observed dependence is best understood as resulting from the dissociation at high dielectrics of 1 into H^+ and ϕPSS^-, which do not react with nitrile.
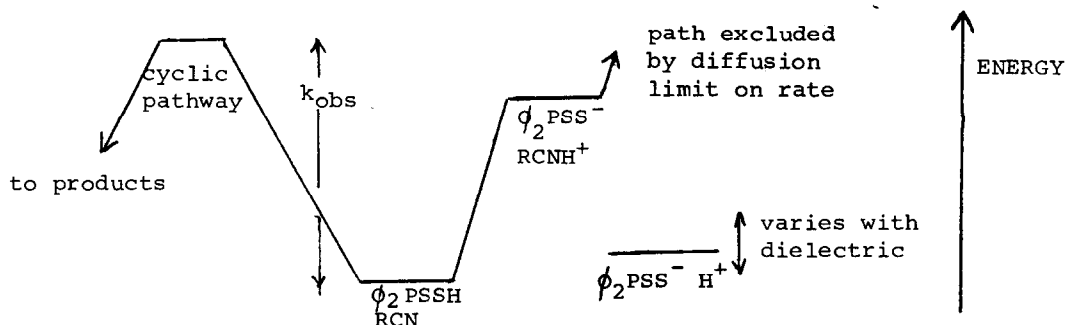
Together, these facts suggest that $\underset{\sim}{1}$ reacts with nitriles via a cyclic six-membered transition state having little charge separation. The fact that k_1 is virtually independent of substituent for a series of four p-substituted benzonitriles (H, Cl, NO_2 and OMe) provides further evidence for a transition state (Table I). Activation parameters for the reaction of $\underset{\sim}{1}$ with p-chlorobenzonitrile were determined by measuring k_1 in methanol at ten temperatures between 5 – 50 °C; $\Delta H^{\ddagger}$ = 14.5 kcal/moled and $\Delta S^{\ddagger}$ = -22 e.u. These are not inconsistent with a cyclic transition state as drawn above[5] although alternative ionic mechanisms involving ordering of solvent molecules around a transition state are perhaps also consistent.

Thus the data presented on the reaction of $\underset{\sim}{1}$ with nitriles suggests that the first step is analogous to an "ene" reaction,[6] although considering that only one carbon is involved in the chemical event, the process falls more in the purview of inorganic chemistry than organic chemistry. In fact, we know of no "ene" reaction in which heteroatoms participate in as great a number and variety. Particularly interesting is the fact that the first step is reminiscent of a mechanism proposed for the hydrolysis of nitriles catalyzed by the enzyme nitrilase,[7] in which a sulfur nucleophile is presumed to attack the carbon of a nitrile simultaneously with a protonation on nitrogen.[8]

<div align="center">References</div>

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