Formation of Radicals in the Mitsunobu Reaction

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The first step of the Mitsunobu reaction, involving the reaction of triphenylphosphine with diisopropyl (or diethyl) azodicarboxylate, results in the formation of a radical cation. The EPR spectra of the N-centered radicals reveal hyperfine coupling to two nitrogen nuclei, a phosphorus nucleus, and one or two protons from the alkyl CH (or CH_2) groups. The radical is relatively persistent, slowly decomposing at room temperature over a period of about 6 h. When the reaction was carried out in the presence of neopentyl alcohol (1 equiv), the radical still formed. However, in the presence of benzoic acid (1 equiv) or neopentyl alcohol/benzoic acid, no EPR signal was observed. This suggests that the order of addition of reagents in the Mitsunobu reaction may influence the outcome in some cases. A new mechanism, involving single electron transfer, is proposed for the formation of the Morrison–Brunn–Huisgen betaine.

Introduction

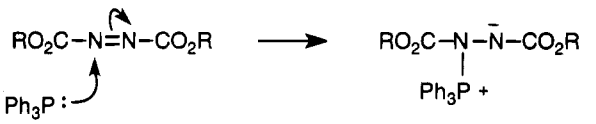
The Mitsunobu reaction,[1,2] employing a mixture of triphenylphosphine and a dialkyl azodicarboxylate, is a particularly useful reaction in organic synthesis.[3] The first step in these reactions involves formation of a betaine (**1**) as originally proposed by Morrison[4] and substantiated by Brunn and Huisgen.[5] It has been generally assumed that the betaine is formed by a Michael-type nucleophilic attack by the phosphine on nitrogen (Scheme 1), and the reaction has been shown to be irreversible by us[6] and by others.[7] Interestingly, the isolated betaine **1** is colorless, but when triphenylphosphine and the azodicarboxylate are mixed in a solvent such as tetrahydrofuran, dichloromethane, or toluene, yellow or orange solutions result. In the absence of solvent, a deep red solution is produced in an exothermic reaction. This color was first noted by Mitsunobu,[8] who suggested that radicals or radical ions might be present.

As part of an ongoing study of the mechanism of the Mitsunobu reaction,[9] we have examined the reaction of triphenylphosphine with a range of dialkyl azodicarboxylates by electron paramagnetic resonance (EPR) spectroscopy.[10]

Results

Triphenylphosphine (Ph_3P, 262 mg, 1 mmol) was dissolved in toluene (1 mL) and the solution bubbled with nitrogen for 30 s. Dropwise addition of this solution over about 5 min to a stirred, cooled (0 °C) solution of diisopropyl azodicarboxylate (DIAD, 200 μL, 1 mmol) in toluene (1 mL) under an atmosphere of nitrogen resulted in a yellow-orange solution. After the solution was warmed to room temperature (10 min), an aliquot was transferred to an EPR tube under nitrogen and the EPR spectrum recorded (Figure 1a). The signal was still present 4–5 h later, but the signal intensity had decreased substantially. Mixing the solutions at room temperature or addition of neat azodicarboxylate to the triphenylphosphine solution (normal Mitsunobu procedure) gave the same EPR spectrum; however, slow addition (7 min) of a solution of the azodicarboxylate (20% in toluene) to the triphenylphosphine solution gave a substantially weaker (though identical) EPR spectrum. The same spectrum was obtained even if a 5-fold excess of triphenylphosphine was employed (262 mg of Ph_3P, 40 μL of DIAD, 2 mL of toluene); however, in the presence of an excess of the azodicarboxylate, the EPR spectrum showed the presence of additional radical species.[11]

Scheme 1



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Analogous results were obtained in tetrahydrofuran or dichloromethane as solvent or in the presence of 1 equiv of an alcohol [DIAD (1 mmol) added to Ph_3P (1 mmol) + neopentyl alcohol (1 mmol) in tetrahydrofuran (2 mL), *or* addition of the neopentyl alcohol last]. However, addition of benzoic acid (1 equiv), either before or after the addition of the azodicarboxylate, or of 2 equiv of an alcohol (ethanol), resulted in no EPR signal.

We attribute the EPR spectrum (Figure 1) to the radical cation (**4**, R = *i*-Pr). Computer simulation of the isotropic EPR spectrum shown in Figure 1a with the *g* and *A* values listed in Table 1 (**4**, R = *i*-Pr) yields the spectrum shown in Figure 1b (LSE = 0.35). Although the resonant field positions have been accurately repro-

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† Griffith University.
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(9) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045–3054 and references contained therein.
(10) The International EPR Society is recommending that the acronym EPR rather than ESR be used to describe this technique.
(11) These additional species are not formed under normal Mitsunobu conditions and are the subject of a separate report (Brecknell, D.; Camp, D.; Hanson, G. R.; Jenkins, I. D., unpublished data).

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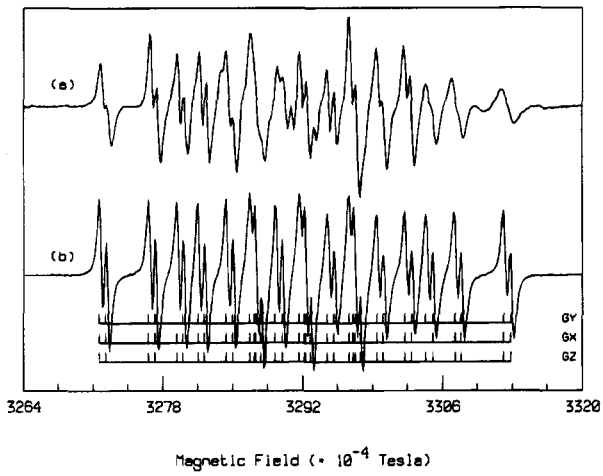


Figure 1. EPR spectra of the radical cation (**4**, R = *i*-Pr): (a) X-band EPR spectrum in tetrahydrofuran, ν = 9.2444 GHz; (b) computer simulation of (a), LSE = 0.35.

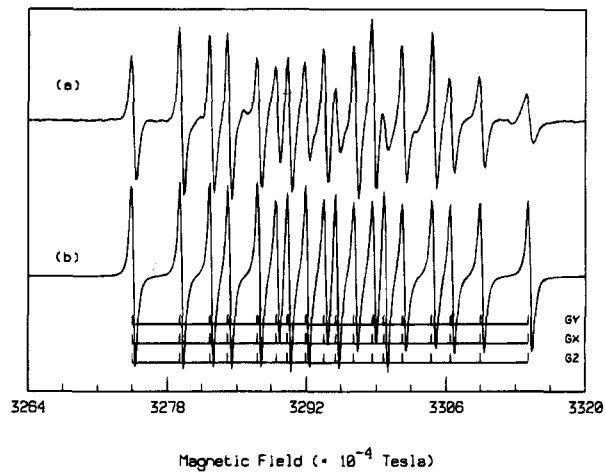


Figure 2. EPR spectra of the radical cation (**4**, R = *tert*-butyl): (a) X-band EPR spectrum in tetrahydrofuran, ν = 9.2444 GHz; (b) computer simulation of (a), LSE = 0.28.

duced, the agreement between the experimental and simulated line shapes is poor. A close examination of the experimental spectrum (Figure 1a) reveals that the line width varies as a function of the nuclear spin quantum numbers for the phosphorus and the two nitrogen nuclei. This line-width variation is a common phenomenon in solution EPR spectra of organic free radicals and transition metal ion complexes and arises through the modulation of the g and A matrices and a spin rotational mechanism.[12] Similar line-width variation was also observed for the radical cations **4** where R = *t*-Bu and R = Et, respectively.

The structural identity of this radical (**4**, R = *i*-Pr) follows from hyperfine coupling to two inequivalent nitrogen nuclei, a phosphorus nucleus, and weak coupling to a methine proton. It is clear from the structure of **4** that the largest N coupling can be unambiguously assigned to the divalent N atom (the contribution of the mesomeric structure **4** would be much more important than that of **4a**). The origin of the weak proton hyperfine coupling was confirmed by using di-*tert*-butyl azodicarboxylate which resulted in a simpler spectrum (Figure 2), and diethyl azodicarboxylate, where additional hyperfine coupling (to the methylene group) was observed. The g, A_N, A_P, and A_H values for all of these N-centered radicals are given in Table 1. These values are consistent with values reported previously for hydrazyl radicals.[13]

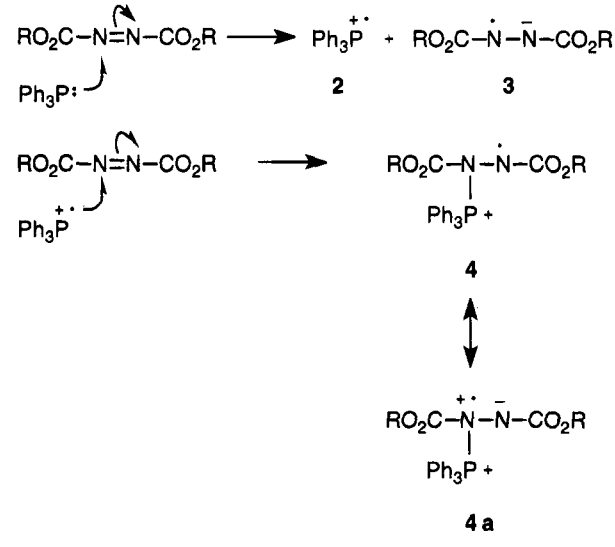
A possible mechanism for the formation of **4**, involving single electron transfer from phosphorus to the azodicarboxylate, is shown in Scheme 2. Azodicarboxylates are well-known dienophiles and electron acceptors possessing a low-lying LUMO,[14,15] and the addition of the phosphonium radical cation to the azodicarboxylate would be expected to be rapid by analogy with the rapid

Table 1. EPR Data for Radical Cations 4 and Radical Anion 3

		hyperfine coupling[a]			
radical	g	A_P	A_N[b]	A_N[c]	A_H
4, R = Et	2.007	14.2 (1)[d]	7.2 (1)	4.6 (1)	0.9 (2)
4, R = *i*-Pr	2.006	14.1 (1)	7.3 (1)	4.6 (1)	0.6 (1)
4, R = *t*-Bu	2.005	13.6 (1)	7.3 (1)	4.5 (1)	
3, R = *i*-Pr	1.999		5.4 (2)		0.5 (2)

[a] Units: 10^{-4} cm^{-1}. [b] Coupling to divalent N atom. [c] Coupling to trivalent N atom. [d] The numbers in parentheses refer to the number of magnetically equivalent nuclei.

Scheme 2



rate of addition ($k \approx 10^6$–10^7 M^{-1} s^{-1}) of phosphorus-centered radicals to alkenes.[16] An analogous single electron transfer from phosphorus to arenediazonium salts (also good electron acceptors) to generate **2** has been reported recently.[17] Neither the phosphonium radical cation **2** nor the diazo radical anion **3** could be detected; presumably both species are too short-lived to be observed under these conditions. Mixing of the phosphine and azodicarboxylate solutions followed by freezing of the solution with liquid nitrogen also failed to provide any

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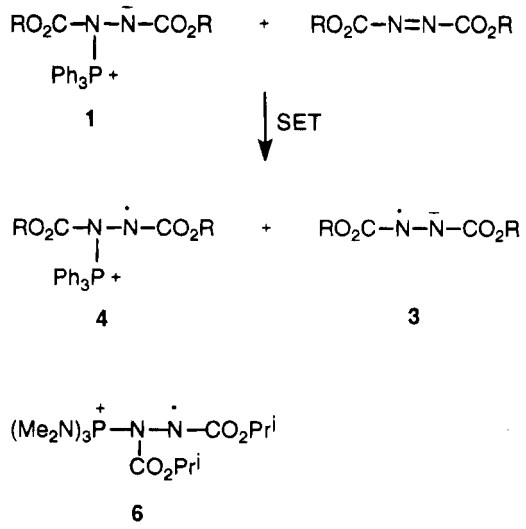
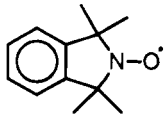
Scheme 3



evidence for **2** or **3**. However, we have obtained the EPR spectrum of (**3**, R = *i*-Pr) by continuously generating it from diisopropyl azodicarboxylate by reduction in the EPR cavity.[6] The EPR spectrum consisted of five resonances (with intensities 1:2:3:2:1) which were further split into three (with intensities 1:2:1). Computer simulation of the spectrum[6] indicated hyperfine coupling to two magnetically equivalent nitrogen nuclei and two magnetically equivalent methine protons (Table 1). In contrast, the radicals **4** were quite persistent and the signal intensity was still strong after standing for 2–3 h at 0 °C. After 5–6 h at room temperature, the signal intensity was very weak.

We have also estimated the concentration of radicals **4** generated under "normal" Mitsunobu conditions. Thus, dropwise addition (over 3–4 min) of diisopropyl azodicarboxylate (100 μL, 0.5 mmol) to a stirred solution of triphenylphosphine (131 mg, 0.5 mmol) in dry toluene (1 mL) at 0 °C under a nitrogen atmosphere produced a pale yellow solution. Comparison of the EPR spectrum of this solution with a 0.1 mM solution of a stable aminoxyl (nitroxide **5**) in toluene, using a dual TE_{104} rectangular cavity (see Experimental Section), showed that the concentration of radicals (**4**, R = *i*-Pr) was approximately 5 μM. With the reverse order of addition (triphenylphosphine to diisopropyl azodicarboxylate), the radical concentration was much higher (22 μM).



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A (second) possible mechanism for the formation of the radicals **4** involves oxidation of the betaine **1** by the azodicarboxylate (Scheme 3). We have been able to confirm the formation of (**4**, R = *i*-Pr) [but not **3**] by this pathway by precipitation of the betaine **1** from cold tetrahydrofuran/ether and then treatment of a solution of **1** in dichloromethane with diisopropyl azodicarboxylate. Similar results were obtained by slow (7 min) addition of a toluene solution of diisopropyl azodicarboxylate (1 mL, 1 M) to a stirred toluene solution of triphenylphosphine (1 mL, 1 M) at room temperature followed by addition of a further 1 equiv of the azodicarboxylate. After addition of the first equivalent, the EPR signal was very weak, but after adding the second equivalent of the azodicarboxylate, a strong EPR signal for **4** (R = *i*-Pr) was obtained.

These experiments do not prove, however, that **4** (R = *i*-Pr) is formed exclusively (or even predominantly) by this alternative pathway (Scheme 3), especially when the order of addition is reversed. Indeed, if Scheme 3 were the only way that radicals **4** were produced, it might be expected that replacing triphenylphosphine by other phosphines should result in analogous results. This was found not to be the case. Thus, treatment of tributylphosphine with diisopropyl azodicarboxylate gave an EPR signal that was weaker (approximately 2–10-fold), whereas tris(dimethylamino)phosphine (hexamethylphosphorous triamide) gave a much more intense (approximately 2 orders of magnitude) EPR signal [corresponding to **6**] than that obtained with triphenylphosphine. Both phosphines react with the azodicarboxylate to give betaines analogous to **1**.[6,18]

The observation of radicals **4** calls into question the mechanism of formation of the betaine **1**. Thus, although **1** could be formed by a simple nucleophilic attack as shown in Scheme 1, a radical chain mechanism seems equally likely (Scheme 4). Step 1 involves single electron transfer from the phosphine to the azodicarboxylate to give the phosphonium radical cation **2** and the diazo radical anion **3**. The rate of coupling of these two species (step 6) should be close to diffusion-controlled. However, under normal Mitsunobu conditions (addition of DIAD to the phosphine), the phosphine will be present in excess, so that step 2 will be competitive with step 6 [the addition of radicals to phosphines is very fast ($\sim 10^8$ M^{-1} s^{-1})[19]]. Step 3, involving a second electron transfer (analogous to step 1), would produce the betaine **1** and the chain carrier **3**. Conversely, if the azodicarboxylate were present in excess (i.e. reverse mode of addition), the phosphonium ion radical **2** would be expected to add rapidly to the azo compound, as mentioned earlier, to produce the (observed) radical cation (step 4). Electron transfer from triphenylphosphine would produce the betaine **1** and the chain carrier **2**. This step (step 5) must be reversible as addition of excess triphenylphosphine caused no change in the EPR signal intensity.

Thus, Scheme 4 predicts that the radical cation **4** should be formed in greatest amount under conditions where the azodicarboxylate is present in excess over the phosphine. This was found to be the case. The strongest signals were always obtained when the phosphine was added to the azodicarboxylate or when there were high local concentrations of both reagents present (this mode of mixing was carried out by adding both reagents and the solvent directly to the EPR tube under nitrogen, stoppering, and mixing by inverting the tube several times).

Irrespective of whether the radicals **4** are formed via a radical chain process (Scheme 4) or by simple oxidation of the betaine **1** by the azodicarboxylate (Scheme 3), it is unlikely that such radicals would interfere in most Mitsunobu esterification reactions. This is because the normal mode of addition is to add the azodicarboxylate to a mixture of triphenylphosphine, the alcohol, and the carboxylic acid, dissolved in a solvent such as tetrahy-

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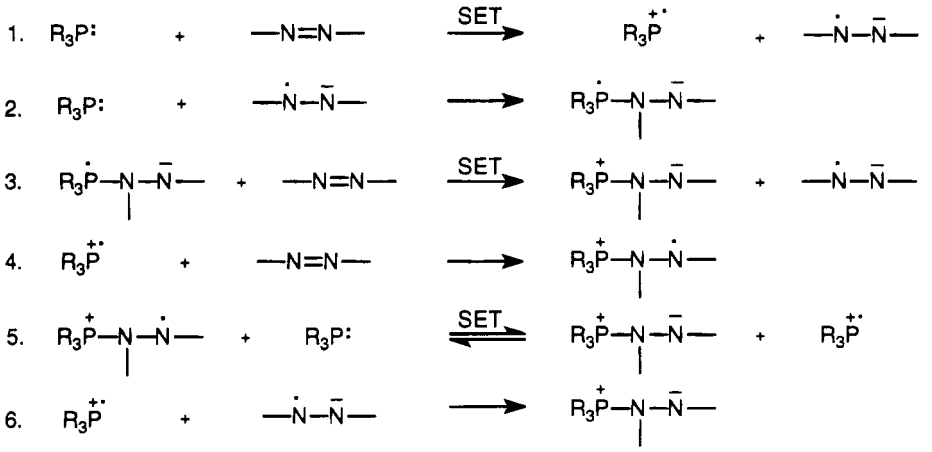
Scheme 4



drofuran or toluene, and under these conditions, the radicals **4** are not observed. However, under conditions where the acid is added last, or when a large excess of azodicarboxylate and triphenylphosphine are used, radicals **4** will certainly be formed. If side reactions involving radicals are a problem, it should be possible to avoid them by employing pre-formed (i.e. crystallized) betaine **1**.

Conclusions

Radicals are formed when triphenylphosphine and an alkyl azodicarboxylate are mixed. A strong EPR signal is observed corresponding to an N-centered radical which shows coupling to two inequivalent nitrogens, a phosphorus and, in some cases, one of the alkyl groups. The structure **4** has been assigned to these radicals. A new (radical chain) mechanism is proposed for the formation of the Morrison–Brunn–Huisgen betaine. Under normal Mitsunobu conditions, when an alcohol and a carboxylic acid are present, these radicals are not observed. It is suggested that the order of addition of reagents in the Mitsunobu reaction may influence the outcome in some cases. The phosphine should not be added to the azodicarboxylate, i.e. the azodicarboxylate should not be present in excess.

Experimental Section

Triphenylphosphine and diethyl, diisopropyl, and di-*tert*-butyl azodicarboxylates were supplied by Aldrich and not purified further. Tetrahydrofuran was dried by distillation from sodium/benzophenone and stored over 4 Å molecular sieves. Toluene was dried by distillation from sodium wire and stored over sodium wire.

X-band EPR spectra of the radical cations **4** and anions **3** were obtained using Bruker ER200D and ESP300E EPR spectrometers at the University of Queensland. Calibration of the microwave frequency and the magnetic field were performed with an EIP 548B microwave frequency counter and a Bruker 035M gaussmeter. SIMOPR, written by Dr. W. Garrett, and version 3.02 of Bruker's esp300e software were employed for data collection on the two spectrometers. An EPR spectrum of **6** was recorded on a Bruker ER200D-SRC X-band EPR spectrometer at the Australian National University.

Spin concentration measurements were performed using the "comparison" method in conjunction with a dual TE_{104} rectangular cavity.[20] The modulation amplitude was calibrated for each of the individual cavities, and the difference in microwave magnetic field strengths (B_1) was overcome by first measuring the aminoxyl radical (standard) and the radical cation (unknown) in the front and back cavities and then swapping the samples and repeating the measurement.

Computer simulation of the isotropic EPR spectra arising from the radical cations and anions were performed using an automatic nonlinear least-squares fitting program epr50fit.f running on a SUN SPARCstation 10/30 workstation.[21] The line-width variation with M_I (for only one nucleus) was modeled using Kivelsons' theory[12] in conjunction with a Lorentzian line shape. The quality of the final simulated spectrum was estimated from the least-squares error parameter (LSE).[22] Spectral subtractions, comparisons, and the determination of LSE were carried out with the EPR software package EPR_PLOT running on the University of Queensland Prentice Computer Centre's VAX 8550 computer.

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Supplementary Material Available: Figure S1: EPR spectra of the radical cation (**4**, R = ethyl) (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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