Structure of the Radicals Formed in the Mitsunobu Reaction

Lennart Eberson,* Ola Persson and Jan Olof Svensson†

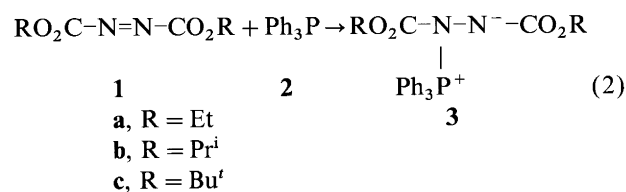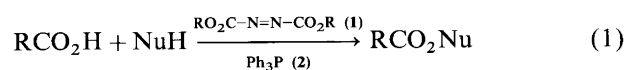Department of Chemistry, Lund University, PO Box 124, S-221 00 Lund, Sweden

Eberson, L., Persson, O. and Svensson, J. O., 1998. Structure of the Radicals Formed in the Mitsunobu Reaction. – Acta Chem. Scand. 52: 1293–1300. © Acta Chemica Scandinavica 1998.

The first step of the Mitsunobu reaction consists of the reaction between a dialkyl azodicarboxylate (1) and triphenylphosphine (2) with formation of a phosphobetaine, $ROOCN(P^+Ph_3)N^-COOR$ (3). It was recently observed by EPR spectroscopy that a low concentration of a radical accompanied 3, and its structure was assigned to the product of one-electron oxidation of 3, the distonic radical cation $ROOCN(P^+Ph_3)N^{\cdot}COOR$ (4), based on EPR spectral evidence. [Camp. D., Hanson, G. R. and Jenkins, I. D. J. Org. Chem. 60 (1995) 2477.]

A study of 3 and similar betaines by cyclic voltammetry revealed that 3 is far too difficult to oxidize (E_{pa} was around 2.0 V vs. Ag/AgCl) to be a credible precursor of the radical species. In combination with an EPR spectral study of a series of 1-R_3P reactions results have been obtained which suggest that the radical species instead is derived from a structure in which the phosphorus atom is connected to the carbonyl oxygen of 1, i.e. $(Ph_3P^+O)(RO)C=N-N^{\cdot}COOR$.

The reaction between 2 and 4-phenyl-4H-1,2,4-triazolinedione (PTAD) produced similar radical species, indicating that radical cation species derived from the cyclization of 4 (P to the carbonyl oxygen) cannot be involved.

The Mitsunobu reaction, a mild and versatile transformation of a carboxylic acid RCO_2H and a nucleophile NuH into RCO_2Nu [eqn. (1)] by aid of a dialkyl azodicarboxylate (1) and triphenylphosphine (2),[1] involves as the initial step the reaction between 1 and 2 to form a zwitterion (3) [eqn. (2)].[2] This reaction has been shown to be irreversible.[2e] Being a 1,3-dipole, the zwitterion can undergo cycloadditions with reactive dienophiles, such as methyl propiolate or dimethyl acetylenedicarboxylate.[2b]

$$RCO_2H + NuH \xrightarrow[\text{Ph}_3P \ (2)]{\text{RO}_2C-N=N-CO_2R \ (1)} RCO_2Nu \qquad (1)$$

$$RO_2C-N=N-CO_2R + Ph_3P \rightarrow RO_2C-\underset{\underset{Ph_3P^+}{|}}{N}-N^--CO_2R \qquad (2)$$

1	2	3

a, R = Et
b, R = Pr^i
c, R = Bu^t

It was assumed that the formation of zwitterion 3 occurred by conventional nucleophilic attack of triphenylphosphine upon one of the nitrogen atoms of 1. Recently[3] it was shown by EPR spectroscopy that persistent radical species, assigned to the structure

* To whom correspondence should be addressed.
† Present address: Astra-Draco AB, Lund.

of hydrazyl radical cations 4, appeared at the 5–20 μmol dm^{-3} level in benzene or tetrahydrofuran (THF) solutions of 1 and 2 (0.5 mol dm^{-3} in each), corresponding to yields of $(1-4) \times 10^{-3}\%$. The radicals 4 persisted over a period of 5–10 h. No radicals appeared in the presence of proton donors. The formation of 4 was discussed in terms of either of two mechanisms, both recognizing the one-electron acceptor properties of the azodicarboxylate 1. One of the mechanisms pictured the reaction occurring as in Scheme 1, the initial formation of the zwitterion 3 being followed by its oxidation to 4 by a second molecule of 1.
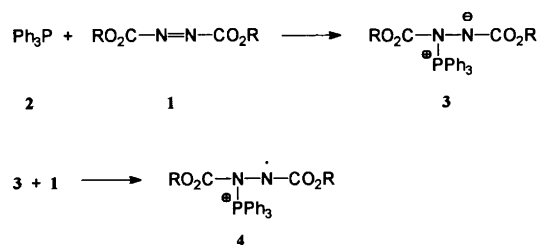
Scheme 1.

The second mechanism involved initial electron transfer between 1 and 2 to give a radical ion pair $1^{\cdot-}$, $2^{\cdot+}$, followed by trapping of $2^{\cdot+}$ by 1 (Scheme 2). It was alternatively suggested that the formation of the zwitter-

ion **3** might occur by a radical chain mechanism initiated by this ET step.

$$Ph_3P + RO_2C{-}N{=}N{-}CO_2R \longrightarrow Ph_3P^{\cdot+} + RO_2C{-}\overset{\ominus}{N}{-}\overset{\cdot}{N}{-}CO_2R$$

2   **1**   **2·+**   **1·⁻**

$$Ph_3P^{\cdot+} + RO_2C{-}N{=}N{-}CO_2R \longrightarrow RO_2C{-}\overset{\cdot}{N}{-}\overset{}{N}{-}CO_2R$$
                                              $\overset{\oplus|}{PPh_3}$

2·+   **1**

4

Scheme 2.

Our attention to the phenomena described above was drawn partly by a longstanding interest in the redox behaviour of zwitterions, partly by the analogy of Scheme 1 to the so-called Forrester–Hepburn mechanism[4,5] for the formation of spin adducts from nitrones [eqn. (3)]. Here a nucleophile Nu⁻ is added to the nitrone function to give a hydroxylamine intermediate, either as the anion shown in eqn. (3) or its protonated form, which is further oxidized to a radical by an added weak oxidant. In Scheme 2 the nature and sequence of events is the same, but the role of the weak oxidant is played by the original electrophile, which happens to be a good electron acceptor. True spin trapping of neutral radicals by azodicarboxylates like **1a** and **1c** has been demonstrated.[6]

$$\underset{\text{nitrone}}{Nu^- + {-}CH{=}N(O)^-} \rightarrow \underset{\text{hydroxylamine anion}}{{-}(Nu)CH{-}N(O^-)^-}$$

$$\rightarrow \underset{\text{spin adduct}}{{-}(Nu)CH{-}N(O^\cdot)^-} \qquad (3)$$

The analogy is extended further when the behaviour of 4-phenyl-4*H*-1,2,4-triazolinedione (**5**, often denoted PTAD and considered to be the most powerful dienophile and dipolarophile known[7]) is considered. Compound **5** is an imide of azodicarboxylic acid, and the corresponding 4-methyl derivative has actually been used as the electrophilic component of the Mitsunobu reaction.[1] Moreover, the role of **5** as a radical trapping reagent (a spin trap) was clearly demonstrated by Alberti and Pedulli, who generated a number of radicals and characterized the hydrazyl radicals **6** formed [eqn. (4)] by EPR spectroscopy.[8] Finally, the electron transfer (ET) steps proposed in Schemes 1 and 2 were of general interest from the viewpoint of ET theory.[9]

$$\underset{5}{\overset{N=N}{\underset{Ph}{\diamond}}} + R^\cdot \longrightarrow \underset{6}{\overset{R\diagdown}{\underset{Ph}{\diamond}}}$$

5   **6**

Results

Electron transfer characteristics of the initial reaction between **1** *or* PTAD *and* **2**. Cyclic voltammetry of

triphenylphosphine **2** at a Pt electrode in dichloromethane–Bu$_4$NPF$_6$ showed an irreversible oxidation process with E_{pa} of 1.28 V (lit.[10] 1.3 V) vs. Ag/AgCl (all potentials given in this paper will be referred to this electrode), whereas diethyl azodicarboxylate (**1a**) was reduced in a chemically reversible process at $E_{rev} = -0.56$ V (lit.[11] -0.46 V at the dropping Hg cathode). Under the same conditions, PTAD (**5**) was reduced reversibly at $E_{rev} = 0.05$ V (lit.[12] 0.09 V).

Cyclic voltammetry of a solution of **1a** (13.6 mmol dm^{-3}) and **2** (13.6 mmol dm^{-3}) in dichloromethane–Bu$_4$NPF$_6$ showed that the separate electrode processes of **1a** and **2** disappeared almost immediately and were replaced by three new electrode reactions (Fig. 1a and Table 1), a major, chemically irreversible one with $E_{pa} = 1.95$ V and a second, major one at $E_{rev} = -1.23$ V (E_{pa} and $E_{pc} = -0.90$ and -1.56 V, respectively). Besides, there was a minor couple at $E_{rev} = 0.00$ V (E_{pa} and $E_{pc} = 0.03$ and -0.03 V, respectively), the reduced form of

$E_{pa}(Ph_3P^{\cdot+}/Ph_3P)$ $E_{rev}(1a/1a^{\cdot-})$

Fig. 1. (*a*) CV of a solution of triphenylphosphine (**2**, 13.6 mmol dm^{-3}) and diethyl azodicarboxylate (**1a**, 13.6 mmol dm^{-3}) in dichloromethane–Bu$_4$NPF$_6$ (0.15 mol dm^{-3}). The sweep was initiated at -2.0 V, sweep rate 0.2 V s^{-1}, and 10 sweeps in each direction were recorded. (*b*) CV of a solution of triphenylphosphine (**2**, 11.2 mmol dm^{-3}) and diethyl azodicarboxylate (**1a**, 11.2 mmol dm^{-3}) in acetonitrile–Bu$_4$NPF$_6$ (0.15 mol dm^{-3}). The sweep was initiated at -2.0 V, sweep rate 0.2 V s^{-1}, and 10 sweeps in each direction were recorded.
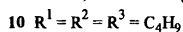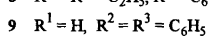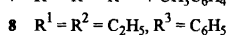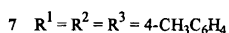
Table 1. Cyclic voltammetry at a scan rate of 0.2 V s^{-1} of various R$_3$P, **1a** or equimolar mixtures of **1a** and R$_3$P.[a]

Substrate(s)[b]	Solvent	Major process I E_{pa}	Major process II			Minor process		
			E_{pa}	E_{pc}	E_{rev}	E_{pa}	E_{pc}	E_{rev}
2	CH$_2$Cl$_2$	1.28						
1a	CH$_2$Cl$_2$		-0.32	-0.81	-0.56	0.1		
1a	CH$_3$CN		-0.44	-0.82	-0.63	0.1		
2+1a	CH$_2$Cl$_2$	1.95	-0.90	-1.56	-1.23	0.03	-0.03	0.00
2+1a	CH$_3$CN	2.05	-0.89	-1.53	-1.21	0.02	—	—
7	CH$_3$CN	1.10						
7+1a	CH$_3$CN	1.74			-1.0	0.01	—	—
11	CH$_3$CN	0.71[c]						
11+1a	CH$_3$CN	0.71[c]	-0.43	-0.63	-0.53	0.01	—	—
8	CH$_3$CN	0.79						
8+1a	CH$_3$CN	2.1	-0.85	-1.57	-1.21	0.00	—	—
9	CH$_3$CN	1.24						
9+1a	CH$_3$CN	2.1			-1.22	0.00		
10	CH$_3$CN	0.97						
10+1a	CH$_3$CN	2.0			-1.2	0.00	—	—

[a]All potentials are given in V vs. the Ag/AgCl electrode. Supporting electrolyte: Bu$_4$NPF$_6$ (0.15 mol dm^{-3}). [b][Substrate] is in the range of 5-15 mmol dm^{-3}; equimolar concentrations were used when two substrates were used. [c]Reversible potential.

which is denoted **X1**. In acetonitrile, a similar experiment showed the occurrence of similar electrode processes (Fig. 1b). The minor one exhibited chemical reversibility at sweep rates of $\geqslant 5$ V s^{-1} ($E_{rev} \approx 0.0$ V).

Similar findings were obtained by CV of equimolar solutions of **1a** and other phosphines, viz. tris(4-tolyl)-phosphine (**7**), diethylphenylphosphine (**8**), diphenylphosphine (**9**) and tributylphosphine (**10**). In all cases the original redox couples due to **1a** and the phosphine disappeared rapidly and were replaced by two major processes at 1.7–2.1 V and −(1.0–1.2) V and a minor one around 0 V (Table 1). In parallel, the yellow colour of **1a** disappeared almost immediately after the addition of any of these phosphines.

R^3—P—R^2 with R^1

7 R^1 = R^2 = R^3 = 4-CH$_3$C$_6$H$_4$

8 R^1 = R^2 = C$_2$H$_5$, R^3 = C$_6$H$_5$

9 R^1 = H, R^2 = R^3 = C$_6$H$_5$

10 R^1 = R^2 = R^3 = C$_4$H$_9$

11 R^1 = R^2 = R^3 = 2,4,6-(CH$_3$)$_3$C$_6$H$_2$
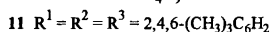
In contrast, when the sterically hindered phosphine, tris(2,4,6-trimethylphenyl)phosphine (**11**, Mes$_3$P), was added to an equimolar amount of **1a** in acetonitrile, the yellow colour of **1a** persisted for many hours, and the cyclic voltammogram of such a solution during this period was essentially a superposition of that of **1a** and Mes$_3$P. The Mes$_3$P$^{\cdot+}$/Mes$_3$P couple showed chemical reversibility under the conditions used, as demonstrated earlier.[13]

An experiment with a colourless solution of PTAD **5** (7.0 mmol dm^{-3}) and **2** (7.0 mmol dm^{-3}) in acetonitrile–Bu$_4$NPF$_6$ showed similar behaviour, with the immediate formation of a major process at $E_{pa} = 1.5$ V, a major

process at $E_{rev} = -0.8$ V and a minor couple at $E_{rev} \approx 0.15$ V, the reduced form of which is denoted **X2**.

EPR spectra from solutions of **1** *or PTAD and* **2** *and their time behaviour.* The EPR spectra previously observed[3] in solutions of azodicarboxylates **1** and triphenylphosphine **2** in solvents of low dielectric constant were reproducible (Table 2) and found to develop as well in dichloromethane or (^{2}H)chloroform but not in acetonitrile. A new critical fact was discovered, in that the radical species responsible for the EPR activity showed a characteristic concentration–time behaviour. Figure 2 shows a few typical EPR spectral intensity–time curves in various solvents, and these curves were representative of all other runs. Rate constants were calculated on the assumption that the kinetics followed a single- or double-exponential function (see legend of Fig. 2).

In order to assess the possible role of oxygen, spectra were recorded in solutions which had been bubbled with air for 1 min or where a deficit (ca. 5%) of 3-chloroperbenzoic had been added. These additives had little effect upon the intensity or quality of the EPR spectrum.

Tri(4-tolyl)phosphine (**7**), diethylphenylphosphine (**8**) or tributylphosphine (**10**) and excess **1a** in (^{2}H)-chloroform with **1a** gave a similar EPR spectrum as **2** (Table 3), whereas neither tris(2,4,6-trimethylphenyl)-phosphine (**11**) nor diphenylphosphine (**9**) gave rise to any paramagnetic activity under these conditions.

PTAD (**5**) with triphenylphosphine **2** gave rise to weak EPR spectra which could be analyzed in terms of three different nitrogen couplings and one phosphorus coupling (Table 4). In 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP) the EPR spectrum of the radical anion of PTAD was observed [lit.[14] a^N 5.08 (2 N), a^N 1.81 (1 N) in DMF-t-BuOH].

The thermal stability of the zwitterion from diethyl azodicarboxylate (**1a**) and **2** was also monitored by ^{1}H

Table 2. EPR spectra recorded from solutions of **1** and **2** in various solvents at 23 °C, generally after standing for 0.5–1.5 h.[a]

1	[1]/M	[2]/M	Solvent	a^N/G	$a^{N'}$/G	a^P/G	a^H/G	Ref.
1a	0.5	0.5	THF	4.6	7.2	14.2	0.9 (2)	3
1a	0.14	0.055	CH_2Cl_2	5.30	7.37	15.83	1.11(2)	
1a	0.14	0.055	CH_2Cl_2–HFP (2%)	b				
1a	0.29	0.11	PhH	4.93	7.68	15.06	1.04(2)	
1a	0.14	0.028	PhH–DCM 7:1	4.92	7.53	15.2	1.05(2)	
1a	0.18	0.043	$CDCl_3$	5.29	7.40	15.9	1.11(2)	
1a	0.18	0.05	CH_3CN	b				
1b	0.5	0.5	THF	4.6	7.3	14.1	0.6 (1)	3
1b	0.25	0.05	THF	4.89	7.77	14.4	0.78(1)	
1b	0.25	0.05	DCM	5.23	7.44	15.4	0.73(1)	
1b	0.25	0.10	$CDCl_3$	5.22	7.45	15.8	0.69(1)	
1b	0.25	0.11	PhH	4.86	7.74	15.03	0.70(1)	
1c	0.5	0.5	THF	4.5	7.3	13.6	—	3
1c	0.3	0.2	PhH	4.76	7.88	12.6	—	
1c	0.3	0.2	DCM	b				
1c	0.25	0.10	$CDCl_3$	5.13	7.64	15.3	—	

[a]The multiplicity is 1, onless otherwise stated (within parentheses). [b]No spectrum appeared.
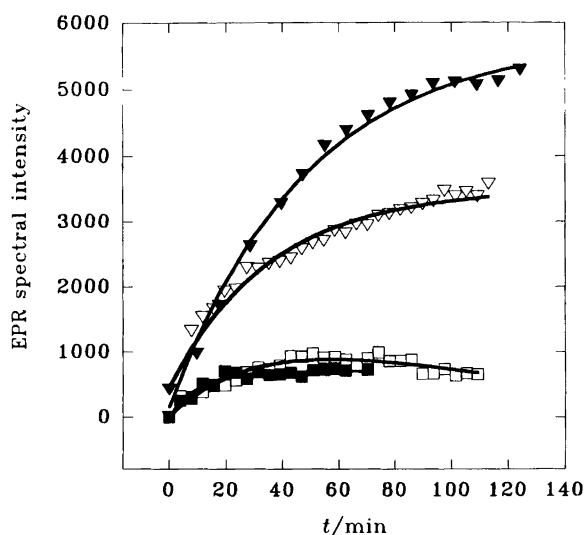
Fig. 2. EPR spectral intensities recorded vs. time from solutions of triphenylphosphine (**2**) and **1** in various solvents. The solid lines represent the best fit of the data to a single or double exponential, with rate constants given in parenthesis. Empty squares, **1a** in dichloromethane ($k_{up} = 0.021$, $k_{down} = 0.015$ min^{-1}); filled squares, **1b** in THF ($k_{up} = 0.096$ min^{-1}); empty triangles, **1b** in benzene ($k_{up} = 0.028$ min^{-1}); filled triangles, **1a** in (^{2}H)chloroform ($k_{up} = 0.021$ min^{-1}).

Table 4. EPR spectra recorded from solutions of PTAD (0.1 mol dm^{-3}) and **2** or **8** (0.03–0.05 mol dm^{-3}) in various solvents at 23 °C, generally after standing for 0.5–1.5 h.[a]

Solvent	a^N/G	$a^{N'}$/G	$a^{N''}$/G	a^P/G
PhH	4.67	8.15	1.42	6.79
CH_3CN	4.73	8.33	1.37	6.96
CH_2Cl_2–8% CH_3CN	4.67	8.23	1.4	6.92
CH_2Cl_2	4.66	8.24	1.38	6.94
HFP–8% CH_3CN	5.39(2)[b]	1.76[b]	—	—
CH_2Cl_2[c]	4.71	6.80	1.44	9.45

[a]The multiplicity is 1, onless otherwise stated (within parentheses). [b]This spectrum was assigned to the radical anion of PTAD. [c]Run with **8**; the spectrum was weak.

NMR spectroscopy in (^{2}H)chloroform in order to check that no significant changes took place during the time periods necessary to perform CV or EPR spectral experiments. No such changes were seen, as is also well documented in previous studies.[2]

Reaction between PTAD and other nucleophiles. Since formal spin adducts of PTAD [**6** in eqn. (4)] have been shown to be persistent at room temperature,[8] and PTAD is a stronger ET oxidant than **1**, it might be expected that the equivalent of the Forrester–Hepburn mechanism [eqn. (3)] with PTAD and other nucleophiles involved

Table 3. EPR spectra recorded from solutions of **1** (0.2–0.3 mol dm^{-3}) and R$_3$P (0.05–0.1 mol dm^{-3}) in various solvents at 23 °C, generally after standing for 0.5–1.5 h.[a]

P compound	1	Solvent	a^N/G	$a^{N'}$/G	a^P/G	a^H/G
8	1a	CH_2Cl_2	5.76	7.13	17.5	1.09(2)
8	1a	$CDCl_3$	5.63	7.13	17.6	1.16(2)
7	1a	$CDCl_3$	5.49	7.28	16.1	1.01(2)
11	1a	$CDCl_3$	b			
9	1c	CH_2Cl_2	b			
10	1a	$CDCl_3$	5.93	7.08	19.6	1.09(2)

[a]The multiplicity is 1, onless otherwise stated (within parentheses). [b]No spectrum seen.

should be feasible. The anticipated reactions are shown in eqns. (5) and (6) and are analogous to those shown in Scheme 1 for 1 and 2.

$$PTAD + Nu^- \rightarrow Nu\text{–}PTAD^- \tag{5}$$

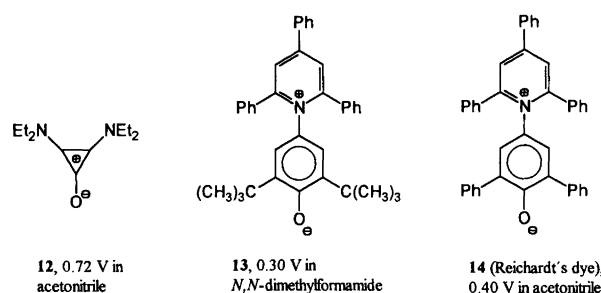$$Nu\text{–}PTAD^- + PTAD \rightarrow Nu\text{–}PTAD^\cdot + PTAD^{\cdot-} \tag{6}$$
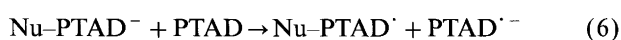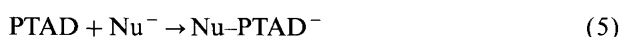
Results of EPR spectral examination of solutions of PTAD and a deficit of various nucleophiles are listed in Table 5. Carboxylate nucleophiles gave rise to the spectrum of the radical anion of PTAD, whereas alkyllithium reagents indeed gave spectra of 6, R = alkyl. The methyl derivative is known from proper spin trapping of the methyl radical by PTAD.[8] No signals appeared in the case of fluoride ion, trinitromethanide ion, tetramethylsuccinimidate anion or benzotriazole or its anion, nucleophiles otherwise prone to participate in the Forrester–Hepburn mechanism.[5]

Tetraphenylborate ion was also allowed to react with PTAD. Obviously, this anion cannot participate in reaction (5), but its redox potential should be low enough for ET between PTAD and Ph_4B^- to be feasible. Cyclic voltammetry of Bu_4NPh_4B in dichloromethane gave $E_{pa}(Ph_4B^\cdot/Ph_4B^-) = 0.90$ V (lit.[15] 0.96 V in acetonitrile), with a second E_{pa} at 2.01 V. The reaction between PTAD and Bu_4NPh_4B gave rise to the EPR spectrum of 6, R = Ph, known[8] from trapping of phenyl radicals from the photolysis of dibenzoyl peroxide by PTAD [$a^N = 7.22$, 5.65, 1.34G; $a^H = 0.6$ (2), 1.44 (2), 1.53 (1) G].

Discussion

Redox characteristics of 1a or PTAD and various phosphines and their mixtures. Table 1 shows the redox characteristics of 1a and six phosphines (2, 7–11) and equimolar mixtures of 1a-phosphine. Except for the sterically hindered 11, all phosphines reacted almost instantaneously with 1a and formed a zwitterion of type 3, as exemplified for triphenylphosphine in Fig. 1. This zwitterion is difficult to oxidize, with E_{pa} values ranging from 1.7 to 2.1 V, and is reduced in the range of −1.0 to −1.2 V. For comparison, E_{rev} for oxidation of some

other zwitterions 12–14 are given below.[16,17] These have the negative charge largely situated on oxygen and are expected to be oxidized at lower potentials than 3, which has its negative charge on nitrogen and, besides, is substituted by the electron-withdrawing alkoxycarbonyl group.

12, 0.72 V in acetonitrile   13, 0.30 V in N,N-dimethylformamide   14 (Reichardt's dye), 0.40 V in acetonitrile

In each case in Table 1 a new, minor redox couple with E_{pa} around 0.0 V was detectable (reduced form X1). It is not possible to assign a definitive structure to this species, but it shows that at least one species capable of undergoing electron transfer to 1 is formed in the reaction between 1 and 2 (see further discussion below).

The electrochemical behaviour of an equimolar mixture of PTAD and triphenylphosphine 2 was analogous to the one displayed by 1a-phosphine mixtures. The zwitterion was again difficult to oxidize, $E_{pa} = 1.5$ V, and a new, minor redox couple with E_{pa} around 0.15 V (reduced form X2) was detectable.

Electron transfer characteristics of reactions between 2 and 1 or PTAD. The putative ET steps proposed previously[3] to explain the formation of paramagnetic species in mixtures of 1 and 2 have been listed in Table 6 and their thermochemistry and kinetics analyzed on the basis of the CV data reported in combination with the Marcus theory.[9] Similar calculations were made for PTAD reactions involving 2 and, for comparison, Ph_4B^-. Also the two new minor redox couples with X1 and X2 as the reduced forms were included as candidates of redox active species.

Table 5. EPR spectra recorded from solutions of PTAD (0.1 mol dm^{-3}) and various nucleophiles (0.03–0.05 mol dm^{-3}) in dichloromethane at 23 °C.[a]

Nucleophile	a^N/G	$a^{N'}$/G	$a^{N''}$/G	a^H/G	Assigned to
$(PhCOO)_2H^-$	5.24(2)	1.67			$PTAD^{\cdot-}$
$(AcO)_2H^-$	5.06(2)	1.71			$PTAD^{\cdot-}$
MeLi	5.84	1.45	7.30	7.3 (3)	6, R = CH$_3$
BuLi	8.03	1.50	7.50	5.29 (2)	6, R = C$_4$H$_9$
BTAzH or BTAz$^-$	b				
F$^-$	b				
$(Me_4$-succinimide)$^-$	b				
$(NO_2)_3C^-$	b				
Ph_4B^-	5.65	1.34	7.22	0.6 (2) 1.44 (2) 1.53 (1)	Ph-PTAD$^\cdot$ (Ref. 8)

[a]The multiplicity is 1, unless otherwise stated (within parentheses). [b]No signal.

Table 6. Thermochemistry and kinetics of putative ET steps of various acceptor (A)–donor (D) pairs, estimated by the Marcus theory[9] for dichloromethane as solvent and at 25 °C.[a]

A	D	$E(A/A^{\cdot-})/V$	$E(D/D^{\cdot+})/V$	e^2/Dr_{12}	$\Delta G°/$ kcal mol^{-1}[b]	$\Delta G^{\ddagger}_{ET}/$ kcal mol^{-1}[b]	$\log(k_{ET}/dm^3\,mol^{-1}\,s^{-1})$[d]
1a	2	−0.56	1.28	7.4	35.0	37.8	−17
1a	3	−0.56	1.95	7.4	50.5	62.1	−35
1a	X1	−0.56	0.00	0; 7.4	12.9; 5.5	13.5; 8.1	1; 5
PTAD	2	0.05	1.28	7.4	21.0	21.0	−4
PTAD	2$^+$-PTAD$^-$	0.05	1.5	7.4	26.0	26.5	−8
PTAD	X2	0.05	0.2	0; 7.4	3.5; −3.9	6.9; 3.2	6; 9
PTAD	Ph$_4$B$^-$	0.05	0.90	0	19.6	19.6	−3

[a]The dielectric constant of dichloromethane was put at 8.9 and the distance between the reactants in the encounter complex, r_{12} at 5 Å. The A–D reorganization energy, λ_{AD}, was put at 20 kcal mol^{-1}. [b]$\Delta G°' = 23.06[E(D/D^{\cdot+}) - E(A/A^{\cdot-}) - e^2/(Dr_{12})]$. [c]$\Delta G^{\ddagger}_{ET} = [\lambda_{AD}(1 + \Delta G°'/\lambda_{AD})^2]/4$. [d]$\log(k_{ET}) = 11 - \Delta G^{\ddagger}_{ET}/(2.303RT)$.

A first conclusion is that the ET reaction between **1a** and **2** is far too endergonic to be a realistic step under any conditions. The situation is even worse for ET oxidation of zwitterion **3** by **1a**. Thus it is highly unlikely that radical cation **4** is formed in the reaction between **1a** and **2**. Radical cation **4** is best described as a high-energy species, reducible at ~2.0 V, and should not possess the persistency of the radical species actually detected by EPR spectroscopy. This is also shown by the lack of chemical reversibility of the **4/3** redox couple.

The same reasoning applies to the PTAD-**2** and PTAD-**2**$^+$-PTAD$^-$ reactions. Here one could anchor the redox properties of PTAD in its ET reaction with Ph$_4$B$^-$ which produced **6**, R = Ph, at least formally by cleavage of Ph$_4$B$^{\cdot}$ to give Ph$_3$B and Ph$^{\cdot}$. As seen from Table 6, the ET reaction between PTAD and Ph$_4$B$^-$ is calculated to be fairly slow, $\log(k_{ET}) = -3$, but such a rate constant is compatible with the slow formation of the Ph-PTAD$^{\cdot-}$ spin adduct. The formation of the latter is an interesting contrast to earlier experiments aiming at trapping the phenyl radical formed in the electrooxidation of Ph$_4$B$^-$ by α-phenyl-*N-tert*-butylnitrone (PBN).[15] No phenyl radicals could be trapped under these conditions (whereas butyl radicals were trapped by PBN from electro-oxidation of Bu$_4$B$^-$), and it was shown that intramolecular coupling of two phenyls originating from one and the same Ph$_4$B$^-$ occurred predominantly. We have no ready explanation for this discrepancy, but note that the conditions used here are unusually mild in redox terms and thus conducive for survival of the phenyl radical.

The new species **X1** or **X2** seen by CV from the reaction between **1a** and **2** or PTAD and **2** in principle qualify for ET reactions with **1a** and PTAD, even though the calculated k_{ET} values would appear to be too large to be compatible with the rates of formation of the paramagnetic species (see below).

Which species is responsible for the EPR spectra? At this stage, we can say that **1a** reacts rapidly and irreversibly with **2** and other phosphines **7–10** to produce a persistent zwitterion **3** and at least one minor redox active species **X1**. Zwitterion **3** is difficult to oxidize to the correspond-

ing radical cation **4**, E_{pa} being between 1.7 and 2.1 V, and therefore the latter cannot possibly be the cause of the EPR spectra recorded from such solutions. Species **X1** or some other, as yet undetected species, also seems to be formed irreversibly, and in principle (Table 6) then can be oxidized by **1a** to produce a radical species with similar time behaviour as that exhibited in Fig. 2. This type of kinetics is expected from a relatively slow reaction between two starting components which are present from the beginning.

If we assume that the reaction between **1** and **2** irreversibly produces a minor species, like **X1** or any other species formed in lower concentration but not conclusively detectable by the CV technique, the solution a few seconds after mixing will contain a residual concen-
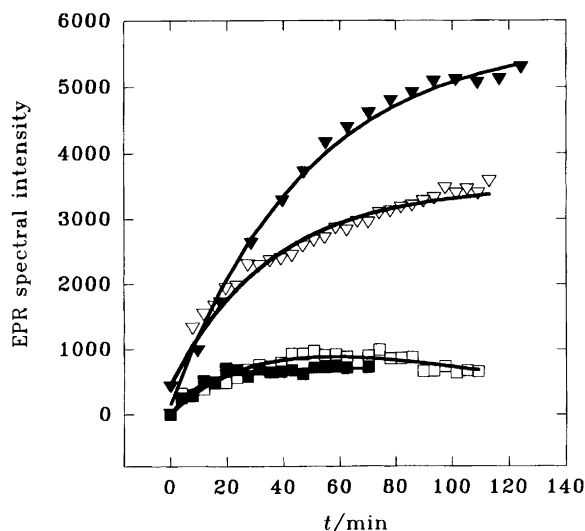

Fig. 2. EPR spectral intensities recorded vs. time from solutions of triphenylphosphine (**2**) and **1** in various solvents. The solid lines represent the best fit of the data to a single or double exponential, with rate constants given in parenthesis. Empty squares, **1a** in dichloromethane ($k_{up} = 0.021$, $k_{down} = 0.015$ min^{-1}); filled squares, **1b** in THF ($k_{up} = 0.096$ min^{-1}); empty triangles, **1b** in benzene ($k_{up} = 0.028$ min^{-1}); filled triangles, **1a** in (^{2}H)chloroform ($k_{up} = 0.021$ min^{-1}).

tration of **1** which in most cases of Table 2 is around 0.1 mol dm^{-3}. From the estimated first-order rate constants (see legend of Fig. 2) and assuming that they represent the pseudo-first-order reaction between **1** in excess and the unknown species, the second-order rate constant for formation of the radical species will be $(0.02-0.1)/0.1/60 \approx (3-17) \times 10^{-3}$ dm^3 mol^{-1} s^{-1}. Such rate constants are distinctly lower than those theoretically estimated for reaction between **1** and **X1** (Table 6), and it therefore does not appear likely that **X1** is the origin of the EPR activity.

In the early days of mechanistic assumptions about the Mitsunobu reaction, it was suggested[18] that triphenylphosphine would nucleophilically attack a carbonyl oxygen of the azodicarboxylate, furnishing **15** as the zwitterionic intermediate. Even if the predominant attack on nitrogen with formation of **3** later became the accepted pathway, it is still possible that small proportion of **15** is formed. Only very little of such an intermediate is necessary to account for the EPR spectra detected; with, say, 0.1% attack in this fashion, the actual yield of the paramagnetic species **15**$^{\cdot+}$ formed after one-electron oxidation of **15** would be of the order of only 1%. Species **15** is expected to be easier to oxidize than **3**, since in **15** the positive charge on phosphorus is further removed from the nitrogen center, and the distonic radical cation **15**$^{\cdot+}$ has its odd electron delocalized in a way which can explain the persistency of the experimentally observed species. In principle, **15**$^{\cdot+}$ can exist as two geometric isomers, but the EPR spectral study gave no indication of more than one radical species being present.
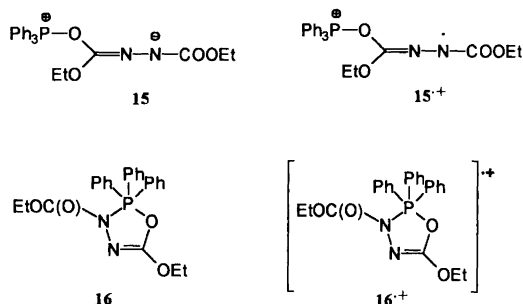
The identification of the radical as **15**$^{\cdot+}$ is compatible with the EPR spectra obtained. Structure **15**$^{\cdot+}$ has alkoxy groups which are in distinctly different chemical environments and hence it is explicable that coupling to only one alkoxy group is observed. On the other hand, for authentic spin adducts ROOC–N(X)–N$^{\cdot}$COOR one sometimes can observe couplings to both alkoxy groups.[6]

Another possible structure was envisaged in the radical cation of **16**, where the phosphorus atom of **3** (or **15**) has attacked a carbonyl oxygen (or nitrogen) intramolecularly and formed a five-membered oxadiazaphosphaheterocycle, a known structure.[19] However, such a structure cannot be formed from the PTAD series, unless one assumes that the EPR spectra observed are derived from derivatives of PTAD which have resulted from

accidental ring-opening of PTAD. One might for example assume that nucleophiles fortuitously present might cause such behaviour, but this assumption has meagre support from data on known decomposition routes of PTAD upon treatment with various nucleophiles, among them water or alcohols.[20]

The Forrester–Hepburn mechanism in the reaction between PTAD and nucleophiles. Equations (5) and (6) in principle are based on the same chemistry as in Scheme 1. The results and reasoning given above rule out that this type of reaction can take place in the particular case of phosphines, for the simple reason that the zwitterion formed is far too difficult to oxidize. This need not apply to other nucleophiles, and the results of Table 5 show that nucleophiles like MeLi and BuLi add to PTAD forming an overall neutral species which is oxidized by a second PTAD to give R–PTAD$^{\cdot}$. Other nucleophiles did not give any EPR signal, presumably because the oxidation step is unfavourable. The two carboxylates with PTAD gave PTAD$^{\cdot-}$ as the only detectable radical species, presumably as a result of the operation of eqns. (5) and (6) [summed in eqn. (7)] and assuming that RCO$_2$–PTAD$^{\cdot}$ is too reactive to be detected under the conditions employed.

$$RCOO^- + 2\,PTAD \rightarrow RCOO–PTAD^{\cdot} + PTAD^{\cdot-} \qquad (7)$$

Experimental

Instruments and methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer. Cyclic voltammetry was performed by the BAS-100 instrument, using an Ag/AgCl electrode as the reference, a 2 mm^2 Pt electrode as the working electrode, and with *iR* compensation. Potentials given and discussed in the text are given with the Ag/AgCl electrode as reference.

EPR spectra were recorded by the Upgrade Version ESP 3220–200SH of a Bruker ER-200D spectrometer. The EPR experiments were performed as described earlier (100 kHz modulation frequency, microwave effect 0.4–1.25 mW, modulation amplitude 0.01–0.04 mT). Simulations were carried out by the public domain programme WINSIM[21] or Simfonia® from Bruker AG. Time–intensity measurements were performed by the auomation routine of the software, and the kinetics were analyzed by the Sigmaplot® program.

Materials. Dialkyl azodicarboxylates (**1**), PTAD, Reichardt's dye (**14**) and phosphines (**2**, **7–11**) were of best commercial quality available. Dichloromethane, acetonitrile and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP) were of Merck Uvasol® quality. Methyllithium, butyllithium and tetrabutylammonium tetraphenylborate were purchased, whereas the remaining nucleophile sources of Table 5 were available as tetrabutylammonium salts from earlier studies.[5]

References

1. Hughes, D. L. *Org. React. 42* (1992) 335.
2. (a) Morrison, D. C. *J. Org. Chem. 23* (1958) 1072; (b) Brunn, E. and Huisgen, R. *Angew. Chem. 81* (1969) 534; (c) Grochowski, E., Hilton, B. D., Kupper, R. J. and Michejda, C. J. *J. Am. Chem. Soc. 104* (1982) 6876; (d) Hughes, D. L., Reamer, R. A., Bergan, J. J. and Grabowski, E. J. J. *J. Am. Chem. Soc. 110* (1988) 6487; (e) Crich, D., Dyker, H. and Harris, R. J. *J. Org. Chem. 54* (1989) 257; (f) Camp, D. and Jenkins, I. D. *Aust. J. Chem. 45* (1992) 47.
3. Camp, D., Hanson, G. R. and Jenkins, I. D. *J. Org. Chem. 60* (1995) 2977.
4. Forrester, A. R. and Hepburn, S. P. *J. Chem. Soc. C* (1971) 701.
5. (a) Carloni, P., Eberson, L., Greci, L., Sgarabotta, P. and Stipa, P. *J. Chem. Soc., Perkin Trans. 2* (1996) 1297; (b) Eberson, L., McCullough, J. J. and Persson, O. *J. Chem. Soc., Perkin Trans. 2* (1997) 133; (c) Alberti, A., Carloni, P., Eberson, L., Greci, L. and Stipa, P. *J. Chem. Soc., Perkin Trans. 2* (1997) 887; (d) Eberson. L. and Persson. O. *J. Chem. Soc., Perkin Trans. 2* (1997) 893, 1689; (e) Eberson, L. and McCullough, J. J. *J. Chem. Soc., Perkin Trans. 2* (1998) 49.
6. Roberts, B. P. and Winter, J. N. *Tetrahedron Lett.* (1979) 3575.
7. Rádl, S. *Adv. Heterocycl. Chem. 67* (1996) 119.
8. Alberti, A. and Pedulli, G. F. *J. Org. Chem. 48* (1983) 2544.
9. For review on electron transfer reactions in organic chemistry, see: (a) Eberson, L. *Adv. Phys. Org. Chem. 18* (1982) 79; (b) Eberson, L. *Electron Transfer Reactions in Organic Chemistry*, Springer-Verlag, Heidelberg 1987.
10. Schiavon, G., Zercchin, S. and Cogoni, G. *J. Electroanal. Chem. 48* (1973) 425.
11. Zweig, A. and Hoffmann, A. K. *J. Am. Chem. Soc. 85* (1963) 2736.
12. Adam, W. and Carballeira, N. *J. Am. Chem. Soc. 106* (1984) 2874.
13. Merzougui, B., Berchadsky, Y., Tordo, P and Gronchi, G. *Electrochim. Acta 42* (1997) 2445.
14. Hall, J. H., Bigard, W. E., Fargher, J. M. and Jones, M. L. *J. Org. Chem. 47* (1982) 1459.
15. Bancroft, E. E., Blount, H. N. and Janzen, E. G. *J. Am. Chem. Soc. 101* (1979) 3092.
16. Eberson, L. and Kubacek, P. *Acta Chem. Scand. 44* (1990) 384.
17. Bock, H. and Herrmann, H.-F. *Helv. Chim. Acta 72* (1989) 1171.
18. Cookson, R. C. and Locke, J. M. *J. Chem. Soc.* (1963) 6062; Mitsunobu, O., Yamada, M. and Mukaiyama, T. *Bull. Chem. Soc. Jpn. 40* (1967) 935.
19. Navech, J., Kraemer, R. and Majoral, J.-P. *Tetrahedron Lett. 21* (1980) 1449.
20. Izydore. R. A.. Johnson. H. E. and Horton. R. T. *J. Org. Chem. 50* (1985) 4589.
21. Duling, D. *Public EPR Software Tools,* National Institute of Environmental Health Sciences, 1996.