Reaction of Unsymmetrical Benzils with Cyanide Ion in Dimethyl Sulfoxide[1]

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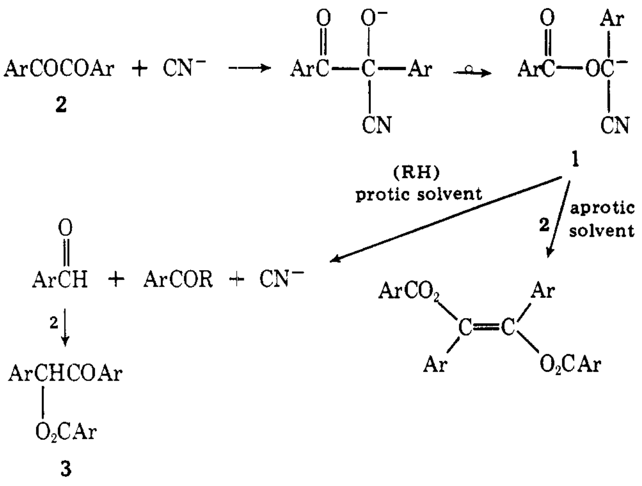
It was reported by others[2–5,7] that the reaction of benzils, **2**, with cyanide ion gives a variety of products depending on the reaction conditions. The reported mechanism assumes cleavage of the central C–C bond after addition of CN^- to form a resonance stabilized carbanion, **1**, which was proposed[3] as the common intermediate that leads to the formation of the observed diversity of products as indicated in part by Scheme I.

Scheme I



Evidence that **1** may indeed be the common intermediate for the products isolated was obtained by Trisler,[5] who reported that 4-nitromandelonitrile benzoate (**10**), the protonated form of **1**, is isolated in good yield when 4-nitrobenzil (**2c**) is made to react with 1 equiv of CN^- in Me_2SO or DMF.

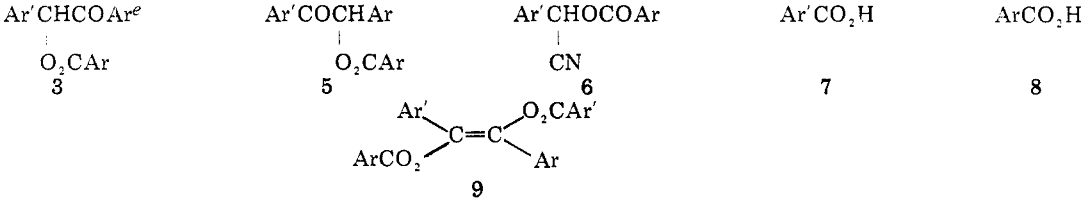
We observed,[6] however, that conversion of mandelonitrile benzoate to products under the same experimental conditions is considerably slower than the rate of conversion of benzil to products, which is inconsistent with the accepted mechanism. Moreover, we noted[6] that the kinetics of the CN^--catalyzed ammonolysis of benzil to afford benzaldehyde and benzamide is also not consistent with this mechanism as discussed previously.[6] It was decided, therefore, to investigate this reaction further using unsymmetrical benzils in the hope of resolving the somewhat ambiguous results thus far reported.

Accordingly, we repeated the reactions of CN^- in Me_2SO with 4-dimethylaminobenzil (**2a**), 4-dimethylamino-4′-chlorobenzil (**2b**), and 4-nitrobenzil[5] (**2c**), using somewhat different experimental conditions to determine the effect on product distribution. The data are collected in Table I. The materials balance ranges from 98 to 25%. The data show that the benzoin esters **3a** and **3b** were isolated as the major products of reaction with **2a** and **2b** in relatively good yields, whereas the alternative esters, **5a** and **5b**, were isolated as minor products in relatively poor yields. Reaction with **2c**, however, gave a product mixture from which the 4′-nitrobenzoate of *trans*-4-nitrostilbenediol (**9c**) was the only product isolated in 25% yield.

The isolation of **9c** as the major product instead of 4-nitromandelonitrile benzoate (**10**) as reported by Trisler,[5] who used an equimolar amount of 4-nitrobenzil and CN^-, is attributable to the difference in reactant ratios. We used a fourfold excess of 4-nitrobenzil so that the intermediate, **1c**, or any other adduct produced by very rapid and complete reaction with available CN^-, had a threefold excess of residual benzil with which to react further to give the stilbene **9c**. Trisler's conditions, on the other hand, produced rapid and complete conversion to **1c** leaving no available benzil for further reaction. The stable carbanion was isolated in good yield, therefore, as **10** when the reaction mixture was quenched with water.[5]

Our isolation of 4-dimethylaminomandelonitrile benzoate (**6a**) in small amount from the reaction mixture obtained with 4-dimethylaminobenzil (**2a**) is an evidence that **1a** may be an intermediate in this reaction, but the isolation of **3a**, **3b**, and **9c** as the major products of reaction with **2a**, **2b**, and **2c**, respectively, suggests that these products may be formed by an alternate pathway. The formation of these products via the accepted mechanism requires that the CN^- and the corresponding carbanions, **1**, add preferentially to the less electrophilic carbonyl center (ArCO), which is contrary to theory.

Table I. Reaction of Unsymmetrical Benzils with NaCN at Room Temperature in Me_2SO under N_2



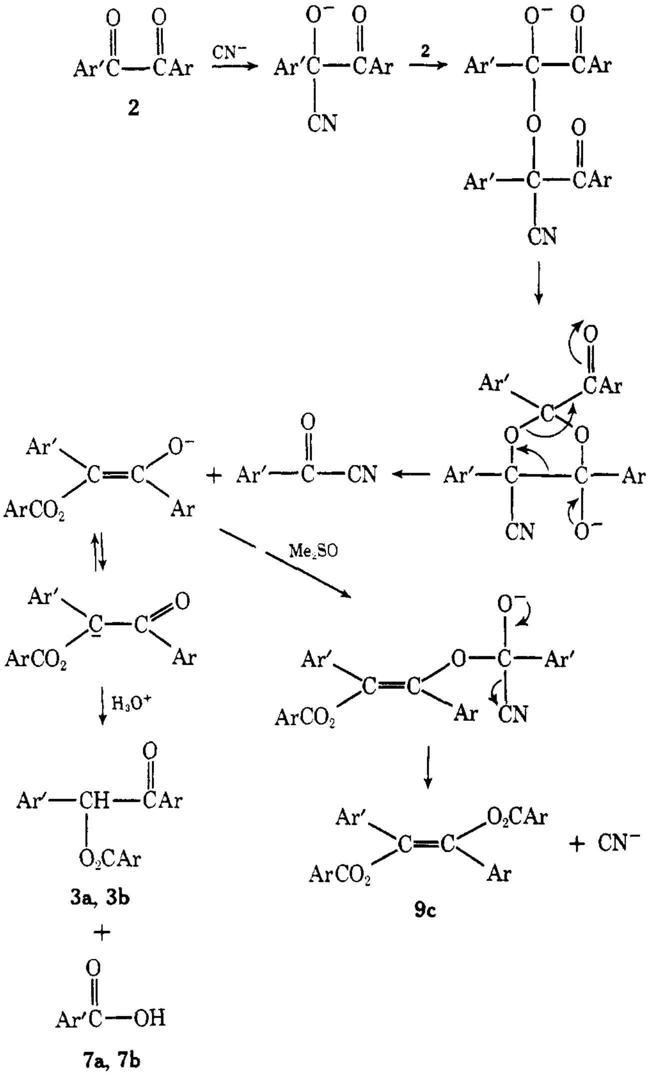
$Ar'CHCOAr^{e}$ with O_2CAr below: **3**; $Ar'COCHAr$ with O_2CAr below: **5**; $Ar'CHOCOAr$ with CN below: **6**; $Ar'CO_2H$: **7**; $ArCO_2H$: **8**; **9**

Reactant					Product, % yield							% benzil units recovery as product
No.[a]	mmol	NaCN, mmol	Solvent, mL	Reaction time, h	3	4[d]	5	6	7	8	9	
2a	4.0	6.6	25	6	34	5[b]	0		10	9		59
2a	5.0	4.0	30	40	48	8[b]	0	21[c]	11	10		98
2a	5.0	9.0	30	8	29	0	4.4		18	15		66
2b	3.5	4.0	20	15	31		2.6		16			50
2b	2.3	2.0	15	10	28		3.5		12	Trace		44
2c	2.6	0.6	15	1							25	25

[a] 2a, *p*-dimethylaminobenzil; 2b, *p*-chloro-*p*′-dimethylaminobenzil. [b] % by weight. [c] Yield of reddish tough mass from which a small amount of 6a was obtained. [d] Unidentified product. [e] Here, Ar′ is the more electron-withdrawing aromatic group of 2.

Because of this discrepancy, we postulate an alternative pathway, which is consistent with product distributions obtained, and involves addition of the anion to the more electrophilic carbonyl (Ar′CO) as shown in Scheme II, where Ar′ is the more electron-withdrawing aromatic group.

Scheme II



a, Ar′ = Ph; Ar = 4-$Me_2NC_6H_4$
b, Ar′ = 4-ClC_6H_4; Ar = 4-$Me_2NC_6H_4$
c, Ar′ = 4-$NO_2C_6H_4$; Ar = Ph

To test the possibility that the enolate ion of the nitrobenzoin benzoate can indeed add to benzoyl cyanide as shown in Scheme II, benzoin benzoate itself was converted to the corresponding enolate ion by reaction with NaH dispersed in mineral oil. Benzoyl cyanide was then added to give a highly colored solution, which was quenched soon thereafter with ice-cold aqueous sulfuric acid. As expected, stilbenediol dibenzoate was isolated in good yield from the product mixture.

More work is needed, of course, to prove or disprove the validity of this postulated alternative pathway, which thus far appears to be more consistent with the product distributions actually obtained than the pathways proposed earlier.

Experimental Section

Infrared, UV, and NMR spectra were recorded on a Perkin-Elmer 337 IR spectrophotometer, a Hitachi 124 spectrophotometer, and a JEOL C-60 HL spectrometer, respectively. Melting points were uncorrected.

Materials. Substituted benzils were prepared according to procedures described previously.[6,9–11] 4-Nitrobenzil (2c) had mp 138–139 °C (lit.[11] 136–137 °C). Benzoin benzoate[6] and benzoyl cyanide[12] were also prepared using procedures reported earlier. Me_2SO was dried over CaH_2 and distilled in vacuo.

Reaction of 4-Dimethylaminobenzil with NaCN. The reaction procedure was similar to that reported by Trisler.[2] To a partly dissolved solution of NaCN (0.2 g, 4 mmol) in Me_2SO (30 mL) was added **2a** (1.27 g, 5 mmol) under N_2. The solution became dark green in color. After 40 h at room temperature, the mixture was separated by filtration. The product was isolated as fine yellow crystals (0.48 g, 48%), mp 240–248 °C dec. The product was purified further by one recrystallization from pyridine as indicated by its melting point (258–262 °C dec). This product was identified as 4′-dimethylaminobenzoin 4-dimethylaminobenzoate (**3a**) by its melting point, IR and NMR spectra, and elemental analysis.

The Me_2SO filtrate from which **3a** was removed by filtration was poured into acidic ice–water. The mixture was extracted with benzene. The benzene extract was washed with aqueous $NaHCO_3$, and then evaporated to dryness to give a reddish, tough mass (ca. 0.7 g) as residue, which on recrystallization from EtOH and treatment with active carbon gave 0.1 g of crystalline material (mp 139–144 °C). This product was purified further by one recrystallization from ethanol to give crystals that melted at 159–161 °C. This material, **4a,** is not yet identified. Evaporation of ethanolic filtrate left a dark brown material as residue (0.29 g, 21% by wt). The IR spectrum of this material was consistent with that of mandelonitrile 4-dimethylaminobenzoate (**6a**). This material was purified further by repeated crystallizations from petroleum ether to give a small amount of **6a** in the form of colorless crystals, mp 70–73 °C. The residue obtained by evaporation of the combined filtrate was dark brown, tarry material, from which no definite product could be isolated further. The aqueous $NaHCO_3$ extract of the benzene solution from which **6a** was isolated was acidified to pH 5 and extracted with CCl_4. The CCl_4 extract was evaporated to dryness. The residue (0.07 g, 10%), mp 215–230 °C, was identified as *p*-dimethylaminobenzoic acid (**8a**) by its melting point and IR spectrum. Acidification of a residual aqueous solution to pH 1 and extraction with CCl_4 gave **7a** (0.07 g, 11%), mp 118–120 °C, which was identified as benzoic acid by its melting point and IR spectra. The unidentified product **4a,** which was isolated in low yield, might be a benzoin benzoate having at least one *p*-dimethylamino group in view of the NMR [τ, 7.03, 6 H for $(CH_3)_2N$–; 1.9–2.9, 15 H aromatic], MS (*m/e* 359, 4.6%), and elemental analysis. Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 75.60; H, 5.88; N, 4.04. The mass spectrum showed a base peak of *p*-$Me_2NC_6H_4CO^+$ (*m/e* 148, 100%) and peaks of $PhCO^+$ (105, 17%) and Ph^+ (77, 12%), but the IR spectrum (ν C═O 1705, 1685, 1665 cm^{-1}) is inconsistent with those of any authentic sample of benzoin 4-dimethylaminobenzoate, 4′-dimethylaminobenzoin benzoate, and **3a** or of their mixtures. Repeated recrystallizations did not change the IR spectrum, and it might be a mixture, since the UV spectrum showed the existence of both *p*-$Me_2NC_6H_4CO$ (346 nm) and *p*-$Me_2NC_6H_4COO$ (318 nm) groups. **4a** is neither symmetrical benzoin nor stilbene derivative in view of spectral data.

3a: IR (KBr) 1680, 1660 cm^{-1}; NMR (Me_2SO-d_6) τ 2.0–3.5 (m, 14 H of aromatic and methine), 7.07 (s, 12 H of NMe); MS *m/e* 402, 148, 120, 77; UV ($CHCl_3$) 323 nm (ε 40 000), 348 (38 000). Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 73.35; H, 6.40; N, 7.81. The sample agreed with the authentic specimen of 4′-dimethylaminobenzoin 4-dimethylaminobenzoate (**3a**) prepared from 4′-dimethylaminobenzoin and 4-dimethylaminobenzoyl chloride.

6a: IR (KBr) 1710 cm^{-1}; NMR (Me_2SO-d_6) τ 2.25 (d, aromatic 2 H, *J* = 10 Hz), 2.50 (m, 5 H of Ph), 3.23 (s, 1 H of methine), 3.32 (d, aromatic 2 H, *J* = 10 Hz), 7.01 (s, 6 H of NMe); UV (MeOH) 318 nm (ε ≥ 10^4). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.21; H, 5.97; N, 9.64. Treatment of the sample with NaOMe in dioxane gave benzaldehyde (79%) and methyl 4-dimethylaminobenzoate (74%) on GLC analysis. Alkaline hydrolysis of the sample followed by acidification gave a positive test (cupric acetate–benzidine) for HCN, which indicates the existence of the CN group in **6a** in spite of no band of CN in its IR spectrum.

Reaction of 4-Chloro-4′-dimethylaminobenzil (2b) with NaCN. The analogous reaction of **2b** (1.44 g) with NaCN (0.45 g) for 8 h gave light green crystals of 4-chloro-4′-dimethylaminobenzoin 4-dimethylaminobenzoate (**3b,** 0.31 g, 29%), mp 252–265 °C dec. The analogous workup of the filtrate gave 4′-dimethylamino-4-chlorobenzoin 4-dimethylaminobenzoate (**5b,** 0.047 g, 4%), mp 254–262 °C, crude 4-dimethylaminobenzoic acid (**8b,** 0.12 g, 15%), and 4-chlorobenzoic acid (**7b,** 0.14 g, 18%).

3b: IR (KBr) 1690, 1660 cm^{-1}; NMR (Me_2SO-d_6) τ 2.2–3.5 (m, 13 H of aromatic and methine), 7.07 (s, 12 H of NMe); MS *m/e* 436, 315, 148, 120, 77; UV ($CHCl_3$) 323 nm (ε 34 000), 350 (31 000). Anal. Calcd for $C_{25}H_{25}ClN_2O_3$: C, 68.76; H, 5.77; N, 6.42. Found: C, 66.49; H, 5.56; N, 5.79. This was same material as the authentic specimen.

5b: IR (KBr) 1715, 1705 cm^{-1}; NMR (Me_2SO-d_6) τ 2.1–3.5 (m, 13 H of aromatic and methine), 7.00 and 7.02 (s, 12 H of NMe); UV ($CHCl_3$) 323 nm (ϵ 54 000). Anal. Calcd for $C_{25}H_{25}N_2O_3Cl$: C, 68.76; H, 5.77; N, 6.42. Found: C, 67.83; H, 5.22; N, 6.64.

Reaction of 4-Nitrobenzil (2c) with NaCN. 4-Nitrobenzil (**2c,** 0.64 g) was added to a solution of NaCN (0.03 g) in Me_2SO (15 mL). Reaction was allowed to occur at room temperature for 1 h and then the mixture was poured into acidic ice–water to produce a light green precipitate. This precipitate was washed with ethanol and recrystallized from benzene–ethanol to give 4-nitrostilbenediol 4′-nitrodibenzoate (**9c**) in the form of light yellow crystals (0.16 g, 25%), mp 212–216 °C, which were identified by IR and NMR spectra and elemental analysis. Only a small amount of yellow solid (0.01 g), mp 175–180 °C, was recovered from the combined ethanol washings and mother liquor.

9c: IR (KBr) 1740, 1520, 1340 cm^{-1}; NMR ($CDCl_3$) τ 1.69 (s, 4 H of 4-nitrobenzoyloxy), 1.7–2.3 (m, 2 H meta to NO_2 and 4 H ortho to C=O; 1.82 d and 2.22 d, $J = 9$ Hz), 2.3–2.7 (m, 5 H of Ph and 3 H meta and para to C=O); MS *m/e* 510, 255, 240, 239, 150, 135, 122, 105. Anal. Calcd for $C_{28}H_{18}N_2O_8$: C, 65.88; H, 3.55; N, 5.49. Found: C, 65.75; H, 3.82; N, 5.69. Treatment of the sample with methanolic MeONa gave an equimolar mixture of methyl benzoate and methyl 4-nitrobenzoate (1:0.84) as determined by GLC analysis.

Reaction of Benzoin Benzoate with Benzoyl Cyanide in the Presence of NaH. Benzoin benzoate (1.58 g, 5 mmol) was converted into the enolate ion by treatment with NaH dispersed in mineral oil (0.50 g, 5 mmol) in Me_2SO (30 mL) under N_2 to give a deep green colored solution. Addition of benzoyl cyanide (0.68, g, 5 mmol) at room temperature caused the solution to become very dark. After 20 min the mixture was poured into ice-cold aqueous H_2SO_4, giving a precipitate (1.84 g). This precipitate was recrystallized from benzene-petroleum to give stilbenediol dibenzoate (SDD) (0.53 g, 25%), in the form of crystals, mp 191–193 °C. An additional SDD (0.13 g, total 31%) was isolated as a second crop (mp 179–193 °C). Evaporation of the filtrate to dryness and crystallization of the residue from EtOH gave benzoin benzoate (0.59 g, 37%) in the form of crystals, mp 124–126 °C.

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Registry No.—**2a,** 22711-20-2; **2b,** 60955-65-9; **2c,** 22711-24-6; **3a,** 62139-42-8; **3b,** 62139-43-9; **5b,** 62139-44-0; **6a,** 62139-45-1; **7a,** 65-85-0; **7b,** 74-11-3; **8a,** 619-84-1; **9c,** 62139-46-2; NaCN, 143-33-9; benzaldehyde, 100-52-7; methyl 4-dimethylaminobenzoate, 1202-25-1; benzoin benzoate, 1459-20-7; benzoyl cyanide, 613-90-1; stilbenediol dibenzoate, 1924-29-4; dimethyl sulfoxide, 67-68-5.

References and Notes

(1) Contribution No. 219.

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(8) However, if the assumption is made that the hydrolysis of Ar $\overline{C}$(CN)OCOAr′ affording ArCHO is preferred exclusively to that of Ar′C(CN)OCOAr (**1a,b**) affording Ar′CHO with a trace amount of water which might exist in the system, then the preferred condensation of **1a,b** with ArCHO should give the benzoate **3** via **5** (Ar = 4-$Me_2NC_6H_4$). The assumption is consistent with the previous observations that the rate of basic hydrolysis with ethyl benzoate is higher by a factor of 40 than with ethyl 4-aminobenzoate: D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1439 (1938); E. Tommila and C. N. Hinshelwood, *ibid.*, 862 (1938). It is not unreasonable.

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Disproportionation and Pyrolysis of *p*-Toluenesulfonylhydrazine

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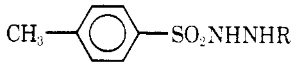
p-Toluenesulfonylhydrazine (**1**) is a standard reagent, widely used in the synthesis of organic compounds.[1] Its chemistry, particularly deviations from the normal behavior of hydrazine derivatives, is thus of interest. In 1965, Chang[2] found that an anomalous reaction between **1** and 12-oxocholane produced 12-oxocholane azine in addition to the expected tosylhydrazone. The azine presumably arose via a disproportionation of **1** into hydrazine and di(*p*-toluenesulfonyl)hydrazine (**2**), but the disubstituted hydrazine was not isolated. We found that a similar disproportionation occurred when 1,3-dioxolen-2-one was heated with **1** in the presence of sulfuric acid; and **2**, shown below to be the 1,2 isomer, was formed in low yield.



1, R = H
2, R = *p*-$CH_3C_6H_4SO_2$

A better synthesis of **2** involved deprotonation of **1** with bases such as *n*-butyllithium or triethylamine followed by reaction with *p*-toluenesulfonyl chloride. Recrystallization from acetonitrile yielded 1,2-di(*p*-toluenesulfonyl)hydrazine as white needles, mp 194–195 °C dec. The compound underwent extensive fragmentation on electron impact and no parent ion was observed in the mass spectrum. Instead, a cluster of peaks due to $C_7H_7SO_2^+$, $C_7H_7SO_2H^+$, and $C_7H_7SO_2H_2^+$, respectively, was observed. The methane chemical ionization mass spectrum showed the *m/e* 157 ($C_7H_7SO_2H_2^+$) ion as the base peak. In contrast, the mass spectrum of **1** showed a readily identifiable M^+ peak at *m/e* 186.

The infrared spectrum of **2** in acetonitrile exhibited strong bands at 1165 and 1345 cm^{-1} due to the sulfonyl groups. An additional band at 3180 cm^{-1}, which shifted to 2350 cm^{-1} on crystallization of **2** from tetrahydrofuran–D_2O, was assigned to ν_{NH}. The presence of only one N–H stretching band implies that only secondary amine groups are present, for otherwise, two bands, symmetric and asymmetric stretch, would be observed.[3] Further evidence that **2** is the 1,2 isomer was obtained from the ^1H NMR spectrum in which the NH protons appeared as a broad singlet at 3.4_2 ppm (Me_2SO-d_6). The shifts of the NH protons are 3.4_2 (2 H) and 4.1_1 ppm (1 H) for **1** and 3.4 ppm for *p*-toluenesulfonamide. This indicates that NH protons adjacent to a *p*-toluenesulfonyl group resonate at ~3.4 ppm, as observed in **2**.

It is probable that **2** is formed by nucleophilic attack by the conjugate base on **1** on toluenesulfonyl chloride. In this case, it is interesting to note that proton abstraction from N-2 takes place rather than from N-1, adjacent to the electron-withdrawing tosyl group.

The melt pyrolysis of *p*-toluenesulfonylhydrazine was studied to determine whether thermal disproportionation would occur. Upon heating at 140 °C under vacuum, the hydrazine derivative decomposed to give nitrogen, ammonium *p*-toluenesulfonate (**3**), *p*-toluenesulfonamide, and *p*-ditolyl disulfide dioxide (**4**). Identification of **3** followed from its elemental analysis and behavior as a 1:1 electrolyte in nitromethane. The electron impact and methane chemical ion-