

## Intermediates in Nucleophilic Aromatic Substitutions. I. Meisenheimer Complexes of Dinitro-Substituted Aromatic Ethers<sup>1</sup>

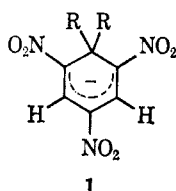
W. E. BYRNE, E. J. FENDLER,<sup>2</sup> J. H. FENDLER, AND C. E. GRIFFIN

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213,  
and Radiation Research Laboratories, Mellon Institute, Pittsburgh, Pennsylvania 15213

Received December 27, 1966

The bright red crystalline Meisenheimer complex isolated from the reaction of 2,4-dinitroanisole and potassium ethoxide was shown to be identical with the adduct prepared from 2,4-dinitrophenetole and potassium methoxide. The crystalline symmetrical Meisenheimer complexes formed by the reactions of potassium methoxide and 2,4-dinitroanisole and potassium ethoxide and 2,4-dinitrophenetole were also isolated. Nuclear magnetic resonance and infrared spectroscopic studies establish both alkoxy groups in these complexes to be bound covalently to the cyclohexadienyl system at the same carbon, *i.e.*, these complexes are potassium 1,1-dialkoxy-2,4-dinitrocyclohexadienylides. The spectroscopic evidence is inconsistent with an alternative charge-transfer formulation for the complexes. The stabilities of these complexes and their role in nucleophilic aromatic substitution are discussed.

The formation of red crystals in an alkaline solution of trinitro-substituted aromatic compounds was first observed over 80 years ago.<sup>3</sup> Meisenheimer<sup>4</sup> isolated identical ionic<sup>5</sup> adducts from the reactions of both 2,4,6-trinitroanisole and ethanolic potassium hydroxide and 2,4,6-trinitrophenetole and methanolic sodium hydroxide; in each case, the adduct decomposed to give the same mixture of trinitroanisole and phenetole. Compounds of this type are now commonly referred to as Meisenheimer complexes.<sup>6</sup> Some uncertainty has existed regarding the structures of these complexes,<sup>6</sup> but recent studies<sup>7</sup> of the proton magnetic resonance (pmr) spectra of complexes formed from 1-substituted 2,4,6-trinitrobenzenes have largely clarified the confusion. This recent evidence established the structure of these complexes to be 1. In an independent study,

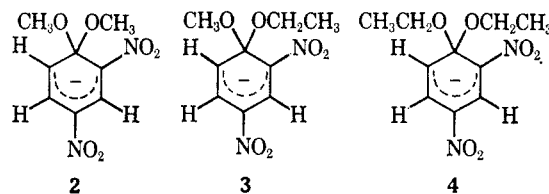


evidence has been presented which indicated that the methoxyl groups of the methyl picrate-potassium methoxide complex (1, R = OCH<sub>3</sub>) are covalently linked to the aromatic ring.<sup>8</sup> Comparable evidence regarding the structures of the complexes prepared from dinitro aromatics has not been presented.

The detection and isolation of Meisenheimer-type complexes have been used as evidence in favor of the two-step mechanism for bimolecular nucleophilic aromatic substitution.<sup>5,9</sup> In a recent study, the mechanism of a symmetrical methoxyl exchange between sodium methoxide and 2,4,6-trinitroanisole in methanol

was shown to involve the formation of a Meisenheimer complex.<sup>10</sup> Similar results were obtained in the corresponding reaction of sodium methoxide and 2,4-dinitroanisole.<sup>10</sup>

To provide further evidence that the dinitro-substituted aromatic alkoxy Meisenheimer complexes are intermediates in nucleophilic aromatic substitutions and that their structures involve covalent bonding of alkoxy groups to the aromatic ring, we report the synthesis, isolation, and chemical and physical properties of the crystalline complexes 2-4.



### Experimental Section

Methanol, ethanol, and dimethyl sulfoxide (DMSO) were dried over molecular sieves. Reagent grade dioxane was dried by refluxing with sodium followed by fractional distillation from sodium. Alcoholic ethoxide and methoxide solutions were prepared by dissolving freshly cut potassium or sodium in the dry alcohol in a flask fitted with a water condenser and a calcium chloride drying tube. The concentrated alkoxide solutions were stored in polythene bottles under nitrogen; concentrations were determined by titration with standard 0.10 N hydrochloric acid using laemoid indicator.

The methoxyl complex (2) of 2,4-dinitroanisole was prepared by the addition of 12 mmoles of potassium methoxide in 2.4 ml of methanol to a solution of 12.5 mmoles of 2,4-dinitroanisole (5) in 3.0 ml of dioxane. A red solution formed immediately upon the addition of methoxide and a large quantity of red crystals was precipitated after approximately 1 min. The precipitate was filtered under nitrogen after 1 min, washed with benzene and anhydrous ether, and dried in a vacuum desiccator: yield 81%, 130-132° dec. *Anal.*<sup>11</sup> Calcd for C<sub>8</sub>H<sub>9</sub>N<sub>2</sub>O<sub>6</sub>K·0.5-C<sub>4</sub>H<sub>8</sub>O<sub>2</sub>: C, 38.5; H, 4.19; N, 8.97; K, 12.5. Found: C, 36.8; H, 4.25; N, 9.20; K, 12.7. Drying the complex at 80° at less than 1-mm pressure for 11 hr, followed by a further 35 hr drying at 50° at the same pressure, resulted in an 8.33% weight loss. No visible decomposition occurred. The weight loss can be reasonably attributed to the dioxane of crystallization.

The same method was used to prepare the methoxyl complex of 2,4-dinitrophenetole (3a) from a methanolic solution of potassium methoxide and 2,4-dinitrophenetole (6), the ethoxy complex of 2,4-dinitroanisole (3b) from an ethanolic solution of potassium

(1) Supported in part by the U. S. Atomic Energy Commission. Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstracts, p S163.

(2) NASA Postdoctoral Fellow, 1966-1967.

(3) P. Hepp, *Ann.*, **215**, 344 (1882); V. Meyer, *Ber.*, **27**, 3153 (1894); C. A. Lobry de Bruyn, *Rec. Trav. Chim.*, **14**, 39 (1885); A. Hantzsch and H. Kissel, *Ber.*, **32**, 3137 (1899).

(4) J. Meisenheimer, *Ann.*, **323**, 219 (1902).

(5) S. D. Ross, *Progr. Phys. Org. Chem.*, **1**, 31 (1963).

(6) For a recent review, see R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(7) K. L. Servis, *J. Am. Chem. Soc.*, **89**, 1508 (1967).

(8) M. R. Crampton and V. Gold, *J. Chem. Soc.*, 4293 (1964).

(9) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951); J. F. Bunnett, *Quart. Rev. (London)*, **12**, 1 (1958).

(10) J. H. Fendler, *J. Am. Chem. Soc.*, **88**, 1237 (1966).

(11) The analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

ethoxide and 2,4-dinitroanisole, and the ethoxyl complex of 2,4-dinitrophenetole (4) from an ethanolic solution of potassium ethoxide and 6. The yields and melting points (with decomposition) of **3a**, **3b**, and **4** are, respectively, 78, 77, 76%, and 134–135, 115–118, 95–98°. *Anal.* Calcd for  $C_9H_{11}N_2O_6K \cdot 0.5C_4H_8O_2$  (**3a**): C, 40.5; H, 4.63; N, 8.59; K, 12.0. Found: C, 39.4; H, 4.44; N, 9.00; K, 12.3. *Anal.* Calcd for  $C_9H_{11}N_2O_6K$  (**3b**): C, 38.3; H, 3.93; N, 9.93; K, 13.8. Found: C, 37.6; H, 4.30; N, 9.03; K, 13.1. *Anal.* Calcd for  $C_{10}H_{13}N_2O_6K$  (**4**): C, 40.7; H, 4.42; N, 9.45; K, 13.2. Found: C, 39.6; H, 4.35; N, 9.35; K, 13.1.

The visible and ultraviolet spectra of the complexes were obtained on a Beckman DU-2 spectrophotometer and the infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer (in Nujol mulls). The pmr spectra were obtained with a Varian Associates A-60 spectrometer at 37° (probe temperature). All spectra were determined on solutions in DMSO-*d*<sub>6</sub> using tetramethylsilane (TMS) as an internal standard; chemical shifts are given on the  $\tau$  scale in parts per million relative to TMS ( $\tau$  10.00) and are accurate to  $\pm 0.03$  ppm. Chemical-shift data were taken from spectra determined at a sweep width of 500 Hz; in some instances, internal methylene dichloride ( $\tau$  4.27 ppm) was used as an internal standard. Because of the instability of the complexes, particularly **2** and **3a**, in solution, spectrum determinations were begun immediately (*ca.* 25 sec) after solution preparation and freshly prepared solutions were employed for each determination (50- or 500-Hz sweep-width spectra or integrations). The reported coupling constants are the average of at least three determinations at 50-Hz sweep widths and are accurate to  $\pm 0.2$  Hz. It is probable that the accuracy of both  $\tau$  and  $J$  determinations are greater than those cited, but these limits are cited because of the instability of the complexes.

## Results

The brick-red crystalline Meisenheimer complexes of dinitro-substituted phenyl ethers are considerably more stable in the solid state than previous reports indicate.<sup>12</sup> These compounds showed no signs of decomposition after storage in a desiccator for over 6 months. They are soluble in water, methanol, ethanol, and alcoholic benzene mixtures, but they decompose instantaneously in these solvents to give yellow solutions of the parent ethers. The complexes are insoluble in benzene, dioxane, chloroform, methylene dichloride, and *t*-butyl alcohol. The red solution formed on dissolution in either acetonitrile or methanolic acetone turns blue on standing at room temperature, a color change probably resulting from the formation of the more stable Janovsky complexes.<sup>13</sup> In DMSO and *N,N*-dimethylformamide, the adducts dissolve to give red solutions which are stable for short periods and then slowly darken.<sup>14</sup>

The extinction coefficient of the adduct (**2**) of potassium methoxide and 2,4-dinitroanisole (**5**) at 495  $m\mu$  was found to be  $20,000 \pm 1500$  by dissolving a known amount of the complex in *N,N*-dimethylformamide at a known time. The decrease of optical density at 495  $m\mu$  was followed and extrapolated to zero time. This value is in reasonable agreement with that calculated by Rochester.<sup>15</sup> The optical densities of **5** at different

alkoxide concentrations in different solvents are summarized in Table I. The blank in each case contained the same concentration of alkoxide ion in the same solvent. The infrared absorption spectra of the complexes and the parent ethers are given in Table II; the pmr parameters for the same species are given in Table III.

TABLE I  
OPTICAL DENSITIES OF  $4.24 \times 10^{-5} M$  2,4-DINITROANISOLE  
IN METHANOLIC DIOXANE AT 25.0°<sup>a</sup>

[NaOCH <sub>3</sub> ], <i>M</i>	[KOCH <sub>3</sub> ], <i>M</i>	% dioxane in methanol, v/v	Optical density at 320 $m\mu$	Optical density at 495 $m\mu$
2.09 <sup>b</sup>		0		0.091
...	...	25	0.190	0.000
2.10		25	0.200	0.120
3.52		25	0.204	0.188
...	...	50	0.210	0.000
1.03		50	0.210	0.080
1.11		50	0.220	0.120
1.22		50	0.245	0.188
1.43		50	0.260	0.285
1.62		50	0.290	0.544
2.06		50	0.380	0.603
	1.26	50	0.325	0.278
	1.33	50	0.338	0.355
	1.42	50	0.350	0.530
	1.71	50	0.375	0.790
	2.63	50	0.435	0.821
...	...	75	0.215	0.000
	0.98	75	0.599	0.049
	1.32	75	0.710	0.168

<sup>a</sup> Using a 1.00-cm cell. <sup>b</sup> Determined by Rochester<sup>15</sup> in  $4.70 \times 10^{-5} M$  2,4-dinitroanisole.

## Discussion

The ease of complex formation with dinitro-substituted aromatic ethers depends on the polarity of the solvent and on the electropositivity of the metal in the methoxide used. Suhr<sup>16</sup> has found that the rate of reaction of piperidine with *p*-nitrofluorobenzene increases markedly with increases in the dielectric constant of the solvent. The optical densities of the band at 495  $m\mu$ , attributable to the complex **2**, for mixtures of methoxide ion and 2,4-dinitroanisole (**5**) in dioxane-methanol, increased with increasing dioxane concentration until the dioxane concentration reached 50%. Using 75% dioxane in methanol as solvent, the optical densities at 495  $m\mu$  were, however, lower than in the 50% solvent mixture at the corresponding methoxide ion concentration. At the same time, the optical densities at 320  $m\mu$  (attributable to **5** plus a second complex<sup>15</sup>) increased with increasing methoxide and dioxane concentration (Table I); the increase in optical density for the 320- $m\mu$  band is more highly favored by increases in dioxane concentration than is the increase in the 495- $m\mu$  band. These results indicate that the interaction between methoxide ion and **5** results in two equilibria and that increasing dioxane concentration in methanol favors the second equilibrium. An attempt has been made to calculate the extinction coefficient and the equilibrium constant for the complex formed between **6** and methoxide ion (KOCH<sub>3</sub> and NaOCH<sub>3</sub>) by the Benesi-Hildebrand

(12) (a) G. S. Gitis, A. I. Glaz, and A. Ya. Kaminskii, *J. Gen. Chem. USSR*, **33**, 3229 (1963); (b) S. Nagakura, *Tetrahedron Suppl.*, **19**, No. 2, 361 (1963).

(13) R. J. Pollitt and B. C. Saunders, *J. Chem. Soc.*, 4615 (1965), and references cited therein.

(14) This color change is followed by the development of the spectrum of a second Meisenheimer complex, presumably formed by migration of alkoxyl from C-1 to C-2. Comparable spectral changes are observed for all four complexes (**2-4**). Related reactions of Meisenheimer complexes derived from trinitroaromatics have been reported recently by Servis.<sup>7</sup> A full study of the transformations of complexes **2-4** in DMSO is in progress and will be reported in a forthcoming publication.

(15) C. H. Rochester, *J. Chem. Soc.*, 2404 (1965).

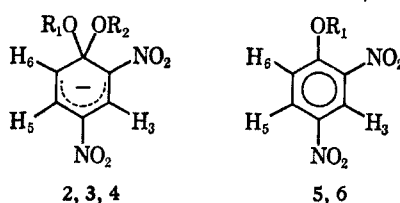
(16) H. Suhr, *Ber. Bunsenges. Physik. Chem.*, **67**, 893 (1963).

TABLE II  
INFRARED SPECTRA OF 2,4-DINITROANISOLE, 2,4-DINITROPHENETOLE, AND THEIR MEISENHEIMER COMPLEXES<sup>a,b</sup>

2,4-Dinitroanisole (5)	2,4-Dinitrophenetole (6)	Potassium methoxide complex of 2,4-dinitroanisole (2)	Potassium methoxide complex of 2,4-dinitrophenetole (3a)	Potassium ethoxide complex of 2,4-dinitroanisole (3b)	Potassium ethoxide complex of 2,4-dinitrophenetole (4)
1621 vs	1618 vs	1621 vs	1618 vs	1618 vs	1619 vs
1563 w	1562 w	1563 w	1562 w	1562 w	1550 w
1543 m, sh	1538 m, sh	1543 m, sh	1541 m	1541 m	1542 m
1499 vw	1504 vw	1499 vw	1504 vw	1504 vw	1498 vw
1486 vw	1487 vw	1486 vw	1487 vw	1487 vw	
1477 vw	1478 vw	1477 vw	1478 vw	1478 vw	
1471 w	1473 w	1471 w	1473 w	1473 w	1471 m, b
1460 w	1467 w, sh	1460 w	1467 vw, sh	1467 vw, sh	
1429 w	1425 w	1441 w	1442 w	1442 w	1429 w
1362 s	1360 s	1385 s, sh	1387 s, sh	1387 s, sh	1379 s, sh
1335 w	1323 w	1331 w	1308 w	1308 w	1297 m
1292 vs	1298 vs	1294 w	1295 w	1295 w	
		1230 m	1261 m	1261 m	1266 w
		1212 w, sh	1212 w, sh	1212 w, sh	1220 m
1195 s	1163 s	1178 vs, b	1178 vs, b	1178 vs, b	1176 vs, b
1143 vw	1117 m	1104 w, sh	1104 w, sh	1104 w, sh	1149 w, sh
		1098 m	1098 m	1098 m	1111 w
		1084 vw	1083 vw	1083 vw	1084 vw
1072 s	1072 s	1063 m	1064 m	1064 m	1064 w
1008 vs	1032 vs	1034 s, b	1036 s, b	1036 s, b	1032 s, b
		975 w	975 w	975 w	976 w
925.0 vs	935.0 s				
	918.0 s, b				
		875.7 s	875.2 s	875.2 s	869.0 m
838.0 vs, b	841.0 s	840.3 w	840.2 w	840.2 w	847.0 w
803.0 w	804 w	814.6 s	814.6 s	814.6 s	843.0 w
		773.9 m	774.0 m	774.0 m	806.0 w
766.5 w	765.0 w	766.0 w	765.0 w	765.0 w	775.0 m
		754.9 m	755.0 m	755.0 m	763.0 w
747.0 vs	745.0 s	746.0 s	746.0 s	746.0 s	746.0 s

<sup>a</sup> Copies of the original spectra may be obtained from the authors upon request. <sup>b</sup> Frequencies (cm<sup>-1</sup>) and intensities of the observed bands are designated by vs very strong, s strong, m medium, w weak, vw very weak, sh shoulder on neighboring band, b broad.

TABLE III  
PMR SPECTRA OF MEISENHEIMER COMPLEXES AND PARENT 2,4-DINITROPHENYL ETHERS<sup>a</sup>



	Compound						Peak multiplicity
	2	3a	3b	4	5	6	
R <sub>1</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub>	
R <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub>	CH <sub>3</sub> CH <sub>2</sub>	CH <sub>3</sub> CH <sub>2</sub>	...	...	
τOCH <sub>3</sub>	7.07	7.07	7.07	...	5.87	...	1
τCCH <sub>3</sub>	...	8.94	8.94	8.90	...	8.57	3
τOCH <sub>2</sub>	...	6.80	6.80	6.92	...	5.59 <sup>c</sup>	C
τC <sub>4</sub> H <sub>5</sub> O <sub>2</sub>	6.42	6.42	...	...	...	...	1
τH <sub>3</sub>	1.29	1.29	1.32	1.32	1.25 <sup>d</sup>	1.25	2
τH <sub>5</sub>	2.75	2.75	2.84	2.79	1.44	1.49	2 × 2
τH <sub>6</sub>	4.94	4.90	4.90	4.90	2.37 <sup>d</sup>	2.40	2
J <sub>35</sub>	2.7	2.8	2.6	2.7	3.1	3.0	
J <sub>56</sub>	10.8	10.8	10.8	10.9	9.8	9.8	

<sup>a</sup> Spectra determined in DMSO-d<sub>6</sub>. Details of method are given in Experimental Section. <sup>b</sup> Peak multiplicities except where noted: 1 = singlet, 2 = doublet, 3 = triplet, 2 × 2 = doublet of doublets, C = unresolved complex. <sup>c</sup> Quartet. <sup>d</sup> Doublet of doublets, J<sub>35</sub> = 0.4 cps.

method.<sup>17</sup> Plots of [5]/optical density at 495 mμ vs. 1/alkoxide ion concentration gave curves, which is not surprising since this method is only satisfactory for the 1:1 complexes which are not complicated by

consecutive or concurrent equilibria.<sup>18</sup> Using an extinction coefficient of 20,000 for adduct 2 at 495 mμ (see Results), one can, however, calculate the concentration of the complex. To obtain an equilibrium

(17) H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949).

(18) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

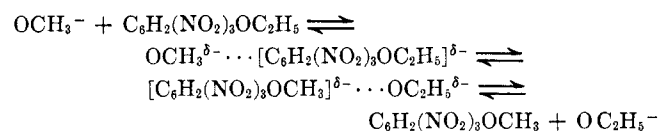
constant, it is desirable to choose an alkoxide ion concentration at which both the complex formation at 495  $m\mu$  is reasonably complete and the interference from the second complex is negligible. Optical densities obtained at 1.62 and 2.06  $M$   $\text{NaOCH}_3$  in 50% methanolic dioxane approximate best these conditions. The calculated equilibrium constant is 1.1 l. mole<sup>-1</sup>, but much significance cannot be attributed to this value because of the uncertainties involved in its calculation. The corresponding equilibrium constants for the formation of the ethoxyl complex of 2,4,6-trinitroanisole in ethanol<sup>19</sup> and the methoxyl complex of the same ether in methanol<sup>20</sup> are several thousandfold greater, indicating the greatly enhanced stability of the trinitro-substituted alkoxyl Meisenheimer complexes. Quantum mechanical calculations also confirm that a reduction in the number of nitro groups in the aromatic substrate should greatly reduce the stability of the addition complex formed by attack of strong nucleophiles.<sup>21</sup>

Potassium methoxide is more effective in converting 2,4-dinitroanisole to the complex (2) than is sodium methoxide (*cf.* Table I). This difference in reactivity is reflected by the fact that all of the dinitro-substituted alkoxyl Meisenheimer complexes isolated by us and by others<sup>12</sup> have been in the form of their potassium salts. The qualitative solubility measurements show that these complexes are more stable in dipolar aprotic solvents (DMSO and *N,N*-dimethylformamide) than in protic solvents (water, methanol, and ethanol). This behavior and the greater stability of the potassium salts are to be expected if the adducts are ionic.<sup>22</sup>

Infrared absorption measurements have contributed significantly to the understanding of the structures of Meisenheimer-type complexes.<sup>6</sup> If the adducts were charge-transfer complexes, one would expect their spectra to resemble closely those of the parent ethers, with the addition of the internal vibrational frequencies of the added alkoxyl group.<sup>23</sup> The infrared spectra of charge-transfer complexes are generally characterized by frequency shifts rather than by the appearance of new absorption bands.<sup>18</sup> As can be seen from Table II, the infrared spectra of the complexes (2–4) are quite different from those of their parent ethers (5, 6). The covalent structure of the alkoxyl adducts would be expected to result in the observation of characteristic ketal bands at 1190–1010  $\text{cm}^{-1}$ .<sup>24</sup> In a previous study,<sup>12b</sup> a strong band was observed at 1250–1075  $\text{cm}^{-1}$  in the spectrum of the methoxyl 2,4-dinitroanisole complex (2) and was assigned to the ketal structure; however, the spectrum was masked by that of the decomposition product, 2,4-dinitroanisole.<sup>12b</sup> We have observed a very strong and broad ketal band at 1178  $\text{cm}^{-1}$  in the spectrum of the same complex. In general, the complexes show absorptions at 1264–1255 (s), 1232–1231 (m-s), 1174–1161 (m), 1103 (m), and 1067–1065 (s)  $\text{cm}^{-1}$ ; two of these bands do not appear in the spectra of the parent 2,4-dinitrophenyl ethers (5, 6). The bands at 1546–1543 and 1364–1362  $\text{cm}^{-1}$  may be assigned to asymmetric and sym-

metric nitro group stretching frequencies<sup>25</sup> and the bands at 1232–1195 and 1062–1010  $\text{cm}^{-1}$  may be assigned to asymmetric and symmetric C–O–C stretching frequencies.<sup>26</sup>

One of the early arguments in favor of the covalent structure for the adduct of alkoxide ion and picryl ethers was that the infrared spectra of the complexes prepared from both 2,4,6-trinitroanisole and sodium ethoxide and 2,4,6-trinitrophenetole and sodium methoxide were identical.<sup>27</sup> This evidence was not intended<sup>28</sup> to constitute an unequivocal proof of the covalency of these adducts since it is equally possible to represent the reaction in charge-transfer equilibria terms.



Assuming that one of these charge-transfer complexes has a greater stability than the other, then only the more stable complex will be isolated.<sup>29</sup> Indeed, Nagakura<sup>12b</sup> does not distinguish between Meisenheimer and charge-transfer complexes but regards the former as a special case of the latter in which the charge-transfer structure predominates over the no-bond structure. We feel, however, that these arguments are quantum mechanical subtleties and have isolated the adduct (3a) formed from 2,4-dinitroanisole and potassium ethoxide and that (3b) from 2,4-dinitrophenetole and potassium methoxide and found them to be identical by a variety of criteria (elemental analyses, infrared and proton magnetic resonance spectra). Evidence derived from pmr spectra demonstrates that the isolated products (3a and 3b) are not equimolar mixtures of the two symmetrical complexes (dimethoxy 2 and diethoxy 4).

In order to substantiate our evidence for the covalency of the Meisenheimer complexes of dinitro-substituted aromatic ethers, we obtained the pmr spectra of the isolated complexes (2–4) in DMSO-*d*<sub>6</sub> solution (Table III). The spectrum was completely consistent with the postulated structure in each case and the observed parameters (coupling constants and chemical shifts) were in excellent agreement with values reported by other workers for similar complexes prepared by the *in situ* reaction of the alkoxide and the aromatic.<sup>7,30–32</sup> For example, the adduct (2) of 2,4-dinitroanisole (5) and potassium methoxide showed a methoxyl singlet at  $\tau$  7.07 ppm and an aromatic AMX pattern (see Table III) with the appropriate integrated intensities for structure 2. The upfield shift (1.20 ppm) observed for the methoxyl protons relative to the methoxyl protons of 5 ( $\tau$  5.87 ppm) is the expected result of the  $\text{sp}^2$  to  $\text{sp}^3$  rehybridization at C-1. With the exception of some minor chemical-shift differences (<0.12 ppm) for H-3 and H-6, the parameters observed for 2 in this study are identical with those reported by Crampton and Gold<sup>30</sup> for the *in situ* reaction product

(25) R. D. Kross and V. A. Fassel, *J. Am. Chem. Soc.*, **78**, 4225 (1956).

(26) A. Katritzky and H. A. Coats, *J. Chem. Soc.*, 2062 (1959).

(27) R. Foster and D. L. Hammick, *ibid.*, 2153 (1954).

(28) L. K. Dyal, *ibid.*, 5160 (1960).

(29) J. N. Murell, *Quart. Rev. (London)*, **15**, 191 (1961).

(30) M. R. Crampton and V. Gold, *J. Chem. Soc., Sect. B*, 893 (1966).

(31) R. Foster and C. A. Fyfe, *Tetrahedron*, **21**, 3363 (1965).

(32) R. Foster, C. A. Fyfe, P. H. Emslie, and M. I. Foreman, *ibid.*, **23**, 227 (1967).

(19) J. B. Ainscough and E. F. Caldin, *J. Chem. Soc.*, 2528 (1956).

(20) V. Gold and C. H. Rochester, *ibid.*, 1687 (1964).

(21) T. Abe, *Bull. Chem. Soc. Japan*, **37**, 508 (1964).

(22) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962).

(23) R. A. Friedel, *J. Phys. Chem.*, **62**, 1341 (1958).

(24) E. D. Bergman and S. Pinchas, *Rec. Trav. Chim.*, **71**, 161 (1952).

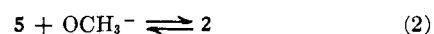
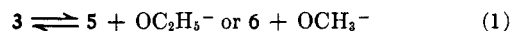
of potassium methoxide and **5**.<sup>33</sup> The observation of the three aromatic protons and the methoxyl singlet confirm C-1 as the point of attack of methoxide on **5**; other possible isomeric complexes would be expected to yield spectra of markedly different types.<sup>7,14</sup> Similar conclusions may be drawn from the spectrum of **4**, the symmetrical adduct formed by the attack of potassium ethoxide on 2,4-dinitrophenetole (**6**). Comparable upfield shifts are observed for the ethyl protons of **4** relative to those of **6** and nonequivalence of the two ethoxyls is not observable; the aromatic resonances of **4** are almost identical with those of **2**.

The spectra of the two samples of the unsymmetrical Meisenheimer complex **3** prepared by the reaction of ethoxide ion with **5** and methoxide ion with **6** are, within the limits of experimental error, identical. The chemical shifts observed for the methoxyl protons of **3a** and **3b** are identical with that observed for the methoxyl protons of complex **2** and the chemical shifts observed for the C-methyl groups are essentially identical with that observed for the comparable protons of the symmetrical diethyl complex **4**. The methylene protons of **3a** and **3b** are shifted slightly downfield (0.12 ppm) from the position of the corresponding resonance in **4**. Only minor differences are observed for the aromatic proton resonances of **3a** and **3b** relative to those of **2** and **4**. All of these data support the identity of **3a** and **3b** and their postulated structures.

A consideration of the pmr data for these complexes provides strong evidence against the possibility of a charge-transfer structure (*vide supra*).<sup>12b</sup> The equivalence of the alkoxy groups in **2** and **4** and the identity of **3a** and **3b** would require a number of accidental equivalencies of chemical shifts for alkoxy groups bonded to C-1 and present as the ion if charge-transfer complexes were involved. The data would not eliminate a charge-transfer complex in which only a negligible separation of the ion from C-1 was involved, but this distinction is subtle and essentially negligible (above). A second observation also tends to rule against a charge-transfer structure for these complexes. The chemical shifts for the methoxyl protons of **2**, **3a**, and **3b** are identical, as are the shifts for the ethoxyl protons of **3a** and **3b**. However, both **2** and **3a** form crystals with tightly associated dioxane and, consequently, the media in which the spectra of **2** and **3a** are determined are different from that for **3b**. Since charge-transfer complexation is sensitive to the dielectric constant of the medium,<sup>18</sup> the observed chemical-shift identities would not be expected if charge-transfer complexes were involved. The observation by Crampton and Gold<sup>30</sup> of essentially identical chemical shifts for **2** in 50:50 methanol-DMSO as we have observed for solution in DMSO-*d*<sub>6</sub> provides further support for this interpretation. These observations are, however, completely consistent with the postulated covalent structures for the complexes.

The observed spectra for the asymmetric complexes (**3a** and **3b**) could also be explained by the postulation of an equilibration process involving dissociation of **3**

to the constituent alkoxides and ethers followed by recombinations to yield the symmetrical complexes **2** and **4** (eq 1-3). A spectrum comparable to that of **3**



would result from a mixture of equivalent quantities of **2** and **4**. However, for this situation to prevail, it would be required that the thermodynamic stabilities of **2** and **4** be sufficiently greater than that of **3** so that the equilibrium concentration of **3** is negligible. The equilibria of eq 1-3 would have to lie completely to the right, since no signals ascribable to **5** or **6** are observable. These conditions seem to be inherently unlikely. The observed spectrum of **3** is not completely compatible with the postulation of an equimolar mixture of **2** and **4**. It can be seen from Table III that, although the chemical shifts for the methoxyl protons of **2** and **3** are identical, the O-methylene shifts for **3** and **4** are not identical. Also, finite and reproducible differences in the chemical shifts of the aromatic protons of **2** and **4** exist, but only a single AMX spectrum is observable for these protons in **3a** and **3b**. Finally, the spectrum of an equimolar mixture of **2** and **4** was examined and was found to be different from that of **3**. The alkoxy proton absorptions of the mixture consisted of a superposition of the component spectra, while the aromatic resonances were broadened appreciably in comparison with the single complexes. Such broadening would be expected since the chemical shifts of the aromatic protons of **2** and **4** differ slightly.

The dioxane of crystallization is clearly discernible in the pmr spectra of **2** and **3a** as a singlet at  $\tau$  6.42 ppm. Integrated intensities indicate the presence of 0.52 mole of dioxane in **2** and 0.57 mole of dioxane in **3a**, findings consistent with the results of elemental analyses of these complexes (see Experimental Section). Complex **4** contained a minor amount (0.078 mole) of dioxane of crystallization; only a trace amount of solvent was observed in complex **3b**. The identity of the solvent of crystallization was established by addition of dioxane to solutions of the complexes in DMSO-*d*<sub>6</sub> (only an increase in the intensity of the  $\tau$  6.42 ppm signal resulted) and by the mass spectra and pyrolytic glpc behavior of the complexes.<sup>34</sup>

The aromatic protons of complexes **2-4** are relatively strongly shielded compared with the corresponding protons of the parent ethers **5** and **6**, an effect previously observed in other Meisenheimer and  $\sigma$  complexes.<sup>7,30-32</sup> These upfield shifts would be expected on the basis of the increased charge density at C-2-6 of the complexes. Similar effects have been observed in the spectra of other aromatic anions, *e.g.*, the vinylic proton absorptions of cyclopentadiene undergo an upfield shift of 1.01 ppm on conversion to cyclopentadienyl anion.<sup>35</sup> The magnitude of this upfield shift ( $\Delta\delta$ ) for the complexes **2-4** varies with position: H-3, 0.04-0.07; H-5, 1.26-1.40; H-6, 2.50-2.57 ppm. The data obtained for **2** by Crampton and Gold<sup>30</sup> are in agreement with these values. The data ob-

(33) These chemical-shift differences are probably the result of solvent effects. The studies reported by Crampton and Gold utilized a 50:50 methanol-DMSO system,<sup>30</sup> while we have employed anhydrous DMSO-*d*<sub>6</sub> without cosolvent. We have observed minor chemical-shift differences (0.04-0.07 ppm) for the aromatic protons of **5** in 50:50 methanol-DMSO compared with pure DMSO.

(34) We are indebted to B. L. Mason and J. J. Shick for the determination of mass spectra and glpc studies.

(35) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Inc. New York, N. Y., 1966, pp 779-782.

tained by Servis<sup>7</sup> for the trinitro complex 1 (R = OCH<sub>3</sub>) give  $\Delta\delta$  0.25 ppm for H-3,5; a quantitative comparison of the magnitude of this value with that obtained for H-3 in this study is not meaningful because of the difference in solvent employed. The large  $\Delta\delta$  observed for H-6 is consistent with expectation; conventional canonical structures for the ions would localize charge at H-2,4,6 at the expense of H-3,5. The difference in  $\Delta\delta$  values for H-3 and H-5 may reflect a difference in charge density at the two positions resulting from the presence of the nitro substituents. However, it is unlikely that these  $\Delta\delta$  values are representative solely of charge density differences. The anisotropy of the substituent groups may well change on the transition from aromatic substrate to complex<sup>35</sup> and any nonqualitative charge density determinations

based on  $\Delta\delta$  values would have to provide an anisotropy correction term.

The results of this study demonstrate that the alkoxy complexes of dinitro-substituted aromatic ethers are structurally similar to those of the more stable trinitro-substituted Meisenheimer complexes<sup>5</sup> and are best represented by the covalent, rather than the charge-transfer complex, structures. The isolation of the methoxy complex of 2,4-dinitroanisole provides further evidence for the previously suggested mechanism of symmetrical methoxy exchange reactions in methanol in which the formation of an intermediate between methoxide ion and 2,4-dinitroanisole was proposed to be rate determining.<sup>10</sup>

Registry No.—5, 119-27-7; 6, 610-54-8.

## A Novel Synthesis of N,N',N''-Trisubstituted Guanidines

DAVID F. GAVIN, WILHELM J. SCHNABEL, EHRENFRIED KOBER, AND MARTIN A. ROBINSON

*Olin Mathieson Research Center and Southern Connecticut State College, New Haven, Connecticut*

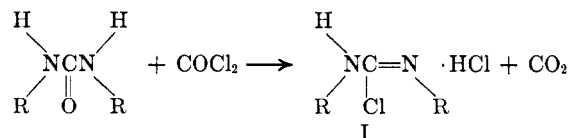
Received January 12, 1967

The action of phosgene on N,N'-disubstituted ureas is described in literature as giving a variety of products depending upon the reaction conditions. However, in no instance has the formation of N,N',N''-trisubstituted guanidines been reported from the above reaction. A novel synthesis is now presented in which these aforementioned guanidines are obtained. This reaction involves the phosgenation of N,N'-dialkyl- or N-alkyl-N'-arylureas at temperatures between 110 and 120° in an inert solvent such as monochlorobenzene. In the case of symmetrically disubstituted alkylureas, the N,N',N''-trialkylguanidines in the form of their hydrochloride salts are obtained. Unsymmetrically substituted ureas upon phosgenation also give guanidines, the type of which, in terms of their substituents, is dependent upon the ability of the urea nitrogen to act as a nucleophile as well as the steric nature of the substituent itself. Thus, phosgenation of N-cyclohexyl-N'-phenylurea gives N,N'-dicyclohexyl-N''-phenylguanidine exclusively. In cases where the substituents on nitrogen atoms of the urea molecule are alike in electron-donating abilities, product distributions are obtained, as with N-cyclohexyl-N'-isopropylurea. Where one urea nitrogen is strongly deactivated, as with N-cyclohexyl-N'-trifluoroethylurea, there is no indication of guanidine formation. Different types of compounds are isolated from these reactions. A mechanism is proposed to account for these observed patterns.

The preparation of symmetrically trisubstituted guanidines was described in 1869 by Hofmann,<sup>1</sup> who prepared the triphenyl derivative from the reaction of diphenylthiourea with iodine in the presence of excess aniline. Twenty-five years later, Nef<sup>2</sup> uncovered a new method which encompassed the reactions of isocyanide dichlorides with substituted primary amines. This valuable reaction can also be adapted to the synthesis of pentasubstituted guanidines by reaction with secondary amines. Preparation of guanidines in which the substituents are not identical was reported by Schenck and Kirchoff,<sup>3</sup> who accomplished the synthesis of N,N'-dimethyl-N''-ethylguanidine through the reaction of trimethylpseudothiourea with ethylamine. Other experimenters devised methods of synthesizing trisubstituted guanidines which involve alkylation of thioureas. Cronshaw and Naughton<sup>4</sup> employed diphenylthiourea and aniline hydrochloride in the presence of lead carbonate while Heuser<sup>5</sup> obtained tritolylguanidine from ditolythiourea and *o*-toluidine in the presence of lead oxide. The formation of trimethylguanidine by the successive methylation of iodocyanogen was described by Schenck.<sup>6</sup>

Snedker<sup>7</sup> reported that the reaction of aniline hydrochloride with diphenylcarbodiimide formed the hydrochloride salt of symmetrical triphenylguanidine.

Reactions of phosgene with ureas have been extensively investigated only in the last 10 years. Reaction conditions such as temperature, steric effects, and solvent play an important part in determining the final products. As late as 1957, Shingu<sup>8</sup> reported that phosgene does not react with symmetrical diphenylurea below 110° but readily forms phenylisocyanate and hydrogen chloride above 120°. In 1960, a review was published by Eilingsfeld<sup>9</sup> which related to various types of imido chlorides. It was stated that disubstituted ureas react with phosgene to form chloroformamide hydrochlorides (I). The reactions



are run at 0–60°, thus negating, in part, the conclusion of Shingu. Upon heating, the chloroformamide hydrochloride is transformed into a disubstituted

(1) A. W. Hofmann, *Ber.*, **2**, 453 (1869).

(2) J. U. Nef, *Ann.*, **270**, 282 (1892).

(3) M. Schenck and H. Kirchoff, *Z. Physiol. Chem.*, **154**, 292 (1926).

(4) J. Cronshaw and W. Naughton, British Patent 224,376 (1923).

(5) R. Heuser, U. S. Patent 1,437,419 (1923).

(6) M. Schenck, *Z. Physiol. Chem.*, **150**, 121 (1925).

(7) S. J. C. Snedker, *J. Soc. Chem. Ind.*, (London), **45**, 353T (1927).

(8) H. Shingu, T. Nishimura, and T. Takeqomi, *Yuki Gosei Kagaku Kyokai Shi*, **15**, 140 (1957).

(9) H. Eilingsfeld, H. Seefelder, and H. Weidinger, *Angew. Chem.*, **73**, 836 (1960).