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Role of the Furan Ring in the Formation of Meisenheimer-Type Adducts

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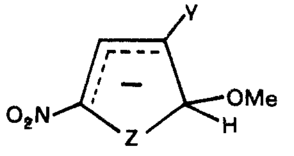
The rate and equilibrium constants for the formation of Meisenheimer adducts from 2-nitrofuran and 4-cyano-2-nitrofuran have been measured in methanol at 25 °C. Kinetic measurements have also been made for the formation of a related adduct from 2,4-dinitrofuran. The comparison of these data with those previously observed for the formation of adducts from the corresponding thiophene derivatives shows an accelerating and stabilizing effect of the furan ring in the formation of adducts. On the other hand, an increased lability of the adducts is also observed in the furan series.

The quantitative aspects of the reactivity of the furan ring in nucleophilic aromatic substitution have been recently compared with those of the thiophene ring.[1–3] The activating effect of the former is stronger than that of the thiophene ring. As to the reaction mechanism, an addition–elimination mechanism via the formation of an anionic intermediate σ complex is well established in the case of thiophene derivatives.[4]

A main piece of evidence in favor of the addition–elimination mechanism is the actual detection or isolation of Meisenheimer-type adducts from several electron-deficient thiophene compounds and nucleophilic reagents.[5–9] Rate and equilibrium constants for the formation of some of these adducts have also been reported, particularly in view of a comparison between adducts formed from benzene and thiophene derivatives.[6,7]

Similar information was lacking as to the formation of Meisenheimer adducts from furan derivatives. Therefore, we have become interested in investigating the following points: (i) whether adducts could be detected or isolated in the interaction between electron-deficient furans and methoxide ion or other nucleophiles; and (ii) to what extent the furan ring, in comparison with the thiophene ring, would affect the equilibrium and rate constants in the formation of adducts.

Following a preliminary communication,[10] where we showed that 2-nitrofuran (1) and 2-nitrothiophene (2) undergo addition of methoxide ion at the hydrogen-bearing α positions, yielding Meisenheimer adducts **5** and **6**, respectively, we report here kinetic and equilibrium data for these reactions in methanol. Moreover, we describe the formation of adducts upon interaction of methoxide ion with 4-cyano-2-nitrofuran (**3**) and 2,4-dinitrofuran (**4**). It was expected that the presence of two electron-withdrawing groups should provide a greater stabilization of the resulting adducts and give more general information on the role of the furan ring.



Y =	H	CN	NO$_2$
Z = O	**5**	**7**	**8**
Z = S	**6**	**11**	**12**

Experimental Section

Melting points are uncorrected. UV–vis, NMR, and mass spectral characterizations of the products were made as described in ref 5b.

Materials. 2-Nitrofuran was obtained according to an optimized procedure.[11] **2-Nitrothiophene,** free from 3-nitrothiophene, was obtained by decarboxylation of 5-nitrothienoic acid.[12]

3-Cyanofuran. The amide of 3-furoic acid was converted to the title compound by a standard procedure. After the usual workup, a solid (mp 24–26 °C) was obtained upon reduced pressure distillation (3-cyanofuran had been previously reported[13] as a liquid); IR (ν_{CN} 2250 cm^{-1}) and NMR data [(in CDCl$_3$) δ 6.60 (m, 1 H), 7.46 (m, 1 H), 7.91 (m, 1 H)] were in accordance with the structure of the compound (yield 73%).

4-Cyano-2-nitrofuran (3). A solution of 3.0 g of 3-cyanofuran in 7 g of acetic anhydride was slowly added to a well-stirred nitrating mixture made up from 20.1 g of 99% HNO$_3$ and 32 g of acetic anhydride at a temperature lower than 10 °C. At the end of the addition, the reaction mixture was poured onto ice and extracted repeatedly with ethyl ether. The residue on evaporation of ether was an oil containing **3** and at least another product. Upon chromatography on silica

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Table I. NMR and UV–vis Data for Substrates 3 and 4 and the Corresponding Adducts 7 and 8 in CH_3OH (CH_3OD)

compd	δ (H_α, H_β)	J, Hz	λ_{max_1}, nm	ϵ, L mol^{-1} cm^{-1}	λ_{max_2}, nm	ϵ, L mol^{-1} cm^{-1}
3	8.45, 7.72	1			286	8.7×10^3
7 (3 + CH_3O^-)	6.13, 7.35	0	242	7.7×10^3	388	1.9×10^4
4	8.84, 7.98	1.5	218	1.06×10^4	286	7.4×10^3
8 (4 + CH_3O^-)[a]	6.35, 7.32	<0.5	270	4.4×10^3	500	1.37×10^4

[a] NMR data observed at −50 °C; UV–vis data obtained from single wavelength measurements (see text).

gel, only 3 was recovered: yield 5%; mp (pentane) 55–55.5 °C; MS *m/e* 138 (M^+); NMR ($CDCl_3$) δ 7.40 (d, 1 H), 7.93 (d, 1 H, J = 1 Hz). It is likely that the side products of this nitration are derived from an addition of nitronium acetate to the substrate. In accordance with this hypothesis, the NMR spectrum of the crude reaction mixture showed, besides the signals of 3, intense signals at δ 2.1, 6.5, and 7.1.

Nitration of 2-Nitrofuran. 2-Nitrofuran (1.0 g, 8 mmol) was heated on a water bath with 10 g of 70% HNO_3 until complete solution, as described for the synthesis of 2,5-dinitrofuran.[14] The reaction mixture was kept another 12 h at 0 °C, neutralized with sodium bicarbonate, and extracted with ethyl ether. The residue, after evaporation of the solvent, was a yellow solid containing (TLC analysis) two compounds, which were separated by chromatography on a Lobar silica gel 60 column (Merck) with a mixture of toluene and ethyl acetate, 7:1. The first fractions yielded a small amount of 2,4-dinitrofuran (4): yield 5%; mp 87–89 °C; MS *m/e* 158 (M^+); NMR (CD_3OD) δ 7.98 (d, 1 H), 8.84 (d, 1 H, J = 1.5 Hz). The subsequent fractions yielded a much larger amount of 2,5-dinitrofuran (yield 67%).

Characterization of the Adducts. NMR spectra for adducts 5 and 6 were previously reported.[10] In methanol, the addition of sodium methoxide to methanolic solutions of 1 and 2, respectively, lead to a decrease of the maximum at 304 nm of 1 and at 312 nm of 2 and to the development of a new absorption band at 318 nm [adduct 5 from 2-nitrofuran (ϵ 1.24×10^4 L mol^{-1} cm^{-1})] and at 330 nm [adduct 6 from 2-nitrothiophene (ϵ 1.23×10^4 L mol^{-1} cm^{-1})].

NMR data for adducts 7 and 8 were recorded upon the addition of an equivalent amount of sodium methoxide in methanol (4 M) to a CH_3OD solution of 3 and 4. With the latter reaction, characterization of the adduct was possible only at low temperature (−50 °C). The UV–vis spectrum of adduct 7 was determined by standard procedures. The UV–vis spectrum of adduct 8 was obtained from single wavelength measurements. A 3.68×10^{-5} M solution of substrate 4 was mixed with a 1.93×10^{-2} M solution of sodium methoxide. The reaction was followed by the stopped-flow technique in the range 240–530 nm at 5-nm intervals. Complete spectra of the reaction mixture at different times were subsequently drawn up by plotting the absorbance at a definite time vs. wavelength. Since the formation rate of the adduct is first order in methoxide ion, whereas its decomposition is independent of methoxide ion concentration, the time required to obtain the absorbance maximum is methoxide concentration dependent

Kinetic determinations for the slow reactions of 1–3 were obtained according to the usual spectrophotometric procedure, by following the absorbance increase at a wavelength corresponding to an absorbance maximum of the adduct, as described in ref 5b, in the presence of an excess of the nucleophile. A thermostatted stopped-flow Durrum 110 apparatus was used for the kinetic measurements with the very reactive dinitro derivative 4. The lability of the adduct formed from 2,4-dinitrofuran precludes any determination of the equilibrium constant for the formation of the adduct (K_f). However, extrapolation to time 0 of the absorbance values corresponding to the decomposition of adduct 8, as obtained by stopped-flow measurements, shows that the addition of a 10^{-4} M methoxide solution to a 5×10^{-5} M solution of 4 causes the practically quantitative conversion of the substrate to the adduct, in accordance with an equilibrium constant larger than 5×10^5 M^{-1}.

In the case of cyanonitrofuran 3, the equilibrium is largely shifted toward the adduct even at a methoxide ion concentration as low as 10^{-4} M. Therefore, we allowed comparable and known amounts of 3 and 2,4,6-trinitroanisole (9), which yields a Meisenheimer adduct (10) whose K_f is known ($K_{f,10}$ = 1.7×10^4 M^{-1} at 25 °C),[5b] to compete for a deficiency in methoxide ion. We measured the absorbance of this mixture in the range 370–500 nm, where only the two adducts show appreciable absorption. From the molar absorption coefficients of the adducts, determined separately, we were thus able to evaluate the concentrations of adducts 7 and 10. The concentrations of 3 and 9 at equilibrium were given by the difference between the initial concentrations of the substrates and those of the corresponding adducts. The ratio between the equilibrium constants was finally given by

$$K_{f,7}/K_{f,10} = \frac{[7][9]}{[3][10]} \tag{1}$$

From several determinations, we obtained 10.5 ± 1.5 as a mean value for this ratio, corresponding to the equilibrium constant reported in Table II.

Equilibrium constants ($K_f = k_1/k_{-1}$) for the reactions of 1 and 2 were obtained from $k_{obsd} = k_1[MeO^-] + k_{-1}$ by plotting the observed rate constants vs. the methoxide ion concentration.

Results and Discussion

Synthesis of 2,4-Dinitrofuran. Owing to the tedious procedures involved in the synthesis of 3-nitrofuran,[15,16] the possibility of obtaining the title compound upon nitration of 3-nitrofuran was discarded. 2,4-Dinitrofuran was in fact obtained upon nitration of 2-nitrofuran, together with a massive amount of 2,5-dinitrofuran. The isomers were separated by chromatography. This synthesis provides a rare example of the formation of a 2,4-disubstituted furan upon electrophilic substitution of a 2-substituted furan. In this ring, the α-directing power of the heteroatom is indeed so strong as to usually overwhelm the directing power of any α substituent.[17]

Formation of Meisenheimer Adducts. The NMR and UV–vis spectrophotometric study of the reactions of 3 and 4 in methanol shows that in both cases the substrate disappears rapidly upon addition of methoxide ion, even at a low concentration of the nucleophile. In the reaction of the cyanonitrofuran, a new species, displaying new UV absorption maxima and a new NMR spectrum, is easily detected (see Table I). The spectrum changes are in accordance with the formation of an anionic adduct; the strong bathochromic shift in the UV region observed in going from 3 to the new species is comparable to that observed in the formation of a Meisenheimer adduct from 4-cyano-2-nitrothiophene.[5b] The upfield shift of the NMR spectrum and the decrease in the coupling constant again follow the same pattern as observed in the formation of an adduct from the corresponding thiophene substrate. A correlation between the NMR data for the product of this reaction and those of the adduct formed from 4-cyano-2-nitrothiophene (δ 6.20 and 7.46) suggests that also in this case methoxide ion attacks at the α position, thus yielding adduct 7.

On the other hand, the pattern of the reaction of the dinitrofuran 4 cannot be deduced immediately from the experimental data. Thus, when the UV–vis spectrum is recorded after the addition of a slight excess of sodium methoxide to a 1.8×10^{-4} M solution of 4, only a strong decrease of absorbance in the UV region, and no trace of absorbance in the visible region is observed, even if the rapid and transient appearance of a red color is seen. Similarly, the addition of 1 equiv of sodium methoxide to a 2.5×10^{-1} M solution of 4 in methanol brings about the complete disappearance of the NMR signals of the substrate without the formation of any detectable signal downfield from δ 5. The spectral data corresponding to the formation of adduct 8, reported in Table I, have been obtained with techniques allowing the very fast recording of the features of the first reaction product before its rapid decomposition. Thus, the NMR spectrum of the adduct has been detected only at low temperature. Under

Table II. Rate and Equilibrium Constants for the Formation of Meisenheimer Adducts in Methanol at 25 °C

compd	Z	k, M^{-1} s^{-1}	K, M^{-1}	k_{-1}, s^{-1}
5	O[a]	1.37×10^{-2}	1.4×10^{2}	10^{-4}
6	S[a]	1.8×10^{-3}	5.6	3.2×10^{-4}
7	O	5.7×10	1.8×10^{5}	3.2×10^{-4}
11[b]	S	7.8×10^{-1}	1.5×10^{2} [a]	5.2×10^{-3}
8	O	4.5×10^{3}	$\geq 5 \times 10^{5}$ [c]	$\leq 9 \times 10^{-3}$ [c]
12[b]	S	1.5×10	8×10^{2}	1.9×10^{-2}

[a] Measurements made at total salt concentration = 0.2 M (balanced with $NaClO_4$). [b] Reference 5b. [c] Estimated.

these conditions, the addition of methoxide ion leads to the disappearance of the signals of the substrate and to the appearance of those reported in the Table I; at the same time, a very intense red color develops. The red color and the NMR spectrum of the adduct disappear upon an increase of temperature.

The UV-vis spectrophotometric course of the reaction has been followed by the stopped-flow technique (see Experimental Section).

Lability is not a peculiarity of the Meisenheimer adduct formed from 2,4-dinitrofuran; the adducts formed from 2-nitrofuran and 4-cyano-2-nitrofuran also undergo decomposition reactions, even if these reactions are much slower than that of the dinitro adduct. This fact explains why Meisenheimer adducts from furan substrates cannot be isolated, so that evidence for their formation has so far been obtained in solution only. It is likely that the decomposition reactions of the adducts formed from 3 and 4 are ring-opening reactions of the same kind observed in the reaction of 2-nitrofuran[18] and 2-nitrothiophene[19] with nucleophiles. However, a study of the decomposition reaction has not yet been carried out. In going from 2-nitrofuran to 3 and 4, rate and equilibrium constants increase markedly because of the presence of two electron-attracting groups. The rate increase is particularly evident in the formation of adduct 8 from dinitrofuran. Also, because of the exceptional lability of this adduct, which precludes the use of the competitive method or of buffer solutions, the equilibrium constant cannot be determined, and only a lower limit for it has been estimated. The data in Table II substantiate the previous qualitative indication that equilibria from furan derivatives are more shifted toward the adducts than those from the corresponding thiophene derivatives. The equilibrium constant increase is mainly to ascribe to the increase of reactivity of the furan substrates in the addition reaction (k_1). This increase corresponds to the finding that nucleophilic aromatic substitution of furan derivatives is generally faster than in similarly substituted thiophene derivatives.[1,3] However, an inspection of the k_{-1} values of Table II shows that also the decreased rate of return of the adducts to the reagents may affect the equilibrium constants in the same way.

Two main factors seem to be involved in determining the higher tendency of furan derivatives to yield adducts. One of them should be the higher electronegativity of the oxygen atom, which is expected to give a more effective contribution than the sulfur atom to the formation of an anionic adduct. Another major factor favoring the addition reaction is the low aromaticity of the furan ring. It is well known that the furan ring is indeed more apt than the thiophene ring to undergo addition reactions, both with polar reagents and in cycloaddition reactions.

A final remark can be made about the different responses of furan and thiophene rings to the nature of the substituent in 3. Our starting point has been the observation that linear free-energy ortho correlations are satisfactory in thiophene[20] and presumably other five-membered rings where steric interactions between vicinal substituents are lower than in the benzene ring. A plot (Figure 1) of log k of furan derivatives against log k of the corresponding thiophene derivatives is linear (slope = 1.4).

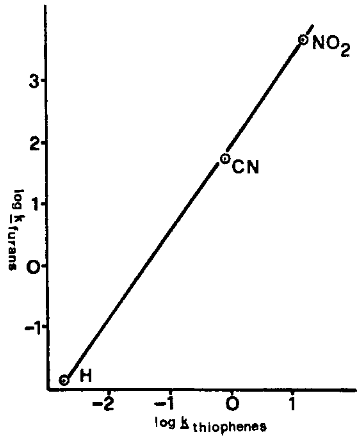

Figure 1. Free energy plot for rates of addition of methoxide ion to 2-nitro-4-X compounds in methanol at 25 °C.

In view of the higher reactivity of the furan ring, the higher selectivity of the same ring could seem surprising. However, a similar reactivity–selectivity pattern has been observed in electrophilic aromatic substitutions and other electronically related reactions. Thus, the selectivity ratio of furan and thiophene ring in the trifluoroacetylation reaction is nearly 1.3,[17] which is surprisingly similar to that observed in our nucleophilic addition. Even if the coincidence of the numerical value is probably fortuitous, it is likely that the same structural factor, low aromaticity of the furan ring, has a role in determining a similar situation in two reactions having different electronic requirements.

Registry No.—**1**, 609-39-2; **2**, 609-40-5; **3**, 67382-56-3; **4**, 67382-57-4; **5**, 67382-54-1; **6**, 67382-55-2; **7**, 67382-26-7; **8**, 67382-27-8; 3-furoic acid amide, 609-35-8; 3-cyanofuran, 30078-65-0.

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