

INVESTIGATION OF THE LABILITY OF FURAN AND ITS DERIVATIVES IN NUCLEOPHILIC
SUBSTITUTION REACTIONS BY THE MINDO/3 METHOD

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The σ complexes of furan, thiophene, pyrrole, pyridine, and benzene with the hydride ion were calculated by the MINDO/3 method. The affinities of the indicated aromatic rings and a number of substituted furans for the H^- ion were estimated. It is shown that the relative magnitude of the affinity correlates qualitatively with the experimental data on the relative rates of the reaction of the examined compounds with nucleophilic reagents. The following order of increasing reactivities of unsubstituted aromatic rings was obtained: pyrrole < furan < benzene < pyridine \leq thiophene. The effect of various types of substituents in various positions on the tendency of the five-membered ring to undergo nucleophilic substitution is discussed.

Among aromatic systems reactions with nucleophilic reagents are most characteristic for nitrobenzenes and pyridines [1, 2]. The possibility of realization of nucleophilic substitution reactions in five-membered aromatic rings (pyrrole, furan, and thiophene) has been investigated to a considerably lesser extent. It is assumed that replacement of the $-HC=CH-$ grouping in benzene by oxygen or sulfur atoms leads to an increase in the reactivity of the ring [3, 4]. Thus chlorine and bromine atoms in furan are replaced by piperidine more easily than in the case of benzene [5]. Halothiophenes that contain a nitro group react with nucleophilic reagents considerably more rapidly than the corresponding benzene derivatives [3, 6]. Bimolecular nucleophilic substitution reactions are as yet unknown for pyrroles [2].

An increase in the susceptibility to nucleophilic attack in the order pyrrole < furan < thiophene has been predicted on the basis of calculations of the electronic structures of furan and its analogs within the π approximation [1]. These systems are classified as π -surplus compounds. The heteroatom here supplies the π system with two electrons and cannot participate in delocalization of the π -electron density in the σ complex. In the opinion of Miller [1], because of the relative instability of the intermediate, the reactivities of furan and its analogs cannot be substantially higher than in the case of π -deficient six-membered aromatic rings (benzene and pyridine). The higher lability of the halogen in furan and thiophene derivatives as compared with the corresponding benzene compounds is explained by the σ -inductive effect of the heteroatom, which increases the electronegativity of the adjacent carbon atom (the reaction center) [1].

Substituents attached to both the reaction center and in other positions of the rings have a substantial effect on the rate of aromatic nucleophilic substitution. The nitro group and halogens are most easily replaced [3, 7-9]. The relative labilities of other groups depend to a considerable extent on the type of nucleophile and the solvent [4, 10, 11]. Electron-acceptor substituents in other positions of the substrate can also facilitate realization of aromatic nucleophilic substitution [1, 12, 13].

In the general case the reactivities of aromatic compounds with respect to nucleophilic attack depend on many factors: the presence of substituents in the ring, the type of heteroatom, the properties of the group that is being replaced, the nucleophilic reagent, and the solvent. The aim of the present research was to obtain a theoretical estimate of the relative reactivities of a number of aromatic systems, particularly furan and its analogs, and

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to ascertain the effect of substituents on the reactivities and the reason for their activating effect. We were interested in the role of the first three factors in "pure form," regardless of the nature of the nucleophile and the solvent. The effect of the solvent is disregarded in this paper, and the hydride ion is a model of the nucleophile.

The calculations were made within the framework of a classical ionic two-step mechanism (addition-cleavage). It is assumed that the first step of the reaction (the formation of a σ complex) is the rate-determining step [1, 2, 11, 14]. In this case the increase in the reaction rate when electron-acceptor substituents are introduced in the ring and the heteroatom is replaced may be due to additional stabilization of the intermediate and the similarly constructed transition state [7]. Reactions involving aromatic nucleophilic substitution of heterorings are realized most readily in the α position relative to the heteroatom [2, 4], and the following systems were therefore studied:



a X=NH; b X=O; c X=S d Y=N; e Y=CH

The σ complexes under consideration may serve as models for the products of addition of nucleophiles to aromatic rings.

We made a quantitative estimate of the affinities of pyrrole, furan and a number of substituted furans, pyridine, and benzene for the hydride ion and determined the structures of anions a-e within the valence approximation by the MINDO/3 method [15]. This method makes it possible to estimate the energies of formation of diverse molecules and ions, including heterocyclic species, with a relatively small error (± 21 kJ/mole in most cases) and to calculate their geometrical parameters quite accurately [15, 16]. It has been used successfully for the study of the mechanisms of various chemical reactions and for the quantitative estimation of the energies of activation [16, 17].

The calculations of anions a-e were made with optimization of the internal coordinates of all of the atoms except the hydrogen atoms. The equilibrium geometry of the corresponding aromatic ring calculated by the MINDO/3 method of Dewar and co-workers [16, 18, 19] was used as the initial geometry. The effect of the substituents on the geometrical parameters of the furan ring and hydrogenated furan b was disregarded.

The minima of the potential energies were found for all systems a-e; this confirms the correctness of the assumption of the possibility of aromatic nucleophilic substitution via a two-step ionic mechanism.

The calculated heats of formation (ΔH_f^σ) of the σ complexes under consideration and the dissociation energies (ΔE) of the $C_{sp^2}-H$ bonds (or the affinities of the corresponding aromatic rings for the hydride ion in the gas phase) are presented in Table 1. The ΔE values were calculated with the aid of the experimental values for the heats of formation (ΔH_f^{exp}) of the aromatic compounds rather than the theoretical ΔH_f values, since the MINDO/3 method underestimates the conjugation energy (Table 1), and this leads to overstated values of the hydride ion affinities. The heat of formation of the hydride ion is 145.9 kJ/mole (the heat of formation of the hydrogen atom is 218.0 kJ/mole [15], and its electron affinity is 72.1 kJ/mole [20]). Thus in this case

$$\Delta E(\text{kJ/mole}) = \Delta H_f^{\text{exp}} + 145.9 - \Delta H_f^\sigma$$

According to our data, pyrrole has the least affinity for H^- among the five-membered aromatic heterocycles, and this explains its inertness to nucleophilic attack. The thiophene ring should be the most reactive ring, since the intermediate is distinguished by its high stability (relative to the substrate); the ability of thiophene to undergo reaction with nucleophilic reagents is no less than that of pyridine.

The position occupied by unsubstituted benzene in the order of increasing susceptibility of the aromatic heterorings to nucleophilic attack — pyrrole < furan < pyridine \leq thiophene — is of great interest. According to our estimate, it should be found between furan and pyridine.

TABLE 1. Hydride Ion Affinities Calculated by the MINDO/3 Method (in kJ/mole)

Compound	ΔH_f	ΔH_f^{exp}	ΔH_f^{σ}	ΔE
Pyrrole	123.4 ¹⁹	102.9 ¹⁹	209.2	39.6
Furan	-33.5 ¹⁹	-34.7 ¹⁹	17.6	93.6
Thiophene	136.0 ¹⁶	115.5 ¹⁶	108.4	153.0
Pyridine	142.7 ¹⁹	144.8 ¹⁹	149.8	140.9
Benzene	120.5 ¹⁸	82.8 ¹⁸	114.2	114.5

TABLE 2. Equilibrium Bond Lengths (\AA) in Anions a-c Calculated by the MINDO/3 Method

Bond	a	b	c
C_2-X	1.418	1.388	1.809
C_2-C_3	1.480	1.472	1.459
C_3-C_4	1.424 (1.433)*	1.427 (1.455)	1.415 (1.463)
C_4-C_5	1.381 (1.391)	1.371 (1.367)	1.365 (1.346)
C_5-X	1.399 (1.368)	1.370 (1.343)	1.771 (1.756)

*The calculated length of the same bond in the corresponding aromatic ring [16, 18, 19] is presented in parentheses.

Experimental data that could confirm the correctness of the result obtained above are not currently available. With the exception of pyridine, replacement of a hydrogen atom by a nucleophile has not yet been observed in any of the compounds [2, 4]. As noted above, there are some comparative data available only for reactions involving replacement of halogen. However, a substituent attached to the reaction center can substantially change the relative magnitude of the affinities of the rings under consideration for H^- . Thus the ΔE values are close for fluoro-substituted furan and benzene (200.7 and 203.8 kJ/mole, respectively). These data do not contradict the fact that the solvolysis of furans with piperidine proceeds somewhat more rapidly than in the case of the corresponding halobenzenes [5] if one takes into account the error in the calculation and the fact that the energy of activation was not estimated directly.

It is interesting that the order of increasing lability of the five-membered aromatic heterocycles that we obtained is in direct opposition to their susceptibilities for electrophilic attack [21, 22]. The most aromatic of these compounds (thiophene) [23] is characterized by the greatest affinity for a nucleophile.

According to the calculations by the MINDO/3 method, all of the examined σ complexes have planar structures. The addition of a nucleophile to five-membered heterorings is accompanied by shortening of the C_3-C_4 bond and lengthening of the C_4-C_5 bond (Table 2). The degree of change in the lengths of these bonds correlates with the increase in the stability of the adduct. The distribution of the π -electron density in anions a-c and the form of the π MO constitute evidence that these systems have structure f.



f $\text{X}=\text{NH, O, S}$ g $\text{Y}=\text{N, CH}$

Despite the fact that heteroatom X does not participate in charge delocalization, the affinity of unsubstituted thiophene for H^- is nevertheless somewhat higher than in the case of pyridine. This fact makes the qualitative concepts that π -surplus aromatic systems cannot give relatively stable intermediates in reactions with nucleophiles [1] untenable. Six-membered rings d and e to a considerable degree have quinoid structure g.

TABLE 3. Hydride Ion Affinity (ΔE , kJ/Mole) of Substituted Furans (with Addition of H^- to the Carbon Atom in the 2 Position)

Compound	ΔH_f	ΔH_f^σ	ΔE
Furan	-33,5	17,6	94,8
2-Fluorofuran	-252,3	-307,1	200,7
2-Nitrofuran	-113,0	-81,2	114,1
3-Nitrofuran	-131,8	-254,4	268,5
4-Nitrofuran	-131,8	-154,4	168,5
5-Nitrofuran	-113,0	-219,7	252,6
3-Carboxyfuran	-461,9	-521,3	205,3
4-Carboxyfuran	-461,9	-446,4	130,4
5-Carboxyfuran	-451,9	-497,1	191,1
3-Methylfuran	-74,1	-57,3	129,1
4-Methylfuran	-74,1	-33,5	105,3
5-Methylfuran	-97,9	-61,1	109,1

The effect of the type of substituent and its position on the stability of the intermediate formed during attack on the furan ring by the nucleophile can be seen in Table 3. The NO_2 and $COOH$ groups are acknowledged as models of the effect of substituents with high and medium electron-acceptor abilities, while the methyl group is considered to be a model of the effect of an electron-donor substituent.

A nitro group and particularly a fluorine atom attached to the reaction center increase the affinity of furan for a hydride ion. The increased stability of the resulting σ complex may be the reason for the fact that they are replaced by a nucleophilic reagent in this heteroring and the fact that replacement of a hydrogen atom has not yet been noted. According to our data, the fluorine atom should be replaced with considerably greater ease than the NO_2 group; this is characteristic for benzene derivatives [11]. Unfortunately, we were unable to estimate the mobility in furan of other halogenes that form weaker bonds with the carbon atom because of the lack of the necessary parameters in the semiempirical MINDO/3 method used.

The activation of furan by substituents in other positions also increases as their electron-acceptor properties become more pronounced: $CH_3 < COOH < NO_2$ (Table 3); even the methyl group, which usually has a + I effect, increases the affinity of the furan ring for a nucleophile, although to a considerably smaller extent than the other two groups. In conformity with the results of the calculation, the experimental data provide evidence that substituents of the NO_2 and $COOH$ type facilitate nucleophilic substitution of halogens in furan [4]. The introduction of a methyl group in the 5 position leads to a decrease of the energy of activation for replacement of iodine in the 2 position [5].

The stabilization of intermediate complex b by an electron-acceptor substituent depends substantially on its position. Substituents attached to the C_3 and C_5 atoms have the greatest effect (Table 3), since the bulk of the negative charge is concentrated precisely on these atoms (Table 4).

The conclusions regarding the effect of substituents as a function of their position on the reactivity of furan in nucleophilic substitution reactions are also evidently valid for its sulfur and nitrogen analogs, since the electronic structures of the resulting intermediates c and a are essentially the same as in the case of complex b (Table 4).

Thus, the calculations show that the ability of aromatic systems to undergo nucleophilic substitution is associated with the relative stability of the σ complex that is formed in the intermediate step. (Of course, this conclusion does not apply to those cases in which the reaction proceeds via an unusual mechanism that includes an electron-transfer step [24, 25]). The reason for the increased mobility of some of the groups undergoing substitution and the activating effect of electron-acceptor substituents in other positions of the ring is an increase in the affinity of the σ complex for the nucleophile.

The results of the calculations indicate that thiophene should have a higher susceptibility to nucleophilic attack than furan. The reactivities of these heterocycles can be increased substantially by incorporation of electron-acceptor substituents in the 3 and 5 positions.

TABLE 4. Total and π Charges on the Atoms in Complexes a-c

Atom	a		b		c	
	$\sigma + \pi$	π	$\sigma + \pi$	π	$\sigma + \pi$	π
X	-0.12	0.15	-0.43	0.09	-0.35	0.03
C ₂	0.36	0.22	0.55	0.25	0.42	0.22
C ₃	-0.48	-0.42	-0.54	-0.61	-0.49	-0.58
C ₄	0.09	0.0	0.06	0.0	0.16	0.08
C ₅	-0.23	-0.38	-0.03	-0.32	-0.20	-0.42

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LITERATURE CITED

1. J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier Publ. Co., Amsterdam-London-New York (1968).
2. J. Joule and G. Smith, *Heterocyclic Chemistry*, Van Nostrand Reinhold (1972).
3. G. Illuminati, *Adv. Heterocycl. Chem.*, 3, 285 (1964).
4. L. A. Paquette, *Principles of Modern Heterocyclic Chemistry*, W. A. Benjamin (1968).
5. D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, 22, 133 (1957).
6. R. Motoyama, S. Nishimura, E. Imoto, Y. Murakami, K. Hari, and Y. Ogawa, *Nippon Kagaku Zasshi*, 78, 950 (1957).
7. R. F. Hudson, in: *Chemical Reactivity and Reaction Paths*, New York (1974).
8. R. Kada and J. Kováč, *Chem. Zvesti*, 29, 402 (1975).
9. V. N. Novikov and S. V. Borodaaev, *Khim. Geterotsikl. Soedin.*, No. 10, 1316 (1976).
10. G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, 10, 125 (1977).
11. H. Becker, *Introduction to the Electronic Theory of Organic Reactions* [Russian translation], Mir, Moscow (1977).
12. V. N. Novikov and L. D. Babeshkina, *Khim. Geterotsikl. Soedin.*, No. 11, 1465 (1976).
13. R. Kada, V. Knoppova, and J. Kováč, *Synth. Commun.*, 7, 157 (1977).
14. P. Sykes, *A Guidebook to Mechanisms in Organic Chemistry*, 4th ed., Halsted Press (1975).
15. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, 97, 1285 (1975).
16. M. J. S. Dewar, *Science*, 187, 1037 (1975).
17. M. J. S. Dewar, *Chem. Brit.*, 11, 97 (1975).
18. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, 97, 1294 (1975).
19. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.*, 97, 1302 (1975).
20. V. I. Vedeneev, L. V. Gurvich, V. N. Kondrat'ev, et al., *Handbook of Energies of Cleavage of Chemical Bonds, Ionization Potentials, and Electron Affinities* [in Russian], Izd. Akad. Nauk SSSR, Moscow (1962).
21. S. Clementi and G. Marino, *Tetrahedron*, 25, 4599 (1969).
22. K. Schwetlick and K. Unverferth, *J. Prakt. Chem.*, Sect. B, 314, 603 (1972).
23. M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, 17, 255 (1974).
24. V. N. Novikov, *Khim. Geterotsikl. Soedin.*, No. 12, 1601 (1976).
25. S. M. Shein, *Zh. Vses. Khim. Ova*, 21, 256 (1976).