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RELATIONSHIPS AND FEATURES OF ELECTROPHILIC SUBSTITUTION REACTIONS IN THE AZOLE SERIES*

L. I. Belen'kii and N. D. Chuvylkin

On the basis of an analysis of the results from quantum-chemical calculations of model systems, together with published experimental data, a study has been made of the influence of the structure of azoles on their capability for electrophilic substitution reactions proceeding either through the traditional addition–abstraction mechanism or through the formation of ylides.

PLACE OF AZOLES AMONG THE HETEROCYCLES, AND POSSIBLE MECHANISMS OF THEIR ELECTROPHILIC SUBSTITUTION REACTIONS

Because of the great diversity of properties of heteroaromatic compounds, there is an urgent need for a classification that is based not only — and possibly not so much — on structural indexes such as the number of rings and the number, nature, and relative positions of the heteroatoms, as on the features of electronic structure of various heterocyclic systems. The foundation of such a classification was laid down by Albert [1], who advanced the concept of π-excessive and π-deficient heterocycles. If benzene is taken as the reference point, the introduction of an electron-donor substituent such as OH or NH_2 into the benzene molecule will increase the π-electron density in the ring, while electron-acceptor substituents such as NO_2 will reduce the π-electron density. Long before the development of electronic theory in organic chemistry, the concept existed that formal replacement of a vinyl fragment by O or NH leads to the activated furan or pyrrole systems (activated primarily with respect to processes that we now call aromatic electrophilic substitution reactions), which resemble phenol or aniline in their properties, and that replacement of a CH fragment by N leads to the deactivated pyridine, with properties similar to those of nitrobenzene. Albert called attention to the fact that this analogy, according to data from quantum-chemical calculations, extends to the π-electron density in heterocycles; and in this light, he called five-membered heterocyclic systems with one heteroatom π-excessive, and azines π-deficient.

Albert classed azoles as π-excessive systems, since he believed that the effect of the "pyrrole" type nitrogen predominates over that of the "pyridine" type nitrogen. But in fact, as we will show below in a large number of examples, many azoles, including triazoles and tetrazoles, are capable of entering into electrophilic substitution reactions under mild conditions. And on the whole, azoles, in terms of reactivity (including that in electrophilic substitution reactions), are intermediate between π-excessive five-membered systems with one heteroatom and the π-deficient azines. This is consistent with their structure, which includes one heteroatom of the "pyrrole" type and one or several "pyridine" nitrogen atoms. Hence it is logical and convenient to classify azoles as π-amphoteric systems as proposed by Pozharskii [2].

The extremely fruitful approach to quantitative estimation of reactivities based on the use of semiempirical relationships such as the Hammett equation, which is being applied extensively to series of five-membered heterocycles with one heteroatom

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N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1535-1563, November-December, 1996. Original article submitted October 7, 1996.

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[3], thus far cannot be applied to azoles, as the available experimental data are inadequate. Seemingly attractive evaluations of reactivity based on the simplest quantum-chemical calculations offer little promise. Consider for example the so-called π-balance that was proposed in [2] (p. 70) as an index of π-excess or π-deficiency, this π-balance being defined as the sum of π-charges on the carbon atoms of the heterocycle as calculated by the Hückel method: This quantity clearly cannot serve the intended purpose. Its unsuitability for quantitative estimates is evident even from an examination of the corresponding data for five-membered heterocycles with a single heteroatom [2] (p. 62), from which one would conclude that thiophene is more π-excessive than furan. In contrast, a large volume of kinetic data leads to the opposite conclusion: Furan is approximately two orders more reactive than thiophene in electrophilic substitution reactions [3]. In view of this situation, it is completely impossible, on the basis of the π-balance for azoles, to draw any conclusion on the higher activity of the sulfur compounds thiazole and isothiazole in comparison with their oxygen analogs. Moreover, as will be shown below, thiazole is less active than oxazole in electrophilic substitution reactions. In any event, calculations of neutral molecules pertain only to their static state, without regard for either the reaction mechanism or the reaction conditions.

Therefore, examination of electrophilic substitution reactions of azoles is necessarily confined to semiquantitative or qualitative evaluations that must include an accounting for the reaction conditions and mechanism. Such an approach was realized in the review [4] in an analysis of electrophilic substitution of various types of heteroaromatic compounds. Here, we have attempted to summarize the available data on the mechanism of electrophilic substitution reactions in the azole series and to give an overall evaluation of their reactivity on the basis of literature data, including the information reported in the last 10 years (since the publication of the review [4]), and also results that we have obtained in calculations of model systems by means of the standard semiempirical method MNDO [5], supplemented by calculations of the indexes i_{AB} [6], reflecting increases or decreases of strength of the bond A–B that result from structural changes, and also estimates of ionization potentials based on Koopmans' theorem.

General information on electrophilic substitution mechanisms in the azole series was presented in the monograph [2]; certain aspects are examined in the following sections of the present review. Let us note here that, in contrast to the prevailing opinion that there is basically a single mechanism of electrophilic substitution, in the case of the azoles we should consider at least two general mechanisms.

The first mechanism is undoubtedly the traditional addition–abstraction mechanism, in the course of which a cationic σ-complex is formed (Wayland intermediate). As will be shown below, the preferred site of attack of the electrophile when such a mechanism is operative is the $C_{(4)}$ atom in the case of 1,2-azoles, and $C_{(5)}$ for 1,3-azoles.

Reactions proceeding through the so-called ylide mechanism are attracting more and more attention. The key stages in this mechanism are the abstraction of a proton with the formation of a carbanion center and the addition of an electrophile at this center, essentially an abstraction–addition mechanism; however, the generation of the carbanion center is facilitated by preferential formation of an azolium cation through addition of an electrophile (which may be a proton) at a "pyridine" nitrogen atom. Reactions proceeding through the ylide mechanism can be identified by a distinctive directional feature, i.e., replacement of hydrogen at a carbon atom located between a "pyridine" nitrogen and a pyrrole-type heteroatom. Such positions are $C_{(2)}$ in 1,3-azoles, and also $C_{(2)}$ and $C_{(5)}$ in 1,3,4-oxadiazoles and 1,3,4-thiadiazoles, $C_{(3)}$ and $C_{(5)}$ in 4-R-1,2,4-triazoles, and $C_{(5)}$ in 1,2,4-oxadiazoles, 1,2,4-thiadiazoles, 1-R-1,2,4-triazoles, and 1-R-tetrazoles. The reasons for such directionality will be examined in our discussion of orientation rules in the azole series.

We will not deal with generally unimportant mechanisms of electrophilic C-substitution of azoles that are not substituted on the nitrogen atom, which may take place with the participation of azolate anions (see the review [4]); nor will we deal with replacement of hydrogen at a "pyrrole" nitrogen atom. Here we will note only that the latter reaction probably includes attack of the electrophile at a "pyridine" nitrogen atom with subsequent deprotonation of the "pyrrole" nitrogen atom [2].

PROPERTIES OF AZOLES AS BASES, AND THEIR RELATIVE ACTIVITIES IN ELECTROPHILIC SUBSTITUTION REACTIONS

As is known primarily from the work of Marino [3, 7], pyrrole is 5-7 orders more reactive than furan in electrophilic substitution, depending on the particular reaction; and thiophene is 1-3 orders less reactive than furan. There are firm grounds for believing that this dependence of reactivity on the nature of the heteroatom, NR > O > S, is also valid for the azoles. Here, however, it should be taken into account that in determining the behavior of azoles under conditions of electrophilic

TABLE 1. Comparison of Azoles as Bases

Azole	pK_a (water, 25°C)*	PA, kcal/mole
N-Methylimidazole	7,33	
Imidazole	6,95	213,6
1-Methyl-1,2,4-triazole	3,20	
Thiazole	2,53	199,8
Pyrazole	2,52	194,5
1,2,4-Triazole	2,45	198,1**
N-Methylpyrazole	2,06	
1-Methyl-1,2,3-triazole	1,25	
1,2,3-Triazole	1,17	192,0**
2-Methyl-1,2,3-triazole	<1	
Oxazole	0,8	200,7
Isothiazole	-0,51	209,8
1,3,4-Oxadiazole	(-1,56) †	184,8
Tetrazole	-2,68 ‡	184,1**
Isoxazole	-2,97	184,4
1,2,4-Oxadiazole	(-4,00) †	
1,2,5-Thiadiazole	-4,9	
1,2,3-Oxadiazole	(-5,95) †	
Furazan [1,2,5-oxadizaole]	(-7,64) †	

*If not otherwise indicated, values of pK_a are cited according to [8], where values summarized in [9-11] were used.

†Estimates from quantum-chemical calculations in STO-3G basis, from [12].

‡Experimental data from [13].

**Data from [14].

substitution, an important and often decisive factor is their properties as bases. These properties determine the ratio of free base and conjugate acid, and hence determine the form in which the compound enters into reaction. In any event, for reactions that proceed through an addition–abstraction mechanism, an acidic medium — or the presence of a protic or aprotic acid as a catalyst — will lower the activity of azoles, either because the azoles enter into reaction in the highly deactivated form of the conjugate acid, or as a consequence of a sharp decrease of the concentration of free base. The influence of an acidic medium on reactions proceeding through the ylide mechanism is not so obvious, since such a medium should facilitate the formation of the azolium ion but should hinder abstraction of the proton from this ion to form an ylide. However, since abstraction of the proton from the azolium ion is apparently the limiting stage of the process, and since the formation of the azolium cation can proceed without participation of a proton of the medium, at the expense of the electrophilic agent itself, such reactions should preferably be performed under nearly neutral conditions.

In view of the enormous differences in the strength of azoles as bases, amounting to almost 15 pK_a units (see Table 1), any comparison of the azoles with respect to activity encounters major difficulties. In a number of cases, the protonation energies ΔE_p calculated by quantum-chemical methods (proton affinity PA) or the calculated charges on the atoms are in satisfactory agreement with the experimental values of pK_a of the azoles [12, 14, 15]. In particular, as shown in Fig. 1, the linear correlation described in [14] between the pK_a values for imidazole, pyrazole, 1,2,3-triazole, and tetrazole, and values of PA obtained from the formula

$$PA = \Delta H_f(H^+) + \Delta H_f(HetH) - \Delta H_f(HetH_2^+),$$

[where the enthalpy of formation of a proton ΔH_f (H^+) = 367.2 kcal/mole, and ΔH_f (HetH) and ΔH_f $(HetH_2^+)$ are the enthalpies of formation of azoles and products of their protonation as calculated by the MNDO-PM3 method] is preserved when using values of these enthalpies obtained by the MNDO method. The same linear relationship is observed for thiazole and 1,3,4-oxadiazole; but for oxazole and isothiazole, the deviations from linearity are substantial. Apparently, better agreement between

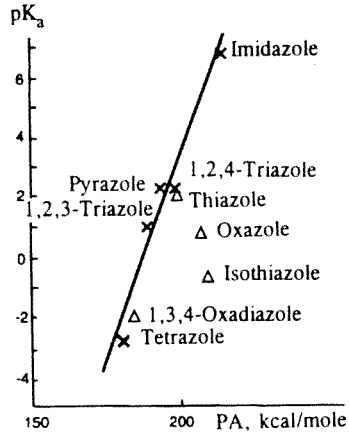
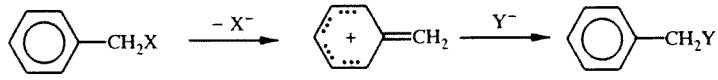


Fig. 1. Correlation of experimental values of pK_a of certain azoles (water, 25°C) with values of proton affinity (PA, kcal/mole) calculated by MNDO method. ×) Data of [14]; Δ) calculated in present work.

calculated and experimental values characterizing the acid-base properties of the azoles can be obtained when the quantum-chemical calculations take into account the specific solvation (hydration) effect [16].

A general evaluation of the activity of azoles, independent of their properties as bases and their ability to enter into electrophilic substitution reactions under real conditions, can be made by investigating the pyrolysis and solvolysis of the corresponding analogs of benzyl halides and benzyl ethers [esters], which are performed in neutral media. It is generally agreed today that the intermediates in such are reactions resemble cationic σ-complexes:



This view is supported by the fact that for benzyl halides and benzyl ethers [esters] having different substituents on the benzene ring, a linear correlation of the Hammett type is observed when using electrophilic constants σ^+. Such a correlation also exists for heteroaromatic analogs of these benzyl derivatives; each heteroatomic group can be characterized by a "substituent" constant, which corresponds formally to the replacement of one or two vinylene groups of the phenyl residue by NH, O, or S, and replacement of one (or several) -CH= groupings in the remaining vinylene groups by -N=. The "substituent" constants thus obtained, σ_{Ar}^+, can be used to calculate partial rate factors for various positions in the azole molecules; however, they are suitable only for rough approximations of reactivity in reactions proceeding through the addition-abstraction mechanism. This is even indicated by the fact that there are substantial differences between values of σ_{Ar}^+ obtained on the basis of pyrolysis and solvolysis data, not only in absolute magnitude (as is natural for reactions with different constants ρ), but also in sign. Such differences caused by specific solvation [17] will naturally be manifested to different degrees for different positions on the ring. Nonetheless, from a comparison of data on values of σ_{Ar}^+ obtained on the basis of solvolysis results [18-30], an important conclusion can be drawn [4]: Azoles, with respect to values of σ_{Ar}^+ and hence with respect to reactivity, are distributed in two groups between pyrrole and pyridine, with imidazole and pyrazole falling into the same group with furan and thiophene, and with another group consisting of thiazole, isoxazole, and isothiazole (no data available for oxazole) with reactivities similar to that of benzene. Thus, the replacement of one -CH= group in pyrrole by -N= lowers the reactivity to approximately the same degree as the replacement of an NH group by O or S. Similar differences in reactivity (at least for the most active positions) are observed when the change is made from furan to isoxazole, and also from thiophene to thiazole and isothiazole.

Discarding the constant term $\Delta H_f(H^+)$, we can attempt to estimate the general reactivity of azoles on the basis of the enthalpies of formation of the azoles and their protonated forms (Tables 2-5), i.e., on the basis of the difference

$$\Delta H_f(\mathrm{HetH}) - \Delta H_f(\mathrm{HetH_2^+}),$$

TABLE 2. Results of MNDO Quantum-Chemical Calculations of 1,3-Azoles (I) and Products of Their N- and C-Protonation and C-Deprotonation That Model σ-Complexes and Bipolar Ions Formed in Electrophilic Substitution (E = H)

Structure (X)	ΔH_f,* kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond AB, i_{AB}, %							
				1-X	2-C	3-N	4-C	5-C	1-H	2-H	3-H	4-H	5-H	i_{1-2}	i_{1-5}	i_{2-3}	i_{3-4}	i_{4-5}	i_{2-H}	i_{4-H}	i_{5-H}
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
I (NH)	33,3	9,1	10,0	−0,25	0,05	−0,23	−0,06	−0,06	0,21	0,13	–	0,10	0,11	3,6	2,9	−1,4	2,3	−1,8	0,8	0,0	0,0
3-*H*-I$^+$	186,9	15,0	9,8	−0,17	0,21	−0,17	0,03	0,03	0,27	0,20	0,27	0,17	0,17	15,5	1,7	−7,4	−0,6	0,5	−2,3	−1,5	−1,5
5-*H*-I$^+$	207,9	17,4	10,6	−0,27	0,35	−0,21	0,17	0,07	0,27	0,20	–	0,17	0,12	24,7	−16,3	−19,8	27,3	−31,8	−5,4	−4,5	−7,6
4-*H*-I$^+$	213,5	16,9	10,1	−0,19	0,16	−0,15	0,02	0,24	0,27	0,20	–	0,14	0,18	−16,7	30,8	12,4	−17,6	−31,3	−2,3	−8,3	−5,3
2-*H*-I$^+$	215,2	17,3	10,4	−0,21	0,16	−0,11	0,02	0,25	0,27	0,13	–	0,18	0,18	−23,0	32,6	−30,9	34,1	−28,1	−6,9	−2,3	−5,3
3,5-I^{+-}	93,9	8,4	8,8	−0,18	0,00	−0,15	−0,18	−0,15	0,21	0,14	0,21	0,12	–	4,0	−1,7	−6,9	−5,1	−10,1	0,8	1,5	–
3,4-I^{+-}	93,9	8,4	8,8	−0,15	0,00	−0,18	−0,15	−0,18	0,21	0,14	0,21	–	0,10	14,9	−2,3	−13,8	−4,0	−8,8	1,5	–	0,8
3,2-I^{+-}	63,0	9,0	10,2	−0,29	0,06	−0,29	−0,05	−0,05	0,21	–	0,21	0,10	0,10	4,0	−2,9	−16,6	−5,1	4,1	–	0,0	0,0

TABLE 2. (continued)

Structure (X)	ΔH_f,* kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond AB, i_{AB}, %							
				1-X	2-C	3-N	4-C	5-C	1-H	2-H	3-H	4-H	5-H	i_{1-2}	i_{1-5}	i_{2-3}	i_{3-4}	i_{4-5}	i_{2-H}	i_{4-H}	i_{5-H}
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
I (O)	-8,2	9,7	10,0	-0,14	0,07	-0,22	-0,07	-0,05	–	0,16	–	0,12	0,13	≡0	≡0	≡0	≡0	≡0	≡0	≡0	≡0
3-*H*-I$^+$	158,3	15,6	9,6	-0,05	0,27	-0,18	0,02	0,06	–	0,23	0,28	0,18	0,20	10,3	-3,5	-5,5	-2,8	1,4	-4,6	-1,5	-2,3
5-*H*-I$^+$	179,8	18,0	10,4	-0,14	0,41	-0,23	0,20	0,06	–	0,23	–	0,19	0,14	16,7	-18,0	-18,4	25,0	-32,7	-7,7	-5,3	-7,6
4-*H*-I$^+$	189,1	17,5	9,8	-0,08	0,17	-0,16	-0,01	0,34	–	0,23	–	0,15	0,20	-21,8	26,2	12,0	-17,0	-32,3	-3,1	-8,3	-7,6
2-*H*-I$^+$	189,6	18,0	10,3	-0,10	0,15	-0,09	-0,01	0,35	–	0,15	–	0,19	0,20	-26,4	27,9	-31,8	34,1	-28,6	-6,9	-2,3	– 7,6
3,5-I^{+-}	52,4	8,9	8,7	-0,07	0,03	-0,15	-0,22	-0,10	–	0,16	0,22	0,12	–	4,0	-1,7	-6,9	-5,1	-10,1	0,8	1,5	–
3,4-I^{+-}	53,7	8,9	8,7	-0,06	0,05	-0,19	-0,13	0,34	–	0,16	0,22	–	0,13	13,2	-5,2	-7,8	-6,2	-7,8	0,8	–	0,8
3,2-I^{+-}	18,5	9,7	10,3	-0,16	0,11	-0,32	-0,05	-0,04	–	–	0,22	0,12	0,13	4,0	-6,4	-17,9	-6,2	5,1	–	0,8	0,0
I (S)	33,2	9,9	9,5	0,31	-0,14	-0,20	-0,02	-0,30	–	0,12	–	0,11	0,11	-19,0	-14,5	2,8	-1,1	1,8	0,8	-1,5	0,8
3-*H*-I$^+$	197,8	15,5	9,1	0,61	-0,07	-0,14	0,07	-0,27	–	0,18	0,27	0,17	0,17	-31,0	4,6	12,9	-15,9	-30,4	0,0	-9,1	-2,3
5-*H*-I$^+$	222,6	16,7	8,8	0,49	0,07	-0,21	0,22	-0,23	–	0,19	–	0,18	0,15	-11,5	-26,7	-15,2	23,3	-28,6	-3,1	-5,3	-6,1
4-*H*-I$^+$	233,8	17,0	9,1	0,62	-0,10	-0,11	0,00	-0,08	–	0,19	–	0,15	0,18	-31,0	4,6	12,9	-15,9	-30,4	0,0	-9,1	-2,3
2-*H*-I$^+$	232,9	17,2	9,1	0,58	-0,10	-0,09	0,02	-0,07	–	0,15	–	0,18	0,18	-35,6	4,1	-29,5	33,0	-25,3	-5,4	-3,0	-3,0
3,5-I^{+-}	101,6	8,3	7,7	0,46	-0,23	-0,12	-0,10	-0,46	–	0,12	0,20	0,11	–	-13,8	-5,8	-5,5	-8,5	0,5	2,3	0,0	–
3,4-I^{+-}	94,2	8,6	7,7	0,40	-0,20	-0,13	-0,15	-0,38	–	0,12	0,22	–	0,11	-6,9	-16,9	-11,5	-5,7	-3,2	1,5	–	0,8
3,2-I^{+-}	74,6	9,5	9,7	0,26	-0,16	-0,24	-0,01	-0,29	–	–	0,22	0,11	0,11	-20,7	-19,2	-10,6	-7,4	6,4	–	-0,8	0,8

*Enthalpy of formation, ΔH_f, kcal/mole.

†Ionization potential, I_f, eV.

‡Difference of LUMO and HOMO energies, $\Delta E_{f\to v}$, eV.

TABLE 3. Results of MNDO Quantum-Chemical Calculations of 1,2-Azoles (II) and Products of Their N- and C-Protonation and C-Deprotonation That Model Cationic σ-Complexes and Bipolar Ions Formed in Electrophilic Substitution (E = H)

Structure (X)	ΔH_f,* kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond AB, i_{AB}, %							
				1-X	2-N	3-C	4-C	5-C	1-H	2-H	3-H	4-H	5-H	i_{1-2}	i_{1-5}	i_{2-3}	i_{3-4}	i_{4-5}	i_{3-H}	i_{4-H}	i_{5-H}
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
II (NH)	45,4	9,6	10,4	−0,18	−0,12	−0,06	0,17	0,00	0,23	–	0,11	0,09	0,10	8,6	5,2	−1,9	3,4	−2,3	0,0	−0,8	0,0
2-*H*-II$^+$	218,1	15,4	9,7	−0,13	−0,13	0,18	−0,16	0,18	0,29	0,29	0,17	0,16	0,17	6,8	11,6	−10,3	13,0	−7,8	−3,0	−0,8	−3,0
4-*H*-II$^+$	221,9	16,8	10,0	−0,07	−0,05	0,06	−0,07	0,21	0,30	–	0,18	0,13	0,18	−6,8	29,1	7,0	−15,8	−30,0	−2,3	−8,3	−3,8
3-*H*-II$^+$	236,0	16,1	9,1	0,03	0,08	−0,02	0,00	−0,03	0,30	–	0,15	0,16	0,18	42,6	−11,6	−33,6	−14,1	5,5	−8,4	−3,0	0,0
5-*H*-II$^+$	234,2	16,3	9,0	−0,10	0,16	−0,09	0,04	0,07	0,30	–	0,18	0,16	0,13	38,9	−20,9	−21,0	23,7	−29,5	0,0	−3,8	−6,9
2,3-II^{+-}	105,6	9,1	9,0	−0,16	−0,21	−0,01	−0,19	0,01	0,15	0,22	–	0,10	0,11	−11,0	−4,6	−11,7	−7,9	2,8	–	−0,8	−0,8
2,4-II^{+-}	133,6	8,0	7,1	−0,18	−0,18	0,10	−0,40	0,10	0,17	0,17	0,11	–	0,11	−5,6	−2,9	−22,0	15,8	−5,5	−0,8	–	−0,8
2,5-II^{+-}	105,6	9,1	9,0	−0,21	−0,17	0,01	−0,19	−0,01	0,22	0,15	0,11	0,10	–	−11,1	9,9	−23,4	26,0	−24,9	−0,8	−0,8	–

TABLE 3. (continued)

Structure (X)	ΔH_f,* kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond AB, i_{AB}, %							
				1-X	2-N	3-C	4-C	5-C	1-H	2-H	3-H	4-H	5-H	i_{1-2}	i_{1-5}	i_{2-3}	i_{3-4}	i_{4-5}	i_{3-H}	i_{4-H}	i_{5-H}
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
II (O)	19,2	10,3	10,4	-0,06	-0,09	-0,05	-0,18	0,01	–	–	0,12	0,11	0,13	≡0	≡0	≡0	≡0	≡0	≡0	≡0	≡0
2-*H*-II$^+$	202,0	16,3	9,7	0,01	-0,13	0,23	-0,17	0,19	–	0,32	0,18	0,17	0,20	-1,8	1,7	-7,5	8,5	-4,1	-3,8	-0,8	-3,8
4-*H*-II$^+$	214,8	17,6	9,9	0,05	-0,01	0,04	-0,10	0,31	–	–	0,19	0,15	0,20	-16,0	22,0	6,5	-15,8	-30,0	-2,3	-8,3	-6,9
3-*H*-II$^+$	235,3	16,7	8,5	0,14	0,20	-0,07	-0,01	-0,01	–	–	0,18	0,18	0,20	31,5	-14,5	-33,2	-13,6	4,6	-9,2	-3,0	-0,8
5-*H*-II$^+$	227,6	17,4	9,0	0,01	0,25	-0,12	0,14	0,03	–	–	0,20	0,17	0,16	21,6	-22,1	-15,4	17,5	-29,5	0,0	-4,5	-8,4
2,3-II$^{+\cdot}$	80,4	9,5	9,5	-0,12	-0,19	0,01	-0,24	0,06	–	0,24	–	0,11	0,13	-13,0	0,0	-12,2	-6,8	1,4	–	0,0	-0,8
2,4-II$^{+\cdot}$	109,4	8,4	7,2	-0,09	-0,17	0,10	-0,41	0,13	–	0,20	0,12	–	0,13	-4,9	-2,3	-25,2	17,9	-7,4	-0,8	–	-1,5
2,5-II$^{+\cdot}$	78,4	9,8	9,3	-0,06	-0,18	0,03	-0,23	0,03	–	0,17	0,12	0,11	–	-17,3	11,0	-22,9	26,6	-25,3	-0,8	0,0	–
II (S)	35,7	9,9	9,6	0,38	-0,32	0,01	-0,13	-0,25	–	–	0,11	0,10	0,11	-13,6	-14,5	5,6	-1,7	1,8	-1,5	-1,5	0,8
2-*H*-II$^+$	203,1	15,5	8,9	0,65	-0,35	0,22	-0,12	-0,16	–	0,28	0,17	0,16	0,17	-11,1	-11,0	-2,8	6,8	-2,8	-3,8	-1,5	-0,8
4-*H*-II$^+$	229,5	16,9	9,2	0,79	-0,30	0,12	-0,08	-0,15	–	–	0,18	0,14	0,18	-17,3	7,0	10,7	-15,2	-29,0	-3,8	-9,0	-0,8
3-*H*-II$^+$	247,5	16,5	8,5	0,93	-0,25	-0,01	0,04	-0,37	–	–	0,16	0,16	0,18	18,5	-9,9	-29,0	-13,6	5,5	-9,9	-3,8	2,3
5-*H*-II$^+$	239,8	16,0	7,8	0,68	-0,16	-0,05	0,13	-0,28	–	–	0,18	0,16	0,16	1,8	-25,0	-9,8	15,2	-26,3	-1,5	-4,5	-6,1
2,3-II$^{+\cdot}$	84,0	9,1	8,8	0,29	-0,34	-0,02	-0,15	-0,21	–	0,23	–	0,10	0,11	-24,7	-16,3	-4,7	-7,3	2,3	–	-1,5	0,0
2,4-II$^{+\cdot}$	111,5	7,9	7,0	0,31	-0,39	0,23	-0,46	-0,10	–	0,21	0,10	–	0,10	-14,2	-27,6	-12,2	15,8	4,1	-2,3	–	0,0
2,5-II$^{+\cdot}$	98,0	8,7	8,4	0,50	-0,45	0,12	-0,19	-0,38	–	0,21	0,10	0,10	–	-21,9	2,9	-8,4	15,8	-12,0	-1,5	-0,8	–

*Enthalpy of formation, ΔH_f, kcal/mole.

†Ionization potential, I_f, eV.

‡Difference of LUMO and HOMO energies, $\Delta E_{f\to v}$, eV.

which can be regarded, in case the rule of noncrossing of potential curves is followed, as a quantity characterizing in the first approximation the height of the activation barrier in substitution through an addition–abstraction mechanism:

imidazole (174.6) > oxazole (187.0) > thiazole (189.4)

pyrazole (176.5) > isothiazole (193.8) > isoxazole (195.6)

4H-1,2,4-triazole (194.3) > 1,3,4-thiadiazole (208.8) ≈ 1,3,4-oxadiazole (209.4)

2H-tetrazole (217.1) > 1H-tetrazole (223.2)

These results are in qualitative agreement with the experimental data within the series of 1,3-azoles; for the 1,2-azoles, the relative positions of isothiazole and isoxazole remain unclear. In the case of azoles with three or four heteroatoms, the high activity of 2H-tetrazole in comparison with the 1H-isomer is unexpected. However, because of the lack of any quantitative data for the compounds of these series, along with the high probability of their conversions through an ylide mechanism (with the exception of the 2H-tetrazole), there is no object in attempting any more detailed judgments. Let us note only that a comparison of the isomeric 1,3- and 1,2-azoles indicates in all cases a higher activity for the 1,3-isomers, whereas from the experimental data this is obvious only for the imidazole–pyrazole pair. The disagreement in the other cases may be due to the fact that thiazole and oxazole are considerably stronger bases that isothiazole and isoxazole, respectively. The difference between the LUMO and HOMO energies, $\Delta E_{f\to\nu}$ (eV), which can characterize reactivity, within the series is consistent with the sequence N > O > S that was mentioned at the beginning of this review; however, the increase of these values when the change is made from 1,3- to 1,2-azoles and then to heterocycles with three and four heteratoms is difficult to explain:

imidazole (10.0) = oxazole (10.0) > thiazole (9.5)

pyrazole (10.4) = isoxazole (10.4) > isothiazole (9.6)

4H-1,2,4-triazole (10.5) = 1,3,4-oxadiazole (10.5) > 2,3,4-thiadiazole (10.2)

1H-tetrazole (11.2) > 2H-tetrazole (11.1)

Under real conditions of electrophilic substitution, imidazole and its derivatives, as the strongest bases, enter into reactions performed in a strongly acidic medium, such as nitration and sulfonation, apparently in the form of conjugate acids; while in bromination in organic solvents without catalyst and in deuterium exchange, they react in the form of the free base [31]. Conversions in the form of the free base, as we will see below, will be all the more probable for other azoles that are weaker bases than imidazole.

The most complete quantitative data on the reactivities of certain azoles were obtained by Katritzky et al. as a result of extremely laborious kinetic studies of electrophilic substitution with a simultaneous determination of which form (free base or conjugate acid) and at what effective concentration the various substrates participate in reactions performed under specific conditions. To this end, criteria were developed on the basis of measurements of reaction rate constants with various acidities of the medium, determination of activation parameters, and comparison of the observed rate with the reaction rate of a related compound known to exist in the form of a cation, for example a haloalkylate [alkyl halide] [32]. For imidazole, pyrazole, thiazole, isothiazole, isoxazole, and certain methyl derivatives of these compounds, comparable quantitative data were obtained, extrapolated for isotope exchange of hydrogen to a moderately acidic medium (pD 0) and a temperature of 100°C [33-35]; and for nitration by nitric acid, these were recalculated to 25°C and H_0 −6.6 [36-40].

It is important to note that in isotope exchange of hydrogen, all of the azoles that were studied (isoxazole, isothiazole, N-methylpyrazole, 3,5-dimethylisothiazole, 1,3,5-trimethylpyrazole) proved to be more active than benzene – even in the protonated form for the last two of these compounds. On the basis of partial rate factors, the most active positions in isothiazole and isoxazole are less active than those in thiophene by 7.5 and 2.5 orders, respectively; N-methylpyrazole is ranked between thiophene and N-methylpyrrole. The most reactive 1,3,5-trimethylpyrazole is more active than N-methylpyrrole by approximately 2 orders. When the change is made from the neutral base to the conjugate acid, the differences in reactivity are

TABLE 4. Results of MNDO Quantum-Chemical Calculations of Certain Azoles with Three Heteroatoms (III) and Products of Their N- and C-Protonation and C-Deprotonation That Model Cationic σ-Complexes and Bipolar Ions Formed in Electrophilic Substitution (E = H)

Structure (X)	ΔH_f, kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond AB, i_{AB}, %						
				1-X	2-C	3-N	4-N	5-C	1-H	2-H	3-H	4-H	5-H	i_{1-2}	i_{1-5}	i_{2-3}	i_{3-4}	i_{4-5}	i_{2-H}	i_{5-H}
				(for III, X = O, S)										(for III, X = O, S)						
				4-N	5-C	1-N	2-N	3-C	4-H	5-H	2-H	1-H	3-H	i_{3-4}	i_{4-5}	i_{1-5}	i_{1-2}	i_{2-3}	i_{5-H}	i_{3-H}
				(for III, X = NH)										(for III, X = NH)						
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
III (NH)	40,1	10,0	10,5	-0,26	0,01	-0,13	-0,13	0,01	0,22	0,14	–	–	0,14	2,9	2,9	-0,9	1,1	-0,9	0,8	0,8
1-*H*-III$^+$	209,3	16,4	10,6	-0,22	0,23	-0,11	-0,04	0,13	0,29	0,21	–	0,31	0,21	0,6	15,0	-3,8	-5,1	1,9	-3,0	-3,8
3-*H*-III$^+$	234,4	17,6	10,2	-0,23	0,10	0,06	-0,01	0,29	0,29	0,15	0,15	–	0,21	-19,6	30,6	-34,9	37,1	-31,6	-6,9	-5,3
1,5-III^{+-}	73,3	10,2	11,1	-0,32	0,09	-0,25	-0,14	0,05	0,22	0,14	–	0,24	–	3,5	-3,5	-14,6	-9,0	5,7	–	0,0
1,3-III^{+-}	96,3	9,3	9,2	-0,25	0,06	-0,11	0,26	-0,06	0,22	0,15	–	0,24	0,15	10,4	-11,6	-3,8	-11,2	-4,2	–	0,0
5,3-III^{+-}	92,3	10,3	9,6	-0,37	0,08	-0,05	-0,12	0,11	0,23	–	–	–	0,06	14,4	-17,3	-36,8	38,8	-35,4	–	-5,3

TABLE 4. (continued)

Structure (X)	ΔH_f, kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond AB, i_{AB}, %						
				1-X	2-C	3-N	4-N	5-C	1-H	2-H	3-H	4-H	5-H	i_{1-2}	i_{1-5}	i_{2-3}	i_{3-4}	i_{4-5}	i_{2-H}	i_{5-H}
				(for III, X = O, S)										(for III, X = O, S)						
				4-N	5-C	1-N	2-N	3-C	4-H	5-H	2-H	1-H	3-H	i_{3-4}	i_{4-5}	i_{1-5}	i_{1-2}	i_{2-3}	i_{5-H}	i_{3-H}
				(for III, X = NH)										(for III, X = NH)						
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
III (O)	-2,2	10,7	10,5	-0,14	0,03	-0,13	-0,13	0,03	–	0,17	–	–	0,17	≡0	≡0	≡0	≡0	≡0	≡0	≡0
3-*H*-III$^+$	180,2	17,2	10,6	-0,08	0,29	-0,12	-0,04	0,16	–	0,24	0,29	–	0,24	9,8	-5,2	-2,8	-6,7	2,4	-6,1	-3,8
2-*H*-III$^+$	207,2	18,4	10,1	-0,10	0,10	0,08	-0,03	0,38	–	0,17	–	–	0,24	-22,5	25,4	-36,3	37,6	-33,5	-7,6	-9,2
3,2-III$^{+\cdot}$	27,8	10,8	11,1	-0,18	–	-0,29	-0,12	0,04	–	–	0,22	–	0,17	3,5	-7,5	-16,5	-9,6	6,6	–	0,0
3,5-III$^{+\cdot}$	53,3	10,0	9,3	-0,13	0,10	-0,10	-0,28	-0,02	–	0,18	0,25	–	–	7,5	-11,6	-3,3	-10,7	-6,1	-0,8	–
2,5-III$^{+\cdot}$	46,0	10,9	9,7	-0,22	0,07	-0,05	-0,15	0,18	–	0,08	–	–	–	-19,6	15,0	-37,3	41,6	-40,1	-5,3	–
III (S)	46,2	11,0	10,2	0,32	-0,20	-0,10	-0,10	-0,20	–	0,14	–	–	0,14	-16,8	-16,8	2,4	-0,6	2,4	0,8	0,8
3-*H*-III$^+$	224,9	17,0	10,1	0,59	-0,06	-0,08	0,00	-0,15	–	0,20	0,31	–	0,20	-12,1	-17,9	-3,3	-5,6	4,7	-1,5	-0,8
2-*H*-III$^+$	255,0	17,8	9,3	0,60	-0,18	0,08	-0,01	0,29	–	0,16	–	–	0,20	-30,6	0,6	-33,1	37,6	-29,7	-5,3	-2,3
3,2-III$^{+\cdot}$	90,8	10,0	9,8	0,24	–	-0,20	-0,10	-0,19	–	–	0,24	–	0,14	-20,8	-23,1	-9,4	-11,2	8,5	–	0,8
3,5-III$^{+\cdot}$	109,6	9,2	8,0	0,33	-0,16	-0,08	-0,18	-0,27	–	0,14	0,23	–	–	-13,9	-26,0	-1,9	-18,0	3,8	0,8	–
2,5-III$^{+\cdot}$	115,2	10,3	8,4	0,20	-0,17	-0,02	-0,10	-0,10	–	0,09	–	–	–	-32,4	-14,4	-34,9	38,2	-32,1	-4,6	–

*Enthalpy of formation, ΔH_f, kcal/mole.

†Ionization potential, I_f, eV.

‡Difference of LUMO and HOMO energies, $\Delta E_{f\to v}$, eV.

TABLE 5. Results of MNDO Quantum-Chemical Calculations of 1H-Tetrazoles (IV) and 2H-Tetrazoles (V) and Products of Their N- and C-Protonation and C-Deprotonation That Model Cationic σ-Complexes and Bipolar Ions Formed in Electrophilic Substitution (E = H)

Structure (X)	ΔH_f, kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond A-B, i_{AB}, %						
				1-N	5-C	4-N	3-N	2-N	1-H	5-H	4-H	3-H	2-H	i_{1-5}	i_{1-2}	i_{4-5}	i_{3-4}	i_{2-3}	i_{5-H}	i_{1-H}
				(for IV)										(for IV)						
				2-N	1-N	5-C	4-N	3-N	2-H	1-H	5-H	4-H	3-H	i_{1-2}	i_{2-3}	i_{1-5}	i_{4-5}	i_{3-4}	i_{5-H}	i_{2-H}
				(for V)										(for V)						
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
IV	53,8	11,4	11,2	-0,22	0,05	-0,16	-0,04	-0,03	0,25	0,16	–	–	–	≡0	≡0	≡0	≡0	≡0	≡0	≡0
1-*H*-IV$^+$	275,8	18,6	11,2	-0,06	0,11	-0,02	0,14	0,06	0,27	0,23	–	–	–	-28,2	-23,6	14,0	-18,8	14,0	-3,8	-7,5
2-*H*-IV$^+$	257,9	17,8	10,8	-0,13	0,22	-0,09	0,20	-0,09	0,32	0,22	–	–	0,34	9,4	0,0	-12,0	17,0	-3,6	-4,6	-3,8
3-*H*-IV$^+$	246,4	17,6	10,9	-0,15	0,14	-0,03	-0,02	0,16	0,32	0,22	–	0,35	–	-2,8	13,4	0,5	-2,3	-7,5	-3,0	-3,8
4-*H*-IV$^+$	236,9	18,1	11,5	-0,17	0,27	-0,17	0,10	0,10	0,32	0,23	0,32	–	–	11,7	-3,5	-3,8	-6,2	4,2	-5,3	-3,0
5-*H*-IV$^+$	277,0	18,7	10,3	-0,08	0,08	0,04	0,07	0,22	0,33	0,17	–	–	–	-29,4	36,3	-32,1	36,4	-35,5	-7,6	-6,8
1,5-IV^{+-}	124,6	11,0	10,1	-0,08	0,03	-0,32	0,10	-0,13	0,20	–	–	–	–	-43,9	-28,6	5,3	-10,8	12,6	–	-5,3

TABLE 5. (continued)

Structure (X)	ΔH_f, kcal/mole*	I_f, eV†	$\Delta E_{f\to v}$, eV‡	Charges on atoms, Q										Indexes of change in strength of chemical bond A-B, i_{AB}, %						
				1-N	5-C	4-N	3-N	2-N	1-H	5-H	4-H	3-H	2-H	i_{1-5}	i_{1-2}	i_{4-5}	i_{3-4}	i_{2-3}	i_{5-H}	i_{1-H}
				(for IV)										(for IV)						
				2-N	1-N	5-C	4-N	3-N	2-H	1-H	5-H	4-H	3-H	i_{1-2}	i_{2-3}	i_{1-5}	i_{4-5}	i_{3-4}	i_{5-H}	i_{2-H}
				(for V)										(for V)						
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
(IV)																				
2,5-IV$^{+\cdot}$	115,9	10,7	9,9	-0,27	0,11	-0,18	0,07	-0,16	0,24	–	–	–	–	3,9	-17,0	-29,7	32,4	-25,2	–	0,0
3,5-IV$^{+\cdot}$	116,4	10,1	9,4	-0,21	-0,02	-0,25	-0,03	-0,01	0,25	–	–	0,27	–	-13,9	8,2	-6,2	-6,2	-7,0	–	-0,8
4,5-IV$^{+\cdot}$	85,8	11,0	11,4	-0,29	0,13	-0,29	-0,02	-0,02	0,25	–	0,25	–	–	-0,6	-7,0	-14,8	-9,7	7,9	–	0,8
V	58,1	11,2	11,1	-0,15	-0,11	-0,04	-0,15	0,03	0,27	–	0,16	–	–	≡0	≡0	≡0	≡0	≡0	≡0	≡0
1-*H*-V^{+}	257,9	17,8	10,8	-0,09	-0,13	0,22	-0,09	0,20	0,34	0,32	0,22	–	–	-2,8	6,9	-6,2	6,4	-5,5	-5,3	-4,6
2-*H*-V^{+}	276,4	18,8	7,3	0,01	-0,10	0,17	0,01	0,13	0,27	–	0,23	–	–	-21,6	-36,4	11,4	-23,3	18,8	-5,3	-6,9
3-*H*-V^{+}	267,8	17,4	10,3	-0,01	0,04	0,03	0,04	-0,01	0,34	–	0,22	–	0,34	10,2	0,0	-9,5	9,8	-11,0	-3,0	-6,9
4-*H*-V^{+}	246,4	17,7	11,0	-0,02	-0,3	0,14	-0,15	0,16	0,35	–	0,22	0,32	–	-2,3	15,0	0,0	1,2	-11,0	-3,8	-6,2
5-*H*-V^{+}	275,2	19,3	11,3	0,00	0,12	0,02	0,01	0,14	0,34	–	0,18	–	–	35,2	-31,8	-32,9	-23,1	17,4	-9,1	-8,5
1,5-V$^{+\cdot}$	116,0	10,7	9,9	-0,16	-0,27	0,11	-0,19	0,07	0,20	0,24	–	–	–	-19,3	-7,5	-11,0	-15,0	6,9	–	2,3
3,5-V$^{+\cdot}$	152,2	9,7	8,0	-0,06	-0,11	-0,12	-0,12	-0,06	0,24	–	–	–	0,24	4,5	-12,7	-16,2	2,9	-16,5	–	-3,8
4,5-V$^{+\cdot}$	116,4	10,1	9,4	-0,03	-0,25	-0,02	-0,21	-0,01	0,27	–	–	0,25	–	-6,8	15,0	-6,2	-11,0	-15,1	–	-2,3

*Enthalpy of formation, ΔH_f, kcal/mole.

†Ionization potential, I_f, eV.

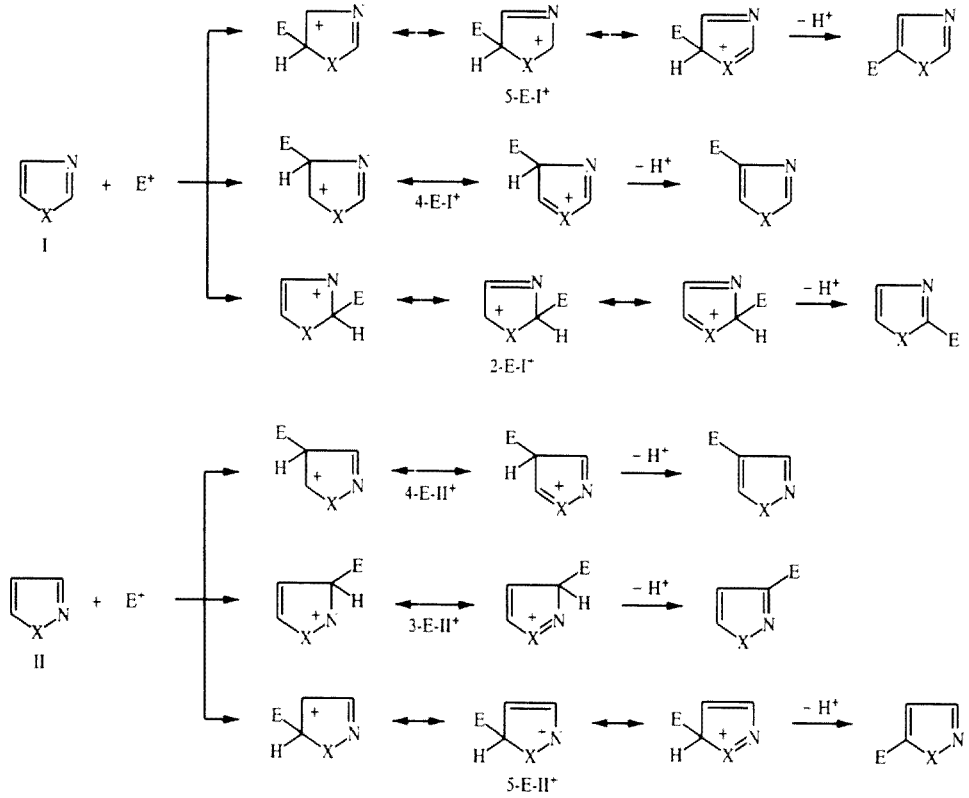
‡Difference of LUMO and HOMO energies, $\Delta E_{f\to v}$, eV.

as great as 6-8 orders. In a more highly acidic medium (in nitration), these same 1,2-azoles are substantially less reactive than not only thiophene but also benzene, approaching the activity of the deactivated acetophenone. Such differences can be explained on the basis that at $H_0 = -6.6$ (75% H_2SO_4), the substrates are almost completely protonated, and the true concentration of free base is very low. If the conjugate acid is subjected to nitration, the reaction rate is still lower by several more orders, such that the protonated forms resemble nitrobenzene in activity.

Of course, the evaluations that have been made are to some degree arbitrary, since they are not based on direct measurements, but rather on results of extrapolation and recalculation; this situation is completely unavoidable in comparing compounds that differ so greatly in reactivity. This circumstance also provides an explanation for the evident incompleteness of the above discussion. For example, in the case of isothiazole derivatives, data are available on nitration of both the free base and the protonated form; but for stronger bases such as pyrazole and imidazole, information is presented on the nitration of only the conjugate acids: Within those limits of acidity of the medium in which the nitration was performed, these compounds are almost completely protonated. In any event, the data that we have examined are extremely important in terms of estimating reactivities of both free bases and conjugate acids in electrophilic substitution.

ORIENTATION RULES AND REACTION CONDITIONS IN ELECTROPHILIC SUBSTITUTION OF AZOLES THROUGH ADDITION-ABSTRACTION MECHANISM

Experimental determinations of the basic relationships in the directionality of electrophilic substitution of azoles are not at all infrequently hindered by limited availability of the first members of the series, so that conclusions on orientation must be drawn on the basis of comparisons of the behavior of various derivatives; owing to the low activities of many azoles in electrophilic substitution reactions, derivatives with activating substituents are most commonly used. Moreover, the evaluation of experimental results is complicated by the possibility of occurrence of reactions through nontraditional mechanisms, including the formation of anions as a result of deprotonation of the nitrogen atom (for heterocycles with an unsubstituted "pyrrole" nitrogen) or of a carbon atom (primarily $C_{(2)}$ in 1,3-azoles). At the same time, when these limitations are taken into account, most of the experimental data for 1,2- and 1,3-azoles are in good agreement with purely qualitative examination of the effect of the heteroatom within the framework of the traditional addition-abstraction mechanism with the intermediate formation of a cationic σ-complex.



The specific rules of orientation in the azole series are determined by the presence of heteroatoms of two types in the azole molecules. A reaction is directed preferentially to that position of the heterocycle that is the least deactivated by the "pyridine" nitrogen atom (the β-position relative to N_{pyrid}). This is especially evident for the 1,2-azoles, in which there is an uncoordinated orientation of the "pyridine" and "pyrrole" heteroatoms, with the electrophile entering primarily at position 4. In the case of the 1,3-azoles, the least deactivated position coincides with position 5, which is the most activated by the "pyrrole" heteroatom.

A more detailed examination of the cationic σ-complexes that are formed by attack at various positions of the azoles [4] (see p. 8) shows that for reactions proceeding by an addition-abstraction mechanism through cationic σ-complexes, owing to the contribution of resonance structures with a bivalent, positively charged nitrogen atom, the formation of 2-derivatives is particularly favorable in the case of the 1,3-azoles, and the formation of 3- and 5-derivatives in the case of the 1,2-azoles. Thus, in the reactions that have been mentioned, the activities of the individual positions vary for the 1,3-azoles in the order 5 > 4 >> 2, and for the 1,2-azoles in the order 4 >> 3 $\approx$ 5.

The above qualitative evaluation of orientation rules is supported by results of quantum-chemical calculations of the corresponding σ-complexes and products of N-protonation (Tables 2 and 3). The preferential substitution at position 5 in the 1,3-azoles and at position 4 in the 1,2-azoles is consistent with the lowest energy of formation of the corresponding σ-complexes in comparison with the energy of formation of σ-complexes with proton attack at other positions that are capable of substitution. Also consistent with such a direction of electrophilic substitution is the charge distribution in the 1,2-azoles [highest negative charge on the $C_{(4)}$ atom] and in part (for thiazole) in the 1,3-azoles [negative charge on the $C_{(5)}$ atom]. These rankings of relative activities of the different positions are in accord with experimental data for the 1,3- and 1,2-azoles that will be examined below. Let us also note that, judging from the values of the change in strength of the chemical bond i_{AB}, the formal distribution of simple and double bonds in the σ-complexes is most adequately reflected by resonance structures with a positively charged double-bonded heteroatom (strengthening of the 1–2 and 3–4 bonds with a simultaneous weakening of the 1–5, 2–3, and 4–5 bonds in 5-H-I^+ ions; strengthening of the 1–5 bonds and weakening of the 3–4 and 4–5 bonds in 4-H-II^+ ions).

Entry into electrophilic substitution reactions is more difficult for azoles with three or four heteroatoms. The structure of these heterocycles is such that any free position in their molecules that is the least deactivated by one of the "pyridine" nitrogen atoms is simultaneously an α- or γ-position relative to one or more of the other N_{pyrid} atoms. Clearly, reactions of these compounds through the traditional mechanism of electrophilic substitution are quite improbable; and conversely, conversions through ylides or azolate anions are more probable. Let us note that the available experimental results are confined almost entirely to the most active of these compounds - the triazoles and tetrazoles.

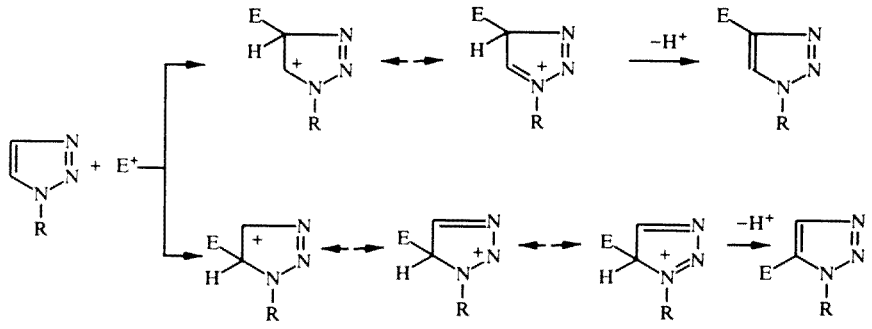
Results from quantum-chemical calculations for 1,3,4-oxadiazole (III, X = O), 1,3,4-thiadiazole (III, X = S), and 4H-1,2,4-triazole (III, X = NH) are presented in Table 4. Data from calculations for 1H-tetrazole (IV) and 2H-tetrazole (V) are presented in Table 5. For greater clarity, the values of the charges on the atoms in all cases are listed in an order corresponding to that adopted for the 1,2- and 1,3-azoles, such that the 4-N "pyrrole" atom of 4H-1,2,4-triazole and the 2-N "pyrrole" atom of 2H-tetrazole are placed in the same column with the 1-N atom of systems III and IV (X = O, S), and the 5-C atom of 1-H-tetrazole is placed with the 2-C atom of the diazoles. For the 5-C atom of 2H-tetrazole, analogy with the 3-C atom of the 1,2-azoles is clearly manifested.

III

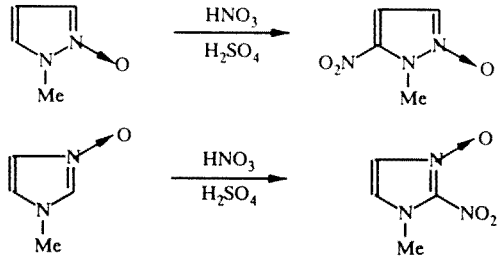
IV

V

As a consequence of the tautomerism exhibited by triazoles and tetrazoles with no substituent on the "pyrrole" nitrogen atom, and also in the case of the tetrazoles as a consequence of the presence of only one carbon atom in the ring, any discussion of orientation rules (for electrophilic substitution on ring carbon atoms) will be meaningful only for N-substituted triazoles. In particular, the fact that the most active position in 1-alkyl-1,2,3-triazoles is not position 5 but rather position 4 [41] can be shown to be incomprehensible; however, an examination of the corresponding σ-complexes points out the unfavorability of attack at position 5 as a consequence of the contribution of a resonance structure with a bivalent, positively charged nitrogen atom:



Conversion of azoles to N-oxides, the same as in the azine series, facilitates electrophilic substitution and may increase its selectivity. Thus, bromination of 2-methyl-1,2,3-triazole requires the use of iron as a catalyst, and the reaction will not stop at the monobromo derivative [42]. The corresponding N-oxide is brominated smoothly to the 5-bromo derivative at room temperature, and even heating for several hours at 60°C fails to introduce any bromine at position 4 [43]. The directionality of electrophilic substitution is also changed, as can be illustrated in the example of derivatives of pyrazole and imidazole [11, 44]:



In concluding our examination of the directionality of electrophilic substitution, let us note that for all of the azoles, the most highly preferred site of attack by an electrophile (or at least, by a proton) is a "pyridine" nitrogen atom; such N-protonation, which deactivates the substrate with respect to subsequent addition of an electrophile, does not change the preferred orientation that is characteristic for the neutral azole molecule (this can be seen by examining the corresponding resonance structures and charge distributions in the azolium ions). Here it is important to emphasize that along with formal reversibility of electrophilic attack at either N or C atoms, the results of the reverse reaction are basically different: The sole product from abstraction of the electrophile from a "pyridine" nitrogen atom is the original neutral molecule, whereas the abstraction of an electrophilic particle from a geminal site of a cationic σ-complex may yield both the original molecule (with abstraction of E^+) and a product of substitution (with deprotonation), the latter direction being practically irreversible.

One of the most important conclusions that follows from the data presented above is that the azoles, if they are not acting in the protonated form, should not behave in electrophilic substitution reactions as analogs of pyridine, but rather should resemble activated five-membered heterocycles with a single heteroatom. The importance of the deactivating effect of the "pyridine" nitrogen atom should not be exaggerated: At least as great an additional deactivation is determined, as we have seen, by protonation of the substrate under the conditions of reaction. Unfortunately, workers in the field of research on azoles have by no means always taken these factors into account. In attempting to achieve success, researchers have very frequently resorted to increasing the severity of the reaction conditions, in particular by increasing the acidity of the medium or increasing the quantity of a catalyst that is capable of forming a deactivated complex with the medium. Meanwhile, in many cases the use of severe reaction conditions is completely unjustified; in contrast, if protonation at the "pyridine" nitrogen atom is excluded, various substituents can be introduced into the azole molecules under mild conditions [4]. Despite the fact that these conclusions were justified and published more than 10 years ago, we find that even in recently appearing reviews devoted to the chemistry of oxazole [45] and the synthesis of nitro derivatives of triazoles [46], the influence of the acidity of the medium on electrophilic substitution reactions of the azoles has been completely ignored. Only in a review on the synthesis of nitroazoles [47] is a clear distinction made between those reaction conditions that bring about protonation of the substrate and those conditions that do not cause protonation.

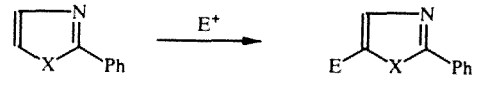
A number of electrophilic substitution reactions of 1,2- and 1,3-azoles are known to proceed under extremely mild conditions, similar to those used for highly active π-excessive five-membered heterocycles with a single heteroatom. This is

true not only for imidazoles and pyrazoles, but also for derivatives of other azoles. For example, thiazole [48], 4-methyl-2-phenylthiazole [49], and phenyloxazoles [50] are readily mercurated by the action of mercury acetate, with all free positions of the heterocycle being substituted. Methyl-phenyl derivatives of oxazole and thiazole are brominated without catalyst in benzene or chloroform under conditions that are in no way different from those in the bromination of their imidazole analog [51].

Bromination (by bromine in the presence of pyridine) and nitration (by nitric acid in acetic acid) have been reported for a number of 4-aryl-2-chlorothiazoles, which are converted with high yields to the corresponding 5-substituted compounds [52]. In the action of bromine in carbon disulfide on 2-(p-acetylaminophenyl)-4-methyloxazole, the bromine atom enters at position 5 of the heterocycle, and the benzene ring is not involved [53]. Bromination (in acetic acid) of 2-aryl-4-chloromethyloxazoles [54] and 2-aryl-4-chloromethylthiazoles [55] is directed to position 5 of the heterocycle. If the bromination is performed in sulfuric acid in the presence of silver sulfate, i.e., under the conditions used for deactivated systems, a mixture of products is formed, containing bromine in the thiazole ring, benzene ring, or both rings [55].

The nitration of 2-(p-tolyl)-4-chloromethylthiazole by nitric acid in acetic anhydride gives the 5-nitro derivative, whereas nitration in sulfuric acid leads to the formation of products of nitration in the benzene ring [55]. Difficulties in obtaining nitrooxazoles and the relative accessibility of acetoxymercuroxazoles and bromooxazoles were responsible for the development of a method for the synthesis of nitrooxazoles [56] based on conversion of bromo and iodo derivatives of oxazoles (the latter are obtained through acetoxymercuro derivatives) to nitrooxazoles under the action of nitrogen tetroxide. Up to quite recently, the only known case of direct nitration in the oxazole ring has been the conversion of 2-dimethylamino-4-phenyloxazole, activated by the substituent in position 2, as a result of which the nitro group enters into both the benzene ring and the oxazole ring [57].

As we have shown, 2-phenyloxazole [58] and 2-phenylthiazole [59] are smoothly brominated by bromine in benzene solution, and are nitrated by N-nitropicolinium tetrafluorobromate in acetonitrile or by nitric acid in acetic anhydride; and 2-phenyloxazole is even formylated in the Vilsmeier reaction, with all of these reactions being directed to position 5 of the heterocycle.



X = O, S, E = Br, NO_2; X = O, E = CHO

It is interesting to note that even 2-(2-thienyl)oxazole is formylated exclusively in position 5 of the oxazole ring; only 2-(2-furyl)oxazole gives a mixture of products of formylation in the furan and oxazole rings [60]. In view of the results obtained in competitive nitration [59] and also the fact that 2-phenylthiazole, in contrast to 2-phenyloxazole, does not undergo Vilsmeier formylation, we can conclude that the oxazole ring is more active than the thiazole ring in electrophilic substitution reactions.

When the reactions are performed in sulfuric acid, i.e., under conditions of protonation of the heterocycles at the nitrogen atom, the substituents (bromine or nitro group) enter the benzene ring [58, 59]. Here, 2-phenylthiazole proves to be more active than 2-phenyloxazole [59]; but in this case we are comparing not the activities of the heterocycles, but rather the deactivating effects of the protonated oxazole and thiazole rings on the benzene ring [61]. Analogous effects have been reported for 1-phenylpyrazole, which in sulfuric acid is nitrated on the benzene ring [62] but in acetic anhydride on the heteroring [63, 64].

In examining the effect of protonation on the reactivity of substituted azoles, it is important that the most active positions of the heterocycle (position 5 for the 1,3-azoles and position 4 for the 1,2-azoles) must be free. Otherwise, the influence of protonation may not be manifested clearly enough, or it may not show up at all. Thus, the nitration of 1-methyl-4-phenylpyrazole in sulfuric acid, as should be expected, is directed to the benzene ring; but nitration in acetic anhydride yields a complex mixture of products, one of which is the 3-nitro derivative [65]. In the case of 1-methyl-4-(2-thienyl)pyrazole under any conditions of nitration or bromination, the electrophile enters almost exclusively at the thiophene ring, not at the pyrazole ring [66]. An interesting system in this aspect is 4-(2-thienyl)thiazole, in which position 5 of the thiazole ring is free and the thiophene ring is not deactivated as much as it might be if it were in position 2 of the thiazole ring. Bromination of 4-(2-thienyl)thiazole in a neutral medium by bromine or N-bromosuccinimide is directed to position 5 of the thiophene ring; but in the case of 2-amino- or 2-acetylamino-4-(2-thienyl)thiazole, the bromination is directed to position 5 of the thiazole ring [67].

Any comparison of the reactivities of imidazole and pyrazole derivatives is hindered by the fact that the imidazoles are far stronger bases than the pyrazoles. Thus, imidazole, in nitration by a mixture of nitric and sulfuric acids, always enters

into reaction in the form of the cation, while pyrazole enters as the cation only with sulfuric acid concentrations above 90% [68]. Pyrazoles, thanks to their high activity and moderate base strength, can even be alkylated successfully through the Friedel–Crafts reaction. Under standard conditions, which require an equimolar quantity of aluminum chloride, it is bound with the substrate as a deactivated complex. The reaction can be performed successfully in the presence of a catalytic quantity of sulfuric acid [69] or $AlCl_3$ (in this case, the reaction is performed in nitrobenzene) [70].

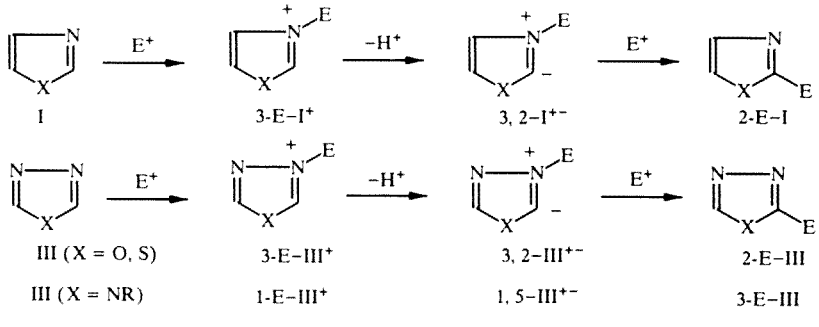
If the azole is a very weak base, it can enter into reaction in the form of a neutral molecule even if the reaction is performed in an acidic medium. Exactly this case was described in [71] for bromination of 3,5-diphenylisoxazole (pK_a = −3.24) in sulfuric acid, yielding the 4-bromo derivative. Conversion of the substrate to the corresponding N-methylisoxazolium ion results in formation of a product that is brominated on the benzene ring.

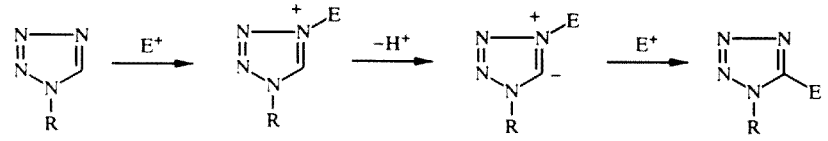
Of course, it is impossible to prevent the formation of an nν-complex with an active electrophile; but even here, the use of additional catalyst is not always necessary. For example, the sulfonation of imidazole and triazole by oleum at respective temperatures of 160° and 170-250°, leading to 5-sulfonic acids, was described many years ago [72, 73]. However, it has been found that this reaction can be accomplished under considerably milder conditions (refluxing with three equivalents of sulfur trioxide in 1,2-dichloroethane), whereas the use of equimolar quantities of reagents gives high yields of only the stable nν-complexes with a donor–acceptor bond between the SO_3 and the "pyridine" nitrogen atom, these complexes also being subject to sulfonation by the action of excess sulfur trioxide [74].

In concluding this section, let us note that under conditions such that complexation with protic or aprotic acids can be excluded, even triazoles and tetrazoles, which have several "pyridine" nitrogen atoms, can be subjected to electrophilic substitution. For these systems, with no criterion such as a different orientation for reactions proceeding through addition–abstraction or abstraction–addition, it is difficult to judge the mechanism; here, however, we can limit ourselves mainly to information on conversions of 1,2,3-triazoles, the structure of which is unfavorable for ylide formation. Chlorination, bromination, and iodination reactions of 1,2,3-triazole and its 1-, 2-, and 4-methyl derivatives under various conditions, directed at the carbon atoms of the heterocycle, were described in [42, 75]. 1-Benzyl-1,2,3-triazole is brominated on position 4 of the heterocycle [76]. Deactivation of the heterocycle for electrophilic attack in an acidic medium is evidenced by data on the substitution of certain aryltriazoles and aryltetrazoles on the benzene ring [77-82]. Let us note here that 2-(p-nitrophenyl)- and 2-(2,4,6-trinitrophenyl)-1,2,3-triazole are nitrated on the triazole ring [78, 82], while 1-(2,4,6-trinitrophenyl)-1,2,3-triazole does not undergo any further nitration [82]. Such a difference is probably related to the fact that this last compound is a stronger base (compare data on pK_a for 1- and 2-methyl-1,2,3-triazoles [83]) and will exist entirely in the protonated form under the conditions of reaction.

ELECTROPHILIC SUBSTITUTION OF AZOLES THROUGH YLIDE MECHANISM

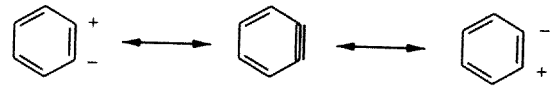
As can be seen from the calculated results presented in Tables 2-5, C-deprotonation of azolium cations with the formation of various bipolar ions is accompanied by a lowering of ΔH_f, with the most favorable of these ions being the ylide corresponding to abstraction of a proton from a carbon atom immediately adjacent to the N-cation center, especially if the other immediate neighbor of this C atom is a "pyrrole" heteroatom. Precisely this situation is realized in the formation of ylides of the type 3,2-I^{+-} from 1,3-azoles (Table 2); 3,2-III^{+-} from 1,3,4-oxadiazole and 1,3,4-thiadiazole, and 1,5-III^{+-} from 4-R-1,2,4-triazoles (Table 4); and 4,5-IV^{+-} from 1-R-tetrazoles (Table 5). This is fully consistent with the experimental data; and, as already mentioned, it qualitatively distinguishes reactions proceeding through an ylide mechanism from processes of electrophilic substitution that are accomplished through the traditional addition–abstraction mechanism.



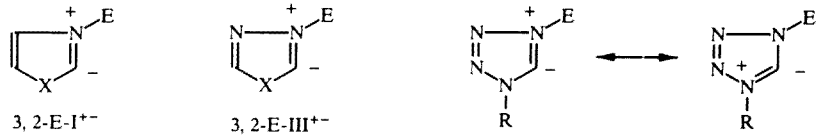


IV 4-E-IV$^+$ 4, 5-IV^{+-} 5-E-IV

As already mentioned, ylide substitution resembles reactions that proceed through an abstraction-addition mechanism. In this connection, it appears logical to compare the structure of the ylides formed by azoles with the bipolar resonance form of dehydrobenzene:



An examination of the data presented in Tables 2, 4, and 5 shows that the ylides under discussion are basically different from dehydrobenzene. First of all, the distribution of charges on the ring atoms is not in accord with that shown in the above formulas of the ylides: The carbon atoms located between two heteroatoms generally carry not a negative but a positive charge; and in turn, both of the neighboring heteroatoms are negatively charged. Only in the ylides formed by thiazole and 1,3,4-thiadiazole does the carbon atom in position 2 carry a negative charge and the sulfur atom a positive charge, apparently explained by the relatively low electronegativity of the sulfur atom. Here, the negative charge on the quaternized nitrogen atom (characteristic for the other ylides) remains the same, obviously as a consequence of transfer of electron density from the hydrogen atom bound to this nitrogen atom. It is particularly significant that the bond between the formally positive and negative centers of the ylides, as can be seen from the values of the index i_{AB}, is not at all strengthened but rather weakened in comparison with the original neutral molecule; i.e., not only does it fail to acquire triple-bond properties, but evidently it has an order below two. Thus, the structure of the ylides may be inadequately represented by the conventional resonance structures:



3, 2-E-I^{+-} 3, 2-E-III^{+-} 1, 5-E-III^{+-} 4, 5-IV^{+-}

On the whole, ylide substitution apparently requires lower activation energies in comparison with reactions proceeding through the traditional mechanism, since the ylide path does not include the generation of intermediate species with energies of formation as high as for cationic σ-complexes. This is illustrated in Fig. 2, where in the example of thiazole we have compared model processes of substitution at the preferred position 5 through a σ-complex (HetH → $HetH_2^+$ → HetH) and through an ylide at position 2 (HetH → $HetH_2^+$ → $HetH^{+-}$ → HetH). This sort of relationship, as can be seen from the data of Tables 2-5, is also valid for other azoles. The formation of ylides from the corresponding azolium cations, the relative probability of which can be estimated from the difference between the enthalpies of formation (kcal/mole) of the N-protonated forms and the ylides obtained from them, becomes easier as the number of heteroatoms in the azole molecule increases (the appearance of each additional "pyridine" nitrogen atom in the azole molecule makes the ylide formation more favorable by 11-15 kcal/mole); and ylide formation also becomes easier upon going from N- to S- to O-heterocycle (dependence on the nature of the "pyrrole" atom, according to data for diazoles and triazoles):

oxazole (139.8) - imidazole (123.9) - thiazole (123.2)

1,3,4-oxadiazole (152.4) - 4H-1,2,4-triazole (136.0) - 1,3,4-thiadiazole (134.1) - 1H-tetrazole (151.1)

The basic features of the ylide mechanism were formulated in a study of isotope exchange of hydrogen in a number of azoles. Interest in such conversions is related to an idea expressed by Breslow [84] regarding the role of thiazolium ylides in metabolism (decarboxylation of pyruvic acid with the participation of thiamine). After the publication of [84], in which thiazolium salts were shown to be capable of hydrogen atom exchange in position 2 under very mild conditions, a number of

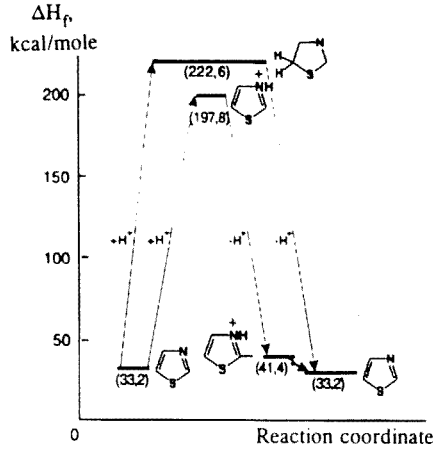
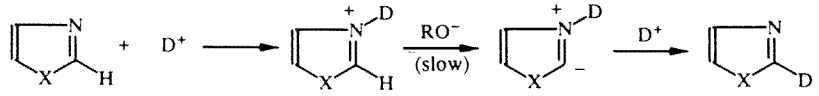


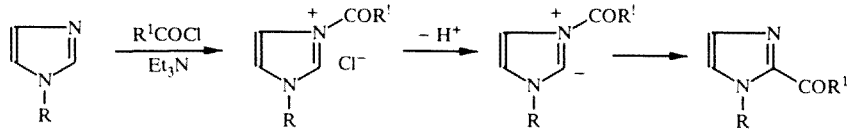
Fig. 2. Schematic comparison of model processes of electrophilic substitution of thiazole through a cationic σ-complex or through an ylide. Values of enthalpy of formation, in kcal/mole, are indicated in parentheses.

reports were published on isotope exchange of hydrogen in various 1,3-azoles and azolium salts [85-93]. For the 1,3-azoles, over a wide range of pH, the proton in position 2 proved to be the most mobile — the proton that should be the least reactive if the reaction were to proceed through the classical addition–abstraction mechanism. It should be noted particularly that when the change is made from an azole to the corresponding azolium salt, a sharp increase of exchange (by several orders) was observed [85], and the exchange rate for the 1,3-azolium salts proved to be several orders higher than for the isomeric 1,2-azolium salts [89]. These results were explained by the intermediate formation of azolium ylides, facilitated by the presence of the adjacent "pyrrole" type heteroatom [88].



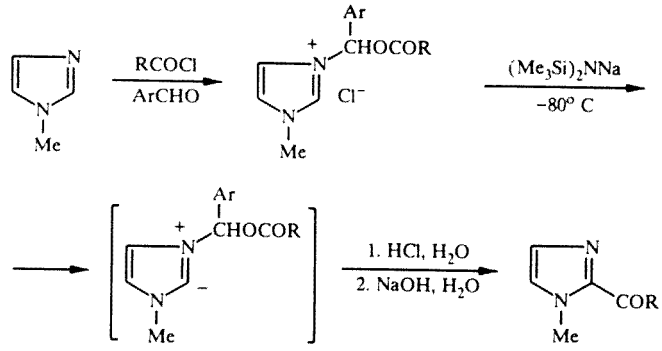
It is not difficult to see that these data are fully consistent with the results of quantum-chemical calculations dealing with the ylide mechanism that were discussed above. In recent years, the importance of this mechanism has become more and more obvious, not only for hydrogen isotope exchange, but also for other electrophilic substitution reactions in the azole series.

N-Substituted imidazoles, in the presence of triethylamine, are very readily acylated at position 2. It is believed that the reaction proceeds through an ylide [94].



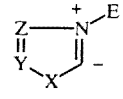
Also acylated under similar conditions are thiazole [95], 4,5-dimethylthiazole, 1-methoxymethyl-1,2,4-triazole, 2-phenyl-1,3,4-oxadiazole, and also benzothiazole and benzoxazole [96]. It can be assumed that ylides are also formed in the process of C-acylation of 1,2,4-triazoles, which proceeds at a high temperature in the absence of any aliphatic tertiary amine [97].

Let us also note an unusual method for the acylation of 1-methylimidazole, which includes the preparation of the azolium salt, its conversion to an ylide, and rearrangement of the ylide [98]. A special feature of this reaction is that it does not require high CH-acidity of the substrate (the deprotonation is effected by the action of a strong base); but the reaction is apparently confined to those substrates that are sufficiently strong as bases to form onium salts of the type shown below (pyridine and isoquinoline also undergo this conversion).



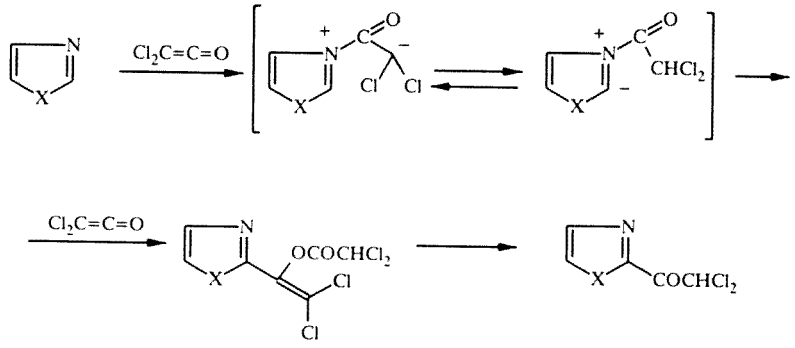
In all of the cases that have been mentioned, the acyl enters at a position of the heterocycle located between "pyridine" and "pyrrole" heteroatoms, as is characteristic for electrophilic substitution through the ylide mechanism. This sort of directionality is also observed for a number of other electrophilic substitution reactions of azoles. For example, in all of the described cases of direct bromination of unsubstituted thiazole, including those taking place under mild conditions (with the action of N-bromosuccinimide [99, 100] or the action of bromine in the presence of a catalytic quantity of $AlCl_3$ [100]), the sole monobromide is 2-bromothiazole. 1-Benzyl- and 1-isopropyl-1,2,4 triazoles are brominated by N-bromosuccinimide at position 5 (also located between "pyridine" and "pyrrole" heteroatoms [101]). 1-Methyl- and 1-ethyltetrazoles are subjected to iodination under the action of iodine in an oxidizing system ($KMnO_4$–H_2SO_4) with the formation of 5-iodo-1R-tetrazoles, and 1,2-bis(1-tetrazolyl)ethane under these same conditions is converted to the 5,5′-diiodo derivative [102, 103].

1,2,4-Triazole and various 1-derivatives, under the action of formaldehyde or formalin, are subjected to hydroxymethylation at the same position 5 [101, 104]. 1-Substituted tetrazoles, when treated with dimethylamine and formalin, are smoothly aminomethylated [105, 106]. For 1-phenyltetrazole, acetoxymercuration at position 5 of the heterocycle has been described [107]. By direct mercuration of 1-R-tetrazoles (R = t-Bu, Ph, allyl, vinyl) by the action of $HgBr_2$ in alcohol in the presence of potassium hydroxide, the corresponding 1,1′-di-R-substituted derivatives of bis(5-tetrazolyl)mercury have been obtained [103, 108]. In all of the cases under consideration, the structure of the substrate favors the intermediate formation of ylides of the type

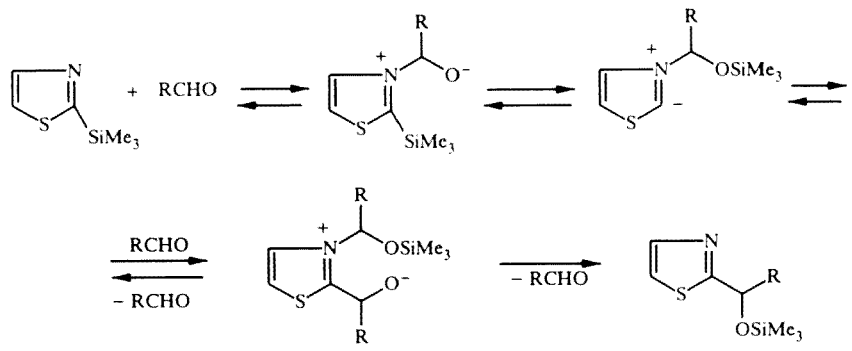


X = NR, O, S; Y and Z = CH, CR, N; E – is an electrophile

Interesting data on the possibility of realizing the ylide mechanism in the action of uncharged electrophiles on azoles were obtained by Dondoni et al. [109], who had described a number of conversions of thiazoles [95, 110] and oxazoles [111] under the action of certain ketenes. It was suggested that the ketenes activate the substrate molecule as a result of intermediate formation of ylides, which then react with a second molecule of the ketene at $C_{(2)}$, after which the acyl group is transferred from N to O, and a 2-acylthiazole or 2-acyloxazole is formed:



A very promising approach developed by Dondoni is the use of 2-silyl derivatives [112-117] and to some extent 2-stannyl derivatives [113] of thiazoles and oxazoles in reactions with carbon electrophiles, proceeding through the formation of ylides. The essence of this mechanism can be illustrated in the example of the reaction of 2-(trimethylsilyl)thiazole with aldehydes [112, 116]:



The oxazole and thiazole derivatives that have been obtained can be used successfully in the synthesis of various naturally occurring compounds, including carbohydrates [112-114]. There can be no doubt that new possibilities of ylide substitution will be revealed in the near future, since this mechanism, which uses both the basic and acidic properties of the azoles, offers a means for bringing into reaction compounds that are deactivated (in the traditional sense) and also a means for directing the entering substituent to a position that is the least active in conventional electrophilic substitution.

Summarizing the data presented in this review, we should point out that the possibility and probability of realizing one or another mechanism of electrophilic substitution in the azole series will depend first of all on the reaction conditions and the substrate structure. Thus, if the reaction is carried out in a strongly acidic medium (or in the presence of an equivalent or greater quantity of a Lewis acid), this will apparently prevent the formation of an ylide and increase the probability that the conversion will proceed through the traditional mechanism with the intermediate formation of a σ-complex. Of course, deactivation of the azole molecule that is bound into a complex with a protic or aprotic acid may make it impossible in practice to carry out the reaction. Electrophilic substitution through the addition–abstraction mechanism is undoubtedly highly probable if the position in the molecule for which proton abstraction may lead to ylide formation is occupied by some substituent. At the same time, if such a position, for example position 2 in 1,3-azoles, is free, the probability of realizing the ylide mechanism is extremely high (compare [100]).

REFERENCES

1. A. Albert, Heterocyclic Chemistry, Athlone Press, London (1959).
2. A. F. Pozharskii, Theoretical Principles of the Chemistry of Heterocycles [in Russian], Khimiya, Moscow (1985).
3. G. Marino, Adv. Heterocycl. Chem., **13**, 235 (1971).
4. L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 6, 749 (1986).
5. T. Clark, A Handbook of Computational Chemistry, Wiley, New York (1985).
6. N. D. Chuvylkin, G. M. Zhidomirov, and V. B. Kazansky, J. Catal., **38**, 214 (1975).
7. G. Marino, Khim. Geterotsikl. Soedin., No. 5, 579 (1973).
8. A. R. Katritzky and J. M. Lagowski, in: Comprehensive Heterocyclic Chemistry, Vol. 4, A. R. Katritzky and C. W. Rees (eds.), Pergamon Press, New York (1984), p. 50.
9. A. Albert, in: Physical Methods in Heterocyclic Chemistry, Vol. 1, A. R. Katritzky (ed.), Pergamon Press, New York (1963), p. 1.
10. A. Albert, in: Physical Methods in Heterocyclic Chemistry, Vol. 3, A. R. Katritzky (ed.), Pergamon Press, New York (1971), p. 1.
11. K. Schofield, M. R. Grimmett, and B. R. T. Keene, in: Heteroaromatic Nitrogen Compounds: The Azoles, Cambridge University Press, London (1976), pp. 60, 68, 281.
12. V. G. Andrianov, M. A. Shokhen, and A. V. Eremeev, Khim. Geterotsikl. Soedin., No. 4, 508 (1989).
13. V. A. Ostrovskii, G. I. Koldobskii, N. P. Shirokova, and V. S. Poplavskii, Khim. Geterotsikl. Soedin., No. 4, 559 (1981).
14. V. A. Ostrovskii, G. B. Erusalimskii, and M. B. Shcherbinin, Zh. Org. Khim., **29**, 1297 (1993).
15. V. A. Ostrovskii, G. B. Erusalimskii, and M. B. Shcherbinin, Zh. Org. Khim., **31**, 1422 (1995).

16. J. Catalan, M. Sanchez-Cabezudo, J. L. G. De Paz, and J. Elguero, J. Mol. Struct. (THEOCHEM), **166**, 415 (1988).
17. R. August, C. Davis, and R. Taylor, J. Chem. Soc., Perkin Trans. 2, No. 8, 1265 (1986).
18. D. S. Noyce, J. A. Virgilio, and B. Bartman, J. Org. Chem., **38**, 2657 (1973).
19. D. S. Noyce and S. A. Fike, J. Org. Chem., **38**, 3316 (1973).
20. D. S. Noyce and G. T. Stowe, J. Org. Chem., **38**, 3762 (1973).
21. D. S. Noyce and B. B. Sandel, J. Org. Chem., **40**, 3762 (1975).
22. D. S. Noyce and G. V. Kaiser, J. Org. Chem., **34**, 1008 (1969).
23. D. S. Noyce and H. J. Pavez, J. Org. Chem., **37**, 2620 (1972).
24. D. S. Noyce and H. J. Pavez, J. Org. Chem., **37**, 2623 (1972).
25. D. S. Noyce, C. A. Lipinski, and R. W. Nichols, J. Org. Chem., **37**, 2615 (1972).
26. D. S. Noyce, C. A. Lipinski, and G. M. London, J. Org. Chem., **35**, 1718 (1970).
27. D. S. Noyce and B. B. Sandel, J. Org. Chem., **41**, 3640 (1976).
28. E. A. Hill, H. L. Gross, M. Stasiewicz, and M. Manion, J. Am. Chem. Soc., **91**, 7381 (1969).
29. T. J. Broxton, G. L. Butt, L. W. Deady, S. H. Toh, R. D. Topsom, A. Fischer, and M. W. Morgan, Can. J. Chem., **51**, 1620 (1973).
30. C. T. Bruce, A. R. Cooksey, and K. J. Morgan, J. Chem. Soc., Perkin Trans. 2, No. 6, 551 (1975).
31. J. Ridd, in: Physical Methods in Heterocyclic Chemistry, Vol. 1, A. R. Katritzky (ed.), Pergamon Press, Oxford (1963), p. 109.
32. A. R. Katritzky and C. D. Johnson, Angew. Chem., **79**, 629 (1967).
33. S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, J. Chem. Soc., Perkin Trans. 2, No. 4, 399 (1974).
34. A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. 2, No. 7, 1065 (1973).
35. S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. 2, No. 12, 1675 (1973).
36. A. R. Katritzky, B. Terem, E. V. Scriver, S. Clementi, and H. O. Tarhan, J. Chem. Soc., Perkin Trans. 2, No. 14, 1600 (1975).
37. A. R. Katritzky, S. Clementi, and H. O. Tarhan, J. Chem. Soc., Perkin Trans. 2, No. 14, 1624 (1975).
38. A. R. Katritzky, C. Ogretir, H. O. Tarhan, H. M. Dow, and J. V. Metzger, J. Chem. Soc., Perkin Trans. 2, No. 14, 1614 (1975).
39. A. R. Katritzky, H. O. Tarhan, and B. Terem, J. Chem. Soc., Perkin Trans. 2, No. 14, 1620 (1975).
40. A. R. Katritzky, S. Clementi, C. Milletti, and G. V. Sebastiani, J. Chem. Soc., Perkin Trans. 2, No. 6, 613 (1978).
41. K. T. Finley, in: Triazoles: 1,2,3, J.A. Montgomery (ed.), Wiley, New York (1980).
42. R. Hüttel and G. Welzel, Liebigs Ann. Chem., **593**, 207 (1955),
43. M. Bergtrup and H. P. Nytoft, Acta Chem. Scand. B, **40**, 262 (1986).
44. I. J. Fergusson, M. R. Grimmett, and K. Schofield, Tetrahedron Lett., No. 27, 2771 (1972).
45. A. Hassner and B. Fischer, Heterocycles, **35**, 1441 (1993).
46. Yuxiang Ou, Boren Chen, Jiarong Li, Shuan Dong, Jianjin Li, and Huiping Jia, Heterocycles, **38**, 1651 (1994).
47. L. I. Larina, V. A. Lopyrev, and M. G. Voronkov, Zh. Org. Khim., **30**, 1081 (1994).
48. G. Travagli, Gazz. Chim. Ital., **85**, 926 (1955).
49. S. L. Gusinskaya, Khim. Geterotsikl. Soedin., No. 3, 345 (1970).
50. O. P. Shvaika and G. P. Klimisha, Khim. Geterotsikl. Soedin., No. 1, 19 (1966).
51. R. Gompper and M. Rühle, Liebigs Ann. Chem., **626**, 83 (1959).
52. H. S. Suri, G. N. Sharma, and K. S. Narang, J. Indian Chem. Soc., **45**, 409 (1968).
53. N. Saito, T. Kurihara, K. Yamanaka, S. Tsuruta, and S. Yasuda, J. Pharm. Soc. Jpn., **88**, 1289 (1968).
54. I. Simiti and E. Chindris, Arch. Pharm., **305**, 509 (1972).
55. I. Simita and M. Farkas, Acta Chim. Hung., **83**, 381 (1974).
56. W. J. Hammar and M. A. Rustad, J. Heterocycl. Chem., **18**, 885 (1981).
57. R. Gompper and O. Christmann, Chem. Ber., **92**, 1944 (1959).
58. L. I. Belen'kii and M. A. Cheskis, Khim. Geterotsikl. Soedin., No. 7, 881 (1984).
59. L. I. Belen'kii, G. P. Gromova, M. A. Cheskis, and Ya. L. Gol'dfarb, Chem. Scripta, **25**, 295 (1985).

60. L. I. Belen'kii, M. A. Cheskis, V. P. Zvolinskii, and A. E. Obukhov, Khim. Geterotsikl. Soedin., No. 6, 826 (1986).
61. L. I. Belen'kii, V. S. Bogdanov, I. A. Abronin, G. P. Gromova, M. A. Cheskis, and R. Z. Zakharyan, Chem. Scripta, **25**, 266 (1985).
62. M. A. Khan, B. M. Lynch, and Y.-Y. Hung, Can. J. Chem., **41**, 1540 (1963).
63. B. M. Lynch and Y.-Y. Hung, Can. J. Chem., **42**, 1605 (1964).
64. M. R. Grimmett, S. R. Hartshorn, K. Schofield, and J. B. Weston, J. Chem. Soc., Perkin Trans. 2, No. 11, 1654 (1972).
65. Cohen-Fernandez [sic] and C. L. Habraken, Rec. Trav. Chim., **91**, 1185 (1972).
66. S. Lijefors and S. Gronowitz, Chem. Scripta, **15**, 102 (1980).
67. V. A. Smirnov, A. V. Zimichev, G. E. Lyzhova, and A. E. Lipkin, Khim. Geterotsikl. Soedin., No. 1, 35 (1982).
68. M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, J. Chem. Soc., No. 2, 1051 (1965).
69. I. I. Grandberg, S. V. Tabak, N. I. Bobrova, A. N. Kost, and A. K. Vasina, Khim. Geterotsikl. Soedin., No. 3, 407 (1965).
70. K. Kano, D. Scarpetti, J. C. Warker, J.-P. Anselme, J. P. Springer, and B. H. Arison, Can. J. Chem., **64**, 2211 (1986).
71. S. D. Sokolov and I. M. Yudintseva, Zh. Org. Khim., **7**, 1765 (1971).
72. F. L. Pyman and L. A. Ravall, J. Chem. Soc., **117**, 1429 (1920).
73. H. Erlenmeyer and U. Kiefer, Helv. Chim. Acta, **28**, 985 (1945).
74. T. P. Bochkareva, B. V. Passet, K. R. Popov, N. V. Platonova, and T. I. Koval'chuk, Khim. Geterotsikl. Soedin., No. 10, 1353 (1987).
75. R. Hüttel and A. Gebhardt, Liebigs Ann. Chem., **558**, 43 (1947).
76. M. Bergtrup, Acta Chem. Scand., **25**, 249 (1971).
77. B. M. Lynch, Can. J. Chem., **41**, 2380 (1963).
78. B. M. Lynch and T. Chan, Can. J. Chem., **41**, 274 (1963).
79. H. El-Khaden, H. A. R. Mansour, and M. H. Meshreki, J. Chem. Soc. C, No. 11, 1329 (1968).
80. E. Lippmann and A. Könnecke, Z. Chem., **15**, 226 (1975).
81. J. L. Riebsomer, J. Org. Chem., **13**, 815 (1948).
82. P. N. Neuman, J. Heterocycl. Chem., **8**, 51 (1971).
83. F. R. Benson, The High Nitrogen Compounds, Wiley, New York (1984), p. 349.
84. R. Breslow, J. Am. Chem. Soc., **79**, 1762 (1957).
85. H. A. Staab, H.-Th. Wu, A. Mannschreck, and G. Schwalbach, Tetrahedron Lett., No. 15, 845 (1964).
86. P. Haake, L. P. Bausher, and W. B. Miller, J. Am. Chem. Soc., **91**, 1113 (1969).
87. J. D. Vaughan, Z. Mughrabi, and E. C. Wu, J. Org. Chem., **35**, 1141 (1970).
88. R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, Tetrahedron, **26**, 685 (1970).
89. R. A. Olofson, W. R. Thompson, and J. S. Michelman, J. Am. Chem. Soc., **86**, 1865 (1964).
90. R. A. Olofson and J. W. Landesberg, J. Am. Chem. Soc., **88**, 4263 (1966).
91. E. C. Wu and J. D. Vaughan, J. Org. Chem., **35**, 1146 (1970).
92. H. Kohn, S. J. Bencovic, and R. A. Olofson, J. Am. Chem. Soc., **94**, 5759 (1972).
93. R. Venkatasubramanian and S. L. N. G. Krichnamachari, Indian J. Chem., Sect. B, **29**, 562 (1990).
94. E. Regel and K.-H. Büchel, Liebigs Ann. Chem., No. 1, 145 (1977).
95. A. Medici, G. Fantin, M. Foragnolo, P. Pedrini, A. Dondoni, and G. D. Andreetti, J. Org. Chem., **49**, 590 (1984).
96. E. Regel, Liebigs Ann. Chem., No. 1, 159 (1977).
97. R. Fusco, F. D'Addo, and A. Masserini, Gazz. Chim. Ital., **96**, 1084 (1966).
98. E. Anders, H.-C. Boldt, R. Fuchs, and T. Gassner, Tetrahedron Lett., **25**, 1715 (1984).
99. B. M. Mikhailov and V. P. Bronovitskaya, Zh. Obshch. Khim., **27**, 726 (1957).
100. Ya. L. Gol'dfarb, G. P. Gromova, and L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 6, 837 (1986).
101. F. Dallacker and K. Minn, Chem.-Ztg., **110**, 275 (1986).
102. P. N. Gaponik, Yu. V. Grigor'ev, and A. O. Koren', Khim. Geterotsikl. Soedin., No. 12, 1699 (1988).
103. Yu. V. Grigor'ev and P. N. Gaponik, Izv. Akad. Nauk Belarusi, Ser. Khim. Nauk, No. 1, 73 (1992).
104. R. G. Jones and C. Ainsworth, J. Am. Chem. Soc., **77**, 1538 (1955).
105. V. P. Karavai and P. N. Gaponik, Khim. Geterotsikl. Soedin., No. 4, 564 (1985).

106. V. P. Karavai and P. N. Gaponik, Khim. Geterotsikl. Soedin., No. 1, 66 (1991).
107. R. Stolle and F. Henke-Stark, J. Prakt. Chem., **124**, 261 (1930).
108. P. N. Gaponik, Yu. V. Grigor'ev, and V. P. Karavai, Metalloorg. Khim., **1**, 846 (1988).
109. A. Dondoni, Phosphorus Sulfur, **24**, 1 (1985).
110. A. Medici, M. Fogagnolo, P. Pedrini, and A. Dondoni, J. Org. Chem., **47**, 3844 (1982).
111. A. Dondoni, G. Fantin, M. Fogagnolo, A. Mastellari, A. Medici, and P. Pedrini, J. Org. Chem., **49**, 3478 (1984).
112. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, J. Org. Chem., **53**, 1748 (1988).
113. A. Dondoni, G. Fantin, M. Fogagnolo, A. Mastellari, A. Medici, E. Negrini, and P. Pedrini, Gazz. Chim. Ital., **118**, 211 (1988).
114. A. Dondoni, Bull. Soc. Chim. Belg., **101**, 433 (1992).
115. A. Dondoni, A. Marra, and D. Perrone, J. Org. Chem., **58**, 275 (1993).
116. A. Dondoni, A. W. Douglas, and J. Shinkai, J. Org. Chem., **58**, 3196 (1988).
117. A. Dondoni, A. Marra, and P. Merino, J. Am. Chem. Soc., **116**, 3324 (1994).