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The Structure-Reactivity-Chemoselectivity Relationship on the Reactions of 1-Unsubstituted Tautomeric 2-Pyridones with Benzyne

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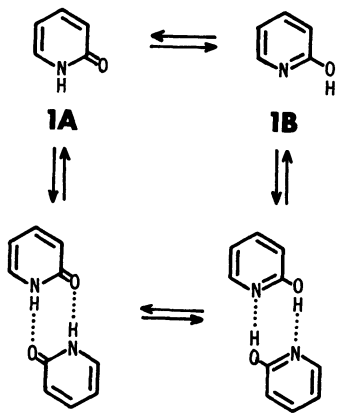
The reactions of 2-pyridones with benzyne were investigated in order to gain some insight into the structure-reactivity-chemoselectivity relationship involved in the tautomeric systems. All reactions examined have resulted in the formation of Diels-Alder and Michael-type adducts. It has been shown that the Diels-Alder reactivities were well correlated with the HOMO energy levels of the 2-pyridone form and the yields of the Michael-type adduct were closely associated with the tautomeric equilibria. In summary, the chemoselectivities of 2-pyridones in the reaction with benzyne were largely affected by the tautomeric properties.

The tautomerism, 2-pyridone⇌2-pyridinol (**1a**), is one of the most frequently investigated tautomeric equilibria present in many heterocyclic systems. It has been well established experimentally and theoretically that there is no significant difference in the fundamental stabilities of the unimolecular state of the tautomers, **1A** and **1B**.[1] Most of 2-pyridone derivatives, however, are known to exist largely in the 2-pyridone form (**A**) as the self-associated dimer in the crystalline state[2] and in solution[3] due to the greater association ability of the 2-pyridone form (**A**), whereas derivatives bearing a 6-polar substituent exist predominantly in the 2-pyridinol form (**B**) in solution.[4]

A delicate balance of such tautomeric properties and/or aggregation forms in solution can be expected to exert an influence upon the chemical reactivity, and such reactions could provide some insight into the structure-reactivity-chemoselectivity relationship involved in the tautomeric systems. Thus, a study of the reaction of these compounds with benzyne will be interesting in connection with a variety of reactions, [*i. e.* Diels-Alder reaction and Michael-type addition].

However, in contrast to the substantial amount of experimental work on the Diels-Alder reaction of 1-substituted 2-pyridones with a variety of dienophiles in recent years,[6] similar reactions of 1-unsubstituted 2-pyrdiones have received only limited attention, and most of such reactions have been concerned only with the Michael-type addition to the oxygen and/or nitrogen atom.[6a,7] The only example of the formation of a Diels-Alder adduct to be found in the literature is the reaction with *N*-phenylmaleimides,[8] and the formation of Diels-Alder adduct with benzyne was not known prior to our preliminary publication.[9]



Scheme 1.

In view of these points of interest, we have studied the reactions of various substituted 2-pyridones with benzyne. In the present paper, we show that the product composition varied with the effect of the tautomeric properties exerted by a substituent, and discuss the structure-reactivity-chemoselectivity relationship observed in such reactions.

Experimental

Measurement of the Relative Diels-Alder Reactivity of 1-Methyl-2-pyridones (2) with Benzyne by Competitive Reactions. Two 2-pyridones (**2x**) and (**2y**) (0.001 mol of each) and isopentyl nitrite (0.53 g, 0.0045 mol) were dissolved in dry chloroform (80 ml). Then, anthranilic acid (0.38 g, 0.0028 mol) in a mixed solvent of acetone (20 ml) and dry chloroform (30 ml) was added dropwise to the solution over a period of 2 h under nitrogen bubbling at 70 °C. The whole was allowed to heat for an additional 2 h at 70 °C and the solvent evaporated under reduced pressure. The yields of the Diels-Alder adduct (**3x**) and (**3y**) were determined from the comparison of the integrated intensity of the peak between the product and the corresponding unreacted starting pyridones, respectively, in the ^{1}H NMR spectra of the reaction mixtures. None of the other product derived from 2-pyridones was observed. Based on the ^{1}H NMR inspection of authentic samples of the Diels-Alder adduct (**3**), the combination of two 2-pyridones (**2x**) and (**2y**) for the competitive reactions was selected so as to permit such a determination of the yield in the ^{1}H NMR spectrum of the reaction mixture. The yields(%) (Y(**3x**) and Y(**3y**)) in each set of competitive reactions are summarized in Table 1.

Reactions of 1-Unsubstituted 2-Pyridones (1) with Benzyne. The reactions were performed on 2-pyridones (**1a—j**, **1l—q**, and **1s—u**) in a similar manner as above. The Diels-Alder adduct (**4**), 2-phenoxypyridine (**5**), and 1-phenyl-2-pyridone (**6**) were isolated by chromatographic separation of the products on alumina in chloroform. The residue of each fraction was weighed after evaporation of the solvent.

Effects of Concentration on the Reactivity and Chemoselectivity. The procedures are essentially identical to those described above. For the reactions in 0.00625 mol dm^{-3} solution, each of 2-pyridones (**1h**), (**1i**), (**1m**), (**1n**), and

Table 1. Product yields in various pairs of competition reactions.

Pair of pyridones (2x) and (2y)	Yield/% Y(3x) and Y(3y)	Pair of pyridones (2x) and (2y)	Yield/% Y(3x) and Y(3y)
2a—2e	14—19	2d—2e	19—21
2a—2u	15—77	2e—2f	19—54
2b—2e	21—19	2e—2m	15—44
2b—2g	19—19	2i—2k	32—15
2b—2h	17—29	2i—2q	29—59
2b—2i	15—39	2i—2s	27—18
2b—2j	10—60	2i—2v	37—24
2b—2m	14—41	2j—2n	67—54
2b—2r	36—24	2k—2l	31—38
2b—2t	36— 9	2m—2n	47—67
2c—2i	10—34	2n—2o	55—73
2c—2k	24—38	2o—2p	79—85

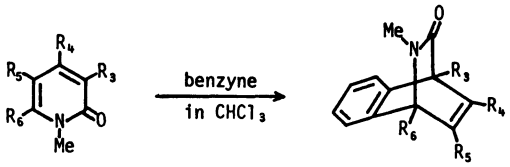
(**1o**) (0.004 mol of each) and isopentyl nitrite (1.06 g, 0.009 mol) in dry chloroform (640 ml) were treated with anthranilic acid (0.76 g, 0.0056 mol) in a mixed solvent of acetone (160 ml) and dry chloroform (320 ml). On a similar workup as above, the product yields of 2-phenoxypyridine (**5**), the Diels-Alder adduct (**4**) and the unreacted 2-pyridone (**1**) were determined from the integrated intensities of the peak characteristic of each compound in the ^{1}H NMR spectra except for **1o**. The crude mixture obtained from **1o** did not show the well defined ^{1}H NMR spectrum. The crude mixture of **1o**, therefore, was chromatographed on alumina in chloroform as an eluent and the product yield then determined from the isolated yield of each of the compounds (**4o**), (**5o**), and (**1o**). For the reactions in 0.1 mol dm^{-3} solution, each of 2-pyridones (**1h**), (**1i**), (**1m**), (**1n**), and (**1o**) (0.004 mol of each) and isopentyl nitrite (1.06 g, 0.009 mol) in dry chloroform (40 ml) were treated with anthranilic acid (0.76 g, 0.0056 mol) in a mixed solvent of acetone (10 ml) and dry chloroform (20 ml), and the product composition analyzed as above.

Molecular Orbital Calculations. The CNDO/2 calculations for methylated 2-pyridones and self-associated dimeric form of 2-pyridone and 2-pyridinol were described in a previous paper.[10] For the comparison of the relative energetics with the same level of approximation, the CNDO/2 calculations of benzyne were performed with the standard parametrizations.[11] The geometric parameters were taken from the *ab initio* (4-31G) study with geometry optimization for singlet benzyne.[12]

Results and Discussion

Substituent Effect on Diels-Alder Reactivity of 1-Methyl-2-pyridones with Benzyne. In order to evaluate the substituent effect on the Diels-Alder reactivity of the 2-pyridone tautomer, we have first studied the reactions of 1-methyl-2-pyridones (**2**) with benzyne to afford 1-methyl-5,6-benzo-2-azabarrelen-3(2*H*)-one derivatives (**3**), several members (**2a—e**) of which were initially studied under somewhat different conditions by Sheinin *et al.*[6a] (Scheme 2). The structural assignment and physicochemical properties of the products (**3**) will be published in a separate paper.[13]

The Diels-Alder reaction of **2** with benzyne is sensitive to the reaction conditions. In fact, the yields



2 **3**

a[14] : $R_3=R_4=R_5=R_6=H$
b[15] : $R_3=Me$, $R_4=R_5=R_6=H$
c[16] : $R_3=R_5=R_6=H$, $R_4=Me$
d[16] : $R_3=R_4=R_6=H$, $R_5=Me$
e[17] : $R_3=R_4=R_5=H$, $R_6=Me$
f[13] : $R_3=R_5=Me$, $R_4=R_6=H$
g[14] : $R_3=R_5=H$, $R_4=R_6=Me$
h[6d] : $R_3=R_4=H$, $R_5=R_6=Me$
i[13] : $R_3=H$, $R_4=R_5=R_6=Me$
j[18] : $R_3=R_4=R_5=R_6=Me$
k[6d] : $R_3=R_5=R_6=H$, $R_4=Ph$
l[6d] : $R_3=R_5=H$, $R_4=Ph$, $R_6=Me$
m[13] : $R_3=R_6=Me$, $R_4=Ph$, $R_5=H$
n[13] : $R_3=H$, $R_4=Ph$, $R_5=R_6=Me$
o[13] : $R_3=R_5=R_6=Me$, $R_4=Ph$
p[13] : $R_3=Me$, $R_4=Ph$, R_5–$R_6=-(CH_2)_3-$
q[13] : $R_3=R_4=R_6=Me$, $R_5=Ph$
r[13] : $R_3=CN$, $R_4=H$, $R_5=R_6=Me$
s[13] : $R_3=Me$, $R_4=R_6=H$, $R_5=Br$
t[4a] : $R_3=R_4=R_5=H$, $R_6=Cl$
u[4c] : $R_3=H$, $R_4=Me$, R_5–$R_6=-CH_2CH_2O-$
v[19] : $R_3=R_4=R_5=H$, $R_6=OMe$

Scheme 2.

of Diels-Alder adducts of 1-methyl-2-pyridones with benzyne were rather poorly reproduced. Accordingly the relative reactivities were determined by the competition reactions between two 1-methyl-2-pyridones (**2x**) and (**2y**). In a competitive reaction, the concentration of highly reactive benzyne to which the two pyridones (**2x**) and (**2y**) are exposed at any time is the same for both, since they are present in the same reaction mixture. So, from the yields(%) (Y(**3x**) and Y(**3y**)) obtained by the competition reaction of **2x** and **2y** (*vide supra*), the competition constant was calculated by

$$\frac{k_{2y}}{k_{2x}} = \frac{\ln([2y]/[2y]_0)}{\ln([2x]/[2x]_0)} = \frac{\ln(1-0.01Y(3y))}{\ln(1-0.01Y(3x))}$$

where $[2x]_0$ and $[2y]_0$ are the initial concentrations of **2x** and **2y**, respectively. From these competition constants, the relative reactivities (k_r) against the parent 1-methyl-2-pyridone (**2a**) were determined, and summarized in Table 2.

The reliability of this competition method was checked on several sets of the competition constants: the reactivity ratio of **2x** and **2x′** was calculated from the competition constants of two pairs of 2-pyridones (**2x**, **2y** and **2x′**, **2y**), and this value was checked against that obtained in a direct competition experiment of **2x** and **2x′**. The scrutinized results are as follows: k_{2k}/k_{2i}(=0.42) was calculated as 0.44 from k_{2i}/k_{2c} and k_{2k}/k_{2c}; k_{2m}/k_{2e}(=3.6) as 3.9 from k_{2e}/k_{2b} and k_{2m}/k_{2b}; k_{2n}/k_{2m}(=1.7) as 1.7 from k_{2m}/k_{2b}, k_{2j}/k_{2b} and k_{2n}/k_{2j}. Thus, the probable errors for the relative reactivities obtained are considered to be within ±10%.

TABLE 2. THE RELATIVE DIELS-ALDER REACTIVITY (k_r) OF 1-METHYL-2-PYRIDONES WITH BENZYNE

Substrate	k_r	Substrate	k_r
2a	1.0	**2l**	2.6
2b	1.6	**2m**	5.4
2c	1.2	**2n**	9.2
2d	1.3	**2o**	15
2e	1.5	**2p**	18
2f	5.2	**2q**	12
2g	1.6	**2r**	0.96
2h	2.8	**2s**	3.0
2i	4.8	**2t**	0.33
2j	14	**2u**	9.0
2k	2.0	**2v**	2.8

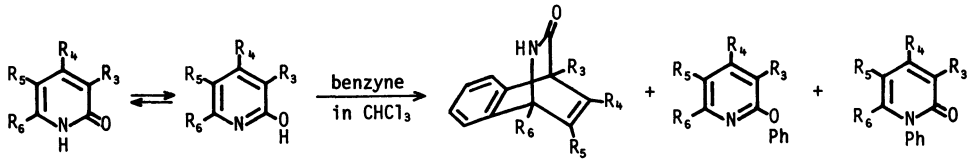
Table 2 shows that on the whole the Diels-Alder reactivities were raised as the number of substituents increased. From the comparison of the results between 3,5-dimethyl (**2f**) and 4,6-dimethyl derivatives (**2g**), and between the two 4-phenyl derivatives (**2l**) and (**2o**), introduction of the substituent into the 3- and 5-position seems to exert the greater influence on enhancement of the reactivity; the 4-phenyl substituent also exhibited further enhancement of the reactivity in a series of 5,6-dimethyl derivatives (**2n**) and (**2o**).

Reaction of 1-Unsubstituted Derivatives with Benzyne. In order to discuss the reactivity and chemoselectivity observed with 1-unsubstituted 2-pyridone derivatives (**1**), the reactions of 1-unsubstituted 2-pyridones (**1**) with benzyne have been carried out according to the procedure similar to those for 1-methyl derivatives (**2**) (Scheme 3). The structural proof of the products (**4**), (**5**), and (**6**) will be published in a separate paper.[13]

The product composition in such reactions was listed in Table 3.

It can be seen from Table 3 that the reactivity and chemoselectivity apparently varied with the substituents. Special features disclosed include the following facts; the most favored reaction is the formation of 2-phenoxypyridine (**5**) which is one of the Michael-type adducts. In all cases, the Diels-Alder reaction also proceeded to give 5,6-benzo-2-azabarrelen-3(2*H*)-ones (**4**), and the polysubstitutions apparently raised the yields of the Diels-Alder adduct, this tendency is in accord with that observed for the 1-methyl derivatives (**2**).

Interestingly, the formation of 1-phenyl-2-pyridones (**6**), another Michael-type adduct, was not observed or occured only in a very low yield for the derivatives which exist in the 2-pyridone form in solution. However, in the case of the derivatives (**1s**) and (**1t**) which tend to exist in the 2-pyridinol form in solution, appreciable amounts of the 1-phenyl-2-pyridones (**6**) were obtained as well as the Diels-Alder adduct (**4**) and the 2-phenoxypyridine (**5**). These facts seem to indicate that the formation of **5** and **6** is derived from the reac-



1 **4** **5** **6**

Scheme 3.

TABLE 3. REACTIONS OF 2-PYRIDONES WITH BENZYNE

2-Pyridones	Substituents				Product composition (%)				Total recovery (%)[c]
	R_3	R_4	R_5	R_6	**4**	**5**	**6**	**1**	
1a	H	H	H	H	7[a]	35	4	1	46
1b[20]	Me	H	H	H	4[a]	48	0	2[a]	54
1c[21]	H	Me	H	H	12[a]	29	0	12[a]	53
1d[20]	H	H	Me	H	17[a]	45	0	31[a]	93
1e[22]	H	H	H	Me	4[a]	74	0	17[a]	95
1f[23]	Me	H	Me	H	15[a]	45	0	27[a]	87
1g[24]	H	Me	H	Me	4	79	0	13[a]	96
1h[6d]	H	H	Me	Me	6	73	0	19	98
1i[24]	H	Me	Me	Me	5	75	0	19	99
1j[25]	Me	Me	Me	Me	8	77	0	11	96
1l[26]	H	Ph	H	Me	8	75	0	15	98
1m[26]	Me	Ph	H	Me	7	69	0	13	89
1n[13]	H	Ph	Me	Me	14	74	0	10	98
1o[25]	Me	Ph	Me	Me	26	66	0	7	99
1p[25]	Me	Ph	$-(CH_2)_3-$		30	41	0	11	82
1q[13]	Me	Me	Ph	Me	14	78	0	7	99
1s[4a]	Me	H	Br	H	7	35	7	0	49
1t[19]	H	H	H	Cl	1	33	11	0	45
1u[26]	H	Me	$-CH_2-CH_2-O-$		30[b]	0	0	0	30

a) Yields with a small amount of contamination. b) Based on a naphthalene derivative derived from a spontaneous retro Diels-Alder reaction. c) The low values are mainly due to the difficulty in recovery of the starting 2-pyridones.

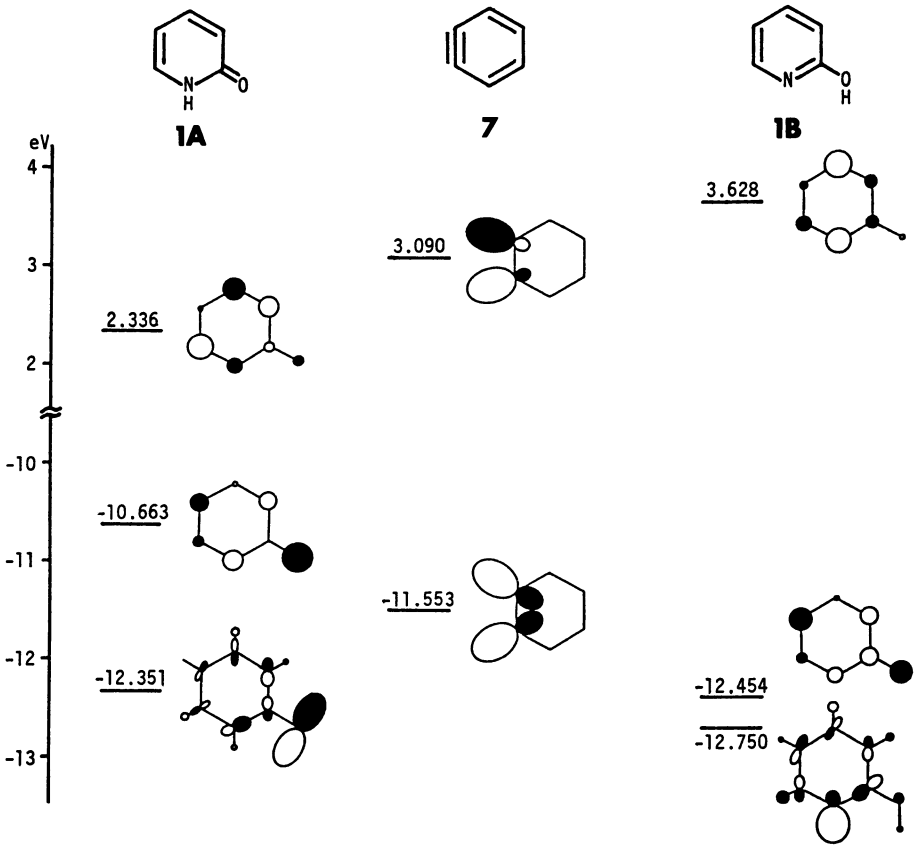


Fig. 1. Frontier molecular orbitals of 2-pyridone–2-pyridinol and benzyne calculated by the CNDO/2 method.

tion of the 2-pyridone form and the 2-pyridinol form with benzyne, respectively.

Another interesting feature is that there is a distinct difference in the yield of **5** between 6-methyl-substituted derivatives and 6-unsubstituted ones, that is, 6-methyl substitution leads to increase in the yield of **5**.

Molecular Orbital Consideration of the Structure–Reactivity–Chemoselectivity Relationship. In order to assess the substituent perturbation on the reactivity and to gain a fundamental insight into the factors controlling the chemoselectivity of this type reactions, the frontier molecular orbital (FMO) interactions were examined based on the CNDO/2 wavefunctions previously calculated.[10]

The FMO energies and the coefficient distributions of 2-pyridone (**1A**) and 2-pyridinol (**1B**) are presented in Fig. 1, together with those of benzyne (**7**).

Special features of these FMO are that the HOMO–LUMO energy separation of 2-pyridinol (**1B**) is larger than that of 2-pyridone (**1A**) and that of benzyne (**7**). This implies that the FMO interaction of **1B** with benzyne is smaller than that of **1A**. Thus, provided the reaction proceeds in accord with the FMO theory, the latter form may be more reactive with benzyne.

Figure 1 also shows that the LUMO of benzyne and the HOMO of 2-pyridone (**1A**) has a smaller separation in energy (13.753 eV) than the reverse pair (13.889 eV). Although the difference in the energy separation

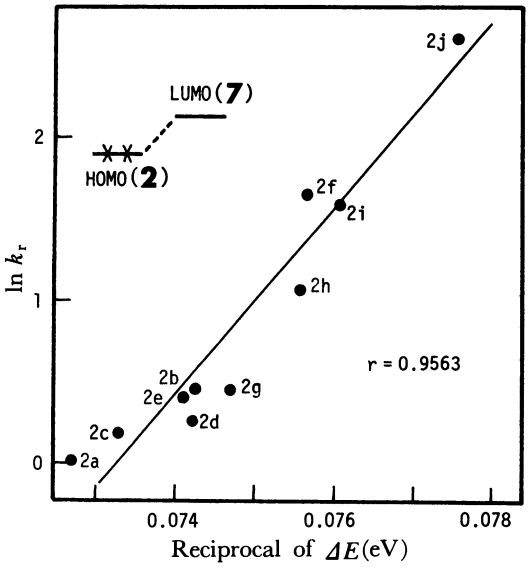


Fig. 2. Plots of the relative Diels-Alder reactivities (k_r) against the reciprocal of the FMO energy separations (ΔE).

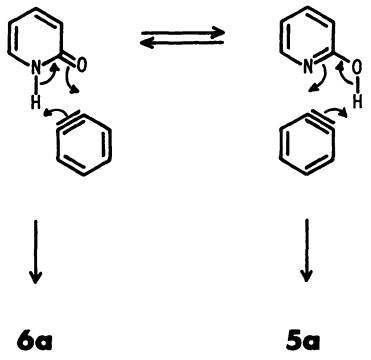
between the two pairs is small, plots of the logarithms of relative Diels-Alder reactivities (ln k_r) of 1-methyl derivatives (**2a—j**) against the reciprocal of the FMO energy separation between the HOMO of 2-pyridones and the LUMO of benzyne displayed a good correlation as shown in Fig. 2. Thus, the dominant HOMO–LUMO interaction for the Diels-Alder reaction should involve the LUMO of benzyne and the HOMO of the 2-pyridione, *i. e.* normal electron demand for a Diels-

Alder reaction.

Little improvement in the correlation was obtained by additional consideration of the orbital interactions of the reverse pair, due to the relatively small difference in the LUMO energies among 2-pyridones.

For reactions of the 1-unsubstituted derivatives which exist largely as self-associated dimers, the FMO of such dimers should be considered. However, the relevant orbital energy diagrams for the formation of the respective dimer in the 2-pyridone (**1A**) and 2-pyridinol (**1B**) calculated by the CNDO/2 method[10] indicated that the π-type orbitals have been little affected, although the σ-type orbitals have undergone a large energy perturbation. Therefore, the essential reactivity of Diels-Alder reaction of 1-unsubstituted 2-pyridones (**1**) would be similarly interpreted as that for the 1-methyl derivatives (**2**).

It should be noted that the formation of 2-phenoxypyridine (**5**) involves the ring structural conversion from the 2-pyridone form (**A**) to the 2-pyridinol form (**B**) and includes an abstruction of the NH proton which locates in the plane of the 2-pyridone ring. Likewise, the formation of 1-phenyl-2-pyridone (**6**) involves an abstruction of the OH proton of 2-pyridinol form as well as the reverse ring structural conversion. Such characteristic features should be associated with the tautomeric properties. It seems unlikely that π-type orbital interaction in the transition state is involved for such reactions and it can be rather otherwise considering that the reaction is charge controlled in view of the electrophilic nature of benzyne; the transition state may be better represented as shown in Scheme 4 for **1a** as an example.



Scheme 4.

We have shown previously, based on the quantum chemical calculations, that the tautomeric equilibria of 6-methyl derivatives were labile to the molecular environment. This is true particularly for 5,6-dimethyl derivatives due to an additional buttressing effect of the 5,6-dimethyl substituents.[10] Futhermore these derivatives are very effective catalysts for the mutarotation of TMG.[15] Also, our recent fluorescence study of various substituted 2-pyridones indicated that the tautomeric equilibria of 6-methyl derivatives were very sensitive to the solvent polarity and concentration. This results in a facile shift in the tautomeric equilibria leading to predominance of the 2-pyridinol form (**B**) over the 2-pyridone form (**A**) in less polar solvent and in diluted solution.[27] The above mentioned tautomeric properties of the 6-methyl derivatives account clearly for the higher yield of the formation of 2-phenoxypyridines (**5**) from the 2-pyridone form (**A**).

A similar rationalization may also be applicable for the 4-phenyl substituent effect on further enhancement of the Diels-Alder reactivity observed with 5,6-dimethyl derivatives. The Diels-Alder reactions involve the destruction of diene character of the pyridone form as the reaction proceeds. This ring structural modification bears some resembrance to the tautomeric conversion to the 2-pyridinol form. Thus, one explanation is the greater buttressing effect of the

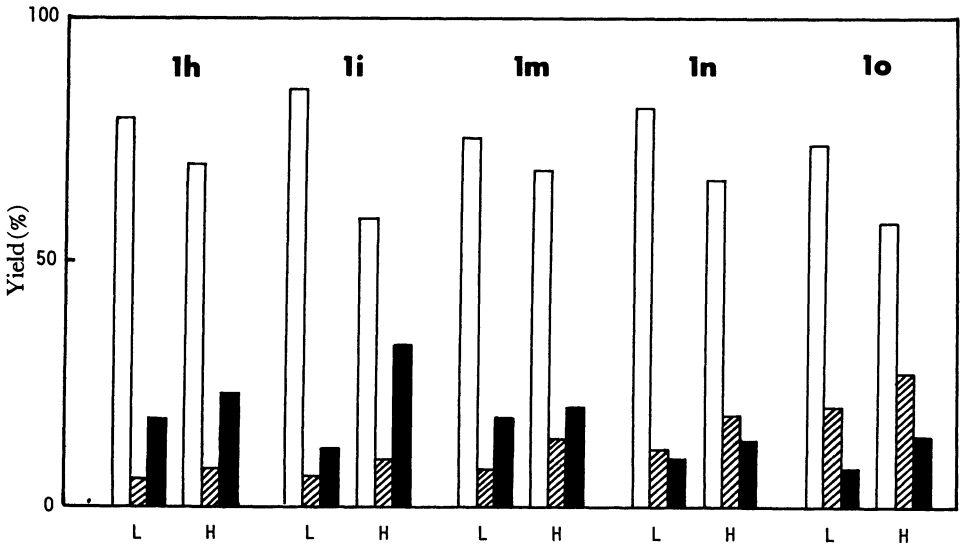


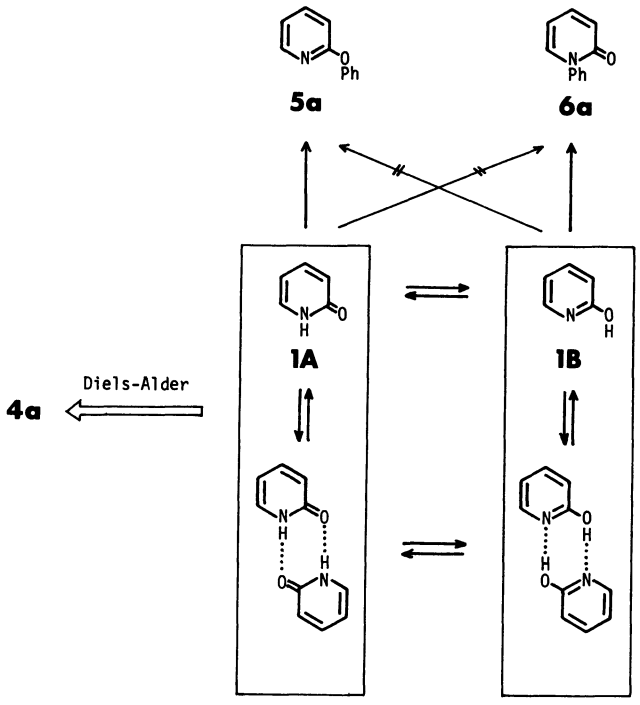
Fig. 3. Effect of concentration on the reactivity and chemoselectivity.
The products (**5**, **4**) and the unreacted 2-pyridone (**1**) were represented by □, ▨, and ■, respectively. L and H denote the reaction in 6.25×10^{-3} mol dm^{-3} solution and 0.1 mol dm^{-3} solution, respectively.

5,6-dimethyl substituents induced by the adjacent 4-phenyl group on lowering the activation energy of the transition state of the Diels-Alder reaction.

Concentration Dependency in Reactions of 1-Unsubstituted 2-Pyridones. Based on the foregoing facts and discussions, it can be considered that the factors determining the tautomeric equilibria [*i.e.* concentration, temperature and solvent] significantly affect the reactivity and the chemoselectivity of the reaction with benzyne. The concentration-dependencies for the reactions of several selected 2-pyridones such as **1h**, **1i**, **1m**, **1n**, and **1o** have been investigated and the results are illustrated in Fig. 3.

As shown in Fig. 3, the yields of 2-phenoxypyridines (**5**) were considerably lowered for the reactions in higher concentration. The recoveries of the starting 2-pyridones (**1**) were inversely raised to a similar extent and the yields of the Diels-Alder adducts (**4**) were slightly raised. Similar results were also obtained in the reaction of **1o** using a hydrogen-accepting solvent (dioxane) and in the reaction at lower temperature. It appears likely that the observed reversal in the yield of products was caused by the tautomeric properties, and indicated the importance of the abundance of the nonassociated forms for the formation of **5**. The observed chemoselectivity, therefore, could be rationalized for the formation of the Diels-Alder adduct (**4**) concomitantly increased as the major reaction (formation of **5**) was suppressed. These reaction schemes are summarized in Scheme 5 for **1a** as an example.

Thus, we have shown a novel example in which the tautomeric properties significantly affect the chemical reactivity and the chemoselectivity; it is of interest in connection with a widely accepted concept that the tautomeric equilibria are closely related to some biologically important properties of nucleic acids such as RNA transcription and DNA replication.



Scheme 5.

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