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Charge-transfer Model in Considering the Reactivity of Heteroaromatic Nitriles with the Enolate Anion

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Synopsis. The reactivity of heteroaromatic nitriles with the enolate anion to give the enamino ketones was discussed on the basis of a reaction index calculated by the charge-transfer model and also using the total electron densities. The results were reasonable in interpreting the reaction mechanism.

Recently Honma and Tada[1] have reported the very useful reaction of heteroaromatic nitriles with the enolate anion to prepare enamino ketones. The reaction is shown in Scheme 1. The reactivity will be considered using the molecular orbital (MO) description of the charge-transfer (CT) theory.[2,3] Supposing that the MO energies of the nitriles and enolate anion are related as Fig 1 shows, and that the CT occurs predominantly as shown by the arrows in Fig. 1, the stabilization energies due to CT can be written approximately by; $\Delta E_{rs}=2\sum_{k}^{\mathrm{VAC}}[(C^{r}_{\mathrm{E.HO}}\cdot C^{s}_{\mathrm{N}.k})^2(H_{rs})^2/(\varepsilon_{\mathrm{E.HO}}-\varepsilon_{\mathrm{N}.k}+V^{\mathrm{E.HO}}_{\mathrm{N}.k})]$. $C^{r}_{\mathrm{E.HO}}$ and $\varepsilon_{\mathrm{E.HO}}$ are the πMO coefficients at the *r*-th atom in the highest occupied MO (HOMO) and the HOMO energy of the enolate anion respectively. Alternatively, $C^{s}_{\mathrm{N}.k}$ and $\varepsilon_{\mathrm{N}.k}$ stand for the πMO coefficient at the *s*-th atom in the *k*-th vacant πMO and the *k*-th πMO energy of nitriles respectively. H_{rs} is the resonance energy between the two πAO's. The intermolecular resonance interaction of the nitrile and the enolate anion was assumed to occur only through the two AO's. The electrostatic interaction energy between the MO's $\psi_{\mathrm{E.HO}}$ and $\psi_{\mathrm{N}.k}$ is expressed by $V^{\mathrm{E.HO}}_{\mathrm{N}.k}=\langle\psi^{*}_{\mathrm{E.HO}}\cdot\psi^{*}_{\mathrm{N}.k}|e^2/r|\psi_{\mathrm{E.HO}}\cdot\psi_{\mathrm{N}.k}\rangle$. For evaluating the $V^{\mathrm{E.HO}}_{\mathrm{N}.k}$ term, the geometrical configuration between each atom in nitriles and the enolate anion should be determined. Since this is quite difficult, we have disregarded the $V^{\mathrm{E.HO}}_{\mathrm{N}.k}$ term in the present calculation.[4] The reagent, the enolate anion, was always the same throughout the present experiments. Also assuming H_{rs} to be constant, we can now evaluate the value of $(\mathrm{CTA})_s=\sum_{k}^{\mathrm{VAC}}[(C^{S}_{\mathrm{N}.k})^2/(\varepsilon_{\mathrm{E.HO}}-\varepsilon_{\mathrm{N}.k})]$. The $\varepsilon_{\mathrm{E.HO}}$ may be put as a constant in all the calculations.[4] Thus, the CTA value (charge-transfer ability) can be used as a measure of the selectivity of the reaction position, to which the first bond is formed to bring about the nucleophilic reaction of the enolate anion with nitriles. Note that the CTA value has a physical meaning very similar to the nucleophilic superdelocalizability.[5] The calculation was done using the PPP SCFMO method of π electron approximation. The parameters pertinent to each atom and each bond were determined by referring to many previous studies.[6] The π-electron energy for the enolate anion was obtained using the molecular model in Fig. 1; we know that the $\varepsilon_{\mathrm{E.HO}}$ is shallow in energy,[7] so the CT to $\varepsilon_{\mathrm{N}.k}$ from $\varepsilon_{\mathrm{E.HO}}$ is the most important one, and, also, the CH_2-group carbon atom in the enolate anion may be the most likely to attack nitriles, because the MO corresponding to $\varepsilon_{\mathrm{E.HO}}$ is mainly localized on the CH_2 group πAO.

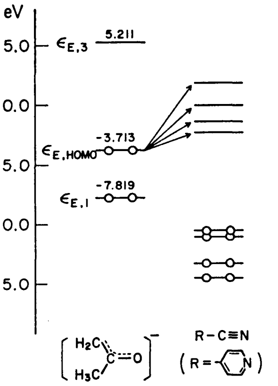
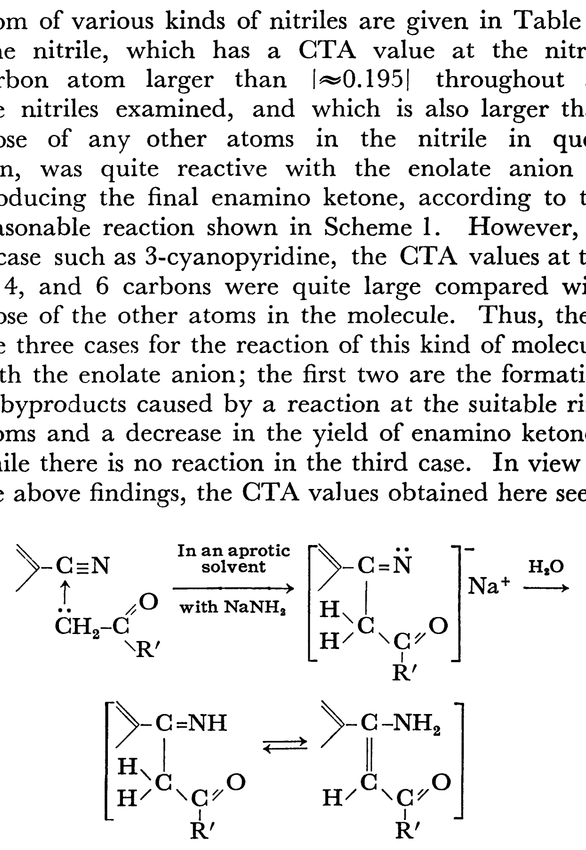


Fig. 1. Calculated MO energies of enolate anion and nitriles. The MO energies of heteroaromatic nitriles are more or less similar to those given in this figure.

The calculation results of the CTA values at each atom of various kinds of nitriles are given in Table 1. The nitrile, which has a CTA value at the nitrile carbon atom larger than |≈0.195| throughout all the nitriles examined, and which is also larger than those of any other atoms in the nitrile in question, was quite reactive with the enolate anion in producing the final enamino ketone, according to the reasonable reaction shown in Scheme 1. However, in a case such as 3-cyanopyridine, the CTA values at the 2, 4, and 6 carbons were quite large compared with those of the other atoms in the molecule. Thus, there are three cases for the reaction of this kind of molecule with the enolate anion; the first two are the formation of byproducts caused by a reaction at the suitable ring atoms and a decrease in the yield of enamino ketones, while there is no reaction in the third case. In view of the above findings, the CTA values obtained here seem



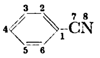
Scheme 1.

Table 1. The calculated results of CTA values (eV^{-1}) at each atom, and the total electron densities in the $>\overset{*}{C}-C\equiv N$ group (ρ^t) and at the C* atom (ρ^*)

Compound No.[a]		CTA[b]								$\rho^*(C^*)$[c]	ρ^t (C^*+C+N)[d]	Yield[e] (%)
		1	2	3	4	5	6	7	8			
I		0.177	0.200	0.175	0.201	0.175	0.200	0.195	0.177	3.961	13.045	g)
II	2CN	0.182	0.204	0.199	0.202	0.204	0.194	0.200	0.190	3.884	12.957	78.6
	3CN	0.159	0.220	0.179	0.230	0.177	0.226	0.198	0.181	3.984	13.064	g)
	4CN	0.185	0.199	0.205	0.209	0.205	0.199	0.207	0.198	3.929	13.007	48.7
III		0.217	0.214	0.223	0.189	0.238	0.202	0.205	0.197	3.907	12.976	g)
IV	2CN	0.180	0.229	0.180	0.222	0.204	0.222	0.205	0.201	3.811	12.868	40.5
	4CN	0.187	0.212	0.187	0.243	0.203	0.231	0.214	0.213	3.855	12.922	75.0 (2, 6-Me$_2$)[i]
	5CN	0.160	0.248	0.160	0.254	0.181	0.254	0.201	0.184	4.006	13.083	f, g) (2, 4-Me$_2$)[i]
V	2CN	0.065	0.149	0.165	0.124	0.176	0.196	0.172	—	3.860	12.930	90.0
	3CN	0.060	0.187	0.120	0.131	0.152	0.176	0.146	—	3.997	13.076	f)
VI	2CN	0.077	0.146	0.162	0.123	0.175	0.191	0.167	—	—	—	g, j)
	3CN	0.070	0.184	0.119	0.130	0.150	0.173	0.142	—	—	—	g, j)
VII	3CN	0.072	0.177	0.161	0.129	0.182	0.190	0.168	—	3.761	12.915	85.5 (5-Me)[i]
	4CN	0.072	0.142	0.166	0.121	0.222	0.181	0.150	—	3.954	13.173	f, g) (3, 5-Me$_2$)[i]
	5CN	0.081	0.168	0.160	0.169	0.186	0.211	0.196	—	3.927	12.857	85.6 (3-Me)[i]
VIII	2CN	0.072	0.180	0.146	0.127	0.173	0.210	0.194	—	3.850	12.822	73.8 (5-Me)[i]
	4CN	0.061	0.177	0.114	0.125	0.183	0.175	0.146	—	4.091	13.042	h)
	5CN	0.068	0.203	0.109	0.169	0.146	0.196	0.172	—	3.794	13.003	29.5 (2, 4-Me$_2$)[i]
IX	3CN	0.187	0.215	0.211	0.235	0.204	0.230	0.206	0.197	3.904	12.917	h, j)
	4CN	0.224	0.193	0.227	0.226	0.251	0.203	0.214	0.209	3.951	13.024	—
X		0.077	0.182	0.153	0.114	0.204	0.213	0.197	—	—	—	—
XI		0.093	0.226	0.175	0.172	0.179	0.198	0.180	—	3.919	12.979	88.2 (4-Me)[i]
XII	2CN	0.254	0.300	0.294	0.279	0.310	0.268	0.209	0.232	3.962	13.003	12.3[1]
	3CN	0.217	0.314	0.291	0.318	0.264	0.333	0.236	0.249	3.933	12.990	—
	4CN	0.280	0.282	0.306	0.319	0.306	0.282	0.242	0.263	3.980	13.056	—

a) The formula and numbering for each substance are as follows:

I,



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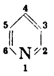

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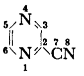

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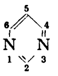
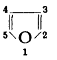


V,



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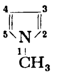
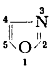
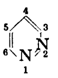


VII,

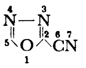
VIII,



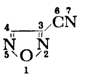
IX,



X,



XI,



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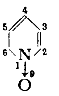

b) CTA is the negative value. The absolute values are given in this Table. c) CNDO/2 total electron density at the C* atom bound to the CN group. d) The sum of the CNDO/2 total electron density on each atom in the $>\overset{*}{C}-C\equiv N$ group. e) See Reference 1 in text. f) Side reactions occurred. g) The starting nitrile was recovered. h) Ring cleavage occurred. i) These mean the methyl substituted compounds which were used as starting materials to prevent the ring cleavage in the reaction process. j) Unpublished data.[1]

to give a reasonable reaction index for interpreting the experimental results (Table 1) except for the cases of a few molecules. With 2- and 4-cyanopyrimidines, the largest CTA value is at the carbon (C*) to which the CN group is bound, in spite of the considerable yield of the enamino ketone. One reason for this may be the several approximations employed in deriving the CTA values, especially the hypothesis of a constant H_{rs}, since the geometrical configuration of the reaction intermediate would not be the same for all nitriles.[8] Another possibility is that the electron density, the CTA value, *etc.*, at the C* atom may also contribute more or less to the reaction process (*vide infra*). Alternatively, the CTA value (0.190) at the nitrile carbon atom of 3-cyanoisoxazole is less than 0.195 (*vide supra*), but the largest among those for the other atoms in the molecule. Since this molecule gives the enamino ketone, the reason may be that the total electron densities in the $>C-C\equiv N$ group are quite small, as the calculations employing the CNDO/2 method *etc.* have shown (Table 1), so that the reaction centers of the enolate anion and the $C-C\equiv N$ group easily become close enough to initiate the reaction by the charge transfer-process.

References

1) T. Honma and Y. Tada, *Heterocycles*, **6**, 1985 (1977).

2) N. Mataga and T. Kubota, "Molecular Interactions and Electronic Spectra," Marcel Dekker, New York (1970), Chap. 6.

3) S. Iwata, J. Tanaka, and S. Nagakura, *J. Am. Chem. Soc.*, **88**, 894 (1966).

4) If the $V_{N\cdot k}^{E\cdot HO}$ term is taken into consideration, the absolute values of CTA become larger than those given in Table 1. As was found in the interpretation of a series of CT spectra,[2] the contribution from the electrostatic interaction energies may be put as a constant. Then, the conclusion derived from the present calculation may not change.

5) K. Fukui, T. Yonezawa, and C. Nagata, *Bull. Chem. Soc. Jpn.*, **27**, 423 (1954), *ect.*

6) M. Yamakawa, K. Ezumi, Y. Mizuno, and T. Kubota, *Bull. Chem. Soc. Jpn.*, **47**, 2982 (1974), *ect.*

7) a) S. Nagakura and J. Tanaka, *J. Chem. Phys.*, **22**, 563 (1954); b) S. Nagakura, *Tetrahedron*, **19**, Suppl. 2, 361 (1963).

8) Nagakura derived the other reaction indexes from the extension of the CT theory.[7] In the case of a nucleophilic reaction, the free valency, localization energy, *etc.* for the anion species of the reactant are important. An examination based on these indices would also be needed.