SITE SELECTIVITY IN THE 1,3-DIPOLAR CYCLOADDITION REACTION OF UNSYMMETRIC PYRIDINIUM BIS(METHOXYCARBONYL)METHYLIDES WITH METHYL PROPIOLATE

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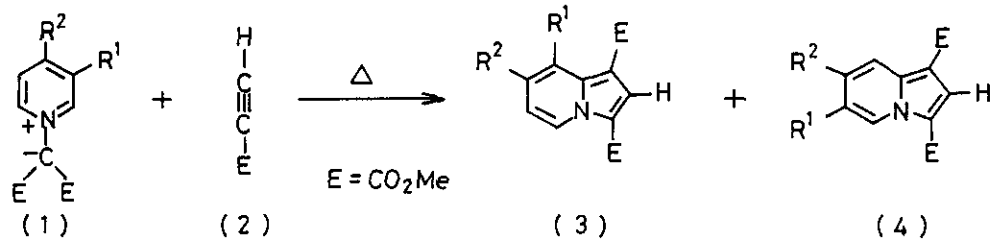
Abstract——The 1,3-dipolar cycloaddition of unsymmetric pyridinium bis(methoxycarbonyl)methylides with methyl propiolate proceeds in moderate to good yields with high to moderate site selectivity with respect to the ylide. Polar 3-substituted pyridinium bis(methoxycarbonyl)methylides generally gave predominantly the corresponding 8-substituted indolizines regardless of the substituents. The results can be explained by dipole-dipole interactions.

The 1,3-dipolar cycloaddition reactions undoubtedly rival Diels-Alder reactions in ubiquity as well as in synthetic utility, their synthetic potential being far from exhausted.[1] Specifically, 1,3-dipolar cycloaddition of heteroaromatic N-ylides with activated alkenes and alkynes provides a convenient route to nitrogen bridged heterocycles such as indolizines,[2a] [2.2.3]cyclazines,[2b] benzo[2.2.3]cyclazines,[3] and quinolizines.[4] Previously, we have reported on the regio- and site selectivities of 1,3-dipolar cycloaddition reactions of pyridinium dicyanomethylides with some activated alkynes both with respect to the dipolarophiles[5] and ylides.[6]

We now briefly describe on the site selectivity of the title reaction of unsymmetrically substituted pyridinium bis(methoxycarbonyl)methylides (1) with

methyl propiolate (2).

The reactions were carried out either in refluxing toluene or benzene or in certain cases, in refluxing xylene in the presence of Pd-C. The isomeric products were conveniently separated by flash chromatography devised recently.[7] The structural assignment of the indolizines (3) and (4) was made on the basis of their ^1H nmr spectra.[8] The isomeric ratios were determined by integration of appropriate signals in the ^1H nmr spectra of the crude products. The results are summarized in Table 1. The reaction of 3-substituted pyridinium bis(methoxycarbonyl)methylides (1) with methyl propiolate (2) gave the corresponding indolizines (3) and (4), (3) generally being predominantly formed regardless of the substituents. Like isoquinolinium dicyanomethylide, isoquinolinium bis(methoxycarbonyl)methylide (1a) underwent site specific cycloaddition to give the indolizine (3a) exclusively.



(1) (2) (3) (4)

Table 1. Reaction of Ylides (1) with Methyl Propiolate (2)

Ylide (1)	R^1	R^2	Solvent	Reaction Time (h)	Yield[a] (%)	Product Ratio (3)/(4)
a	-(CH=CH)$_2$-		toluene	21	65	100/0
b	CH_3	H	toluene	22	66	71/29
c	CH_3	CH_3	toluene	36	17	68/32
			xylene(Pd-C)	3	47	67/33
d	$COCH_3$	H	toluene	21	66	65/35
e	F	H	benzene	5	53	65/35
f	Cl	H	benzene	5	54	64/36
g	Br	H	benzene	5	38[b]	45/55

[a] Isolated yield. [b] Besides (3g) and (4g), 1,3-dimethoxycarbonylindolizine was also isolated in 18% yield.

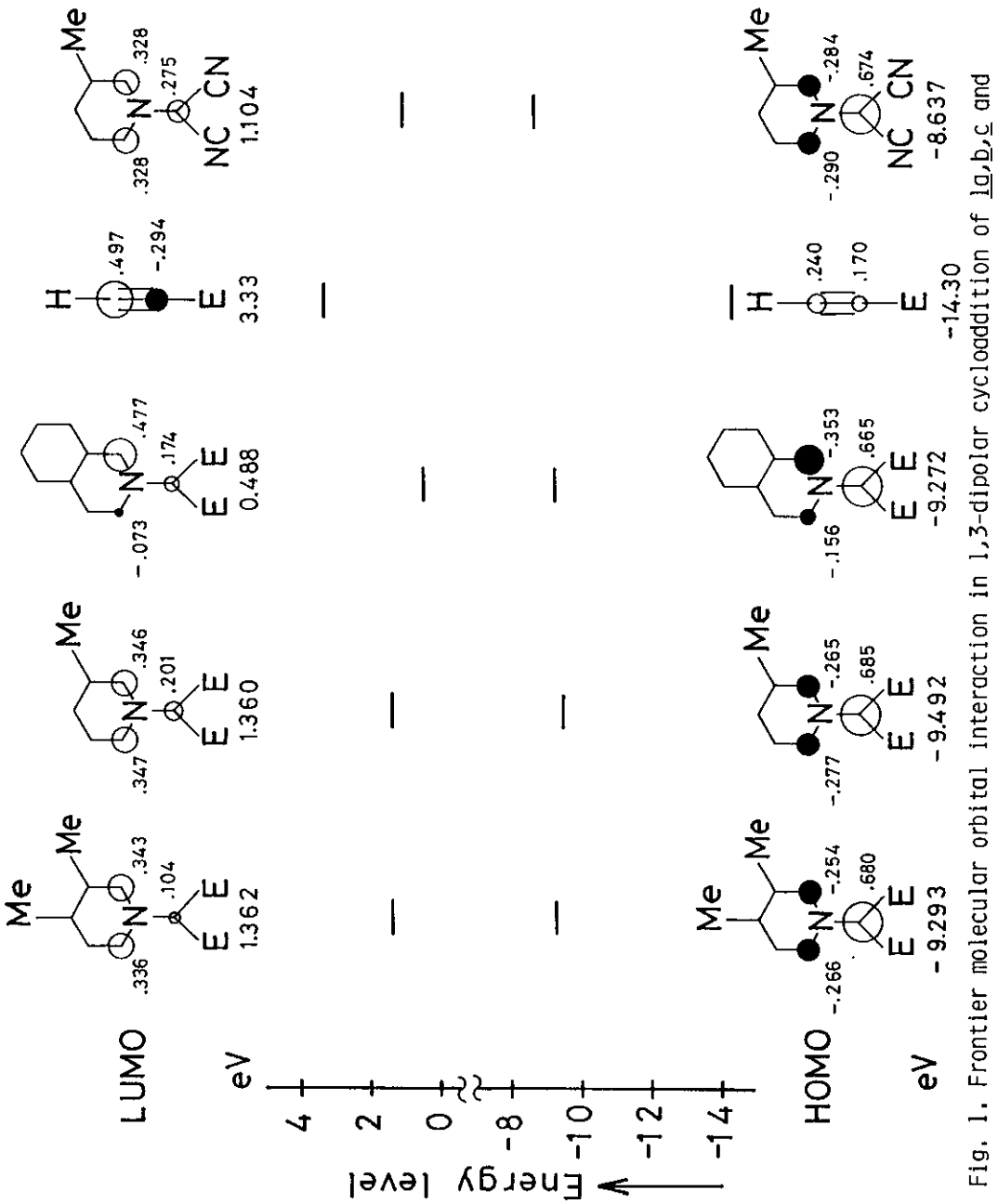


Fig. 1. Frontier molecular orbital interaction in 1,3-dipolar cycloaddition of 1a,b,c and 2-methylpyridinium dicyanomethylide with 2.

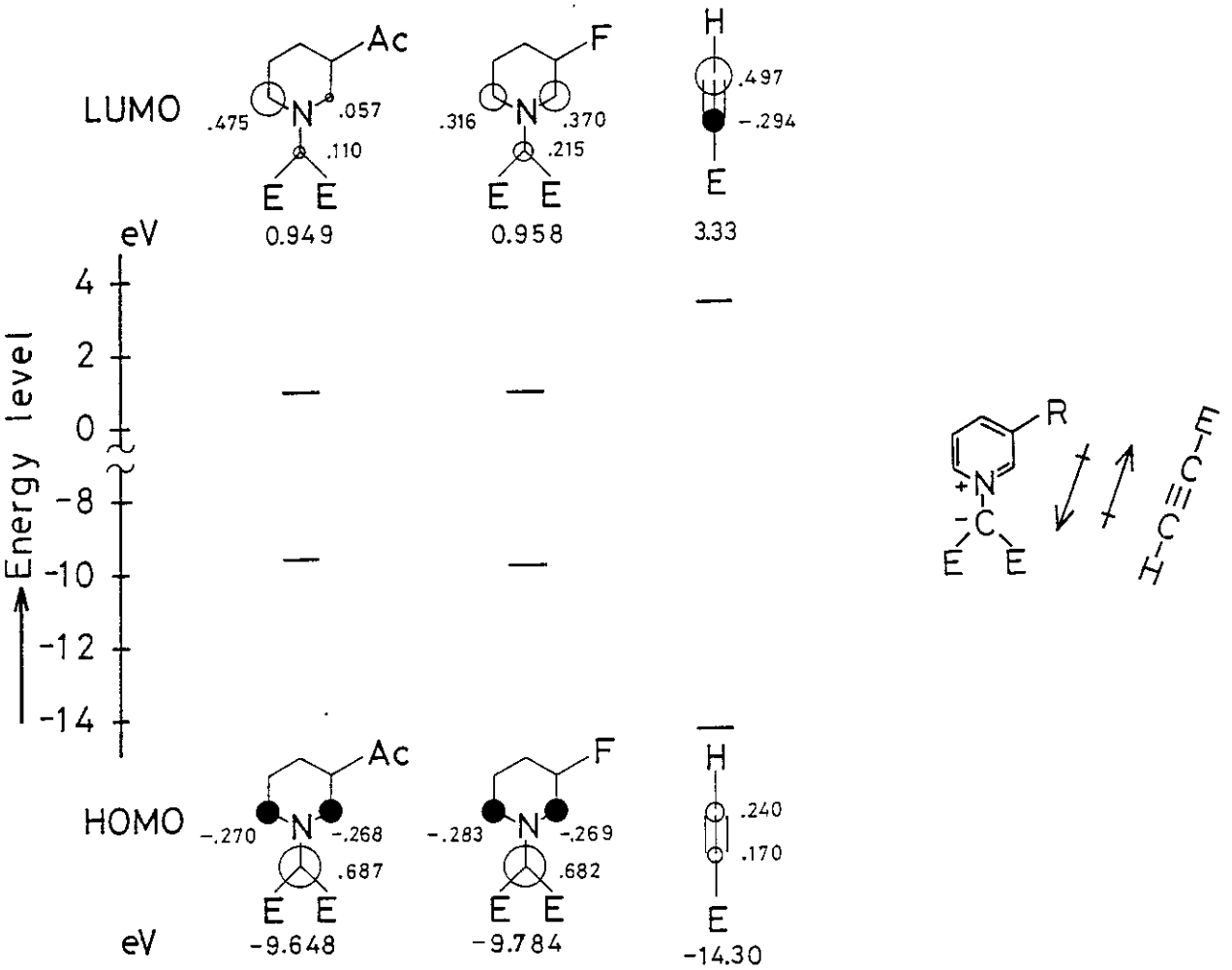


Fig. 2. Frontier molecular orbital interaction in 1,3-dipolar cycloaddition of 1d, e with 2.

The results of CNDO/2 calculations[9] both for the ylides and (2) are shown in Fig. 1 and Fig. 2 ; the present reaction is predominantly HOMO(1,3-dipole)-LUMO(dipolarophile) controlled. Thus, the regiochemical outcome with respect to (2) is in agreement with the FMO interactions. The exclusive formation of (3a) is also in accord with such considerations.[10] The bis(methoxycarbonyl)methylides (1) generally more sluggishly react with (2), in agreement with the HOMO energy levels of (1) lying at lower level than those of the dicyanomethylides.[6] For example, 3,4-dimethylpyridinium bis(methoxycarbonyl)methylide (1c) with (2) gave 17% yield of the indolizines, whereas a similar reaction of 3,4-dimethylpyridinium dicyanomethylide afforded quantitatively the corresponding indolizines. The yield was improved upto 47% upon heating in refluxing xylene in the presence of Pd/C, the ratio being virtually unaffected. The pyridinium ylides (1d-g) possessing an electron withdrawing group reacted more smoothly to produce the indolizines (3d-g) and (4d-g), almost the same degree of site selectivities being observed regardless of nature of the substituents. Since the coefficients of 2- and 6-positions of polar 3-substituted pyridinium bis(methoxycarbonyl)-methylides (1b-g) are almost of the same magnitude, the observed site selectivity could be explained, though only qualitatively, by dipole-dipole interactions as previously proposed by us (Fig. 2).[11] Although the ylides having an acetyl or halogen group should give higher site selectivity than those with an electron donating group, this was not the case in the present reactions (Table 1). This can be speculated by reactivity-selectivity principle; the more reactive ylides show less selectivity, though dipole-dipole interaction would favor higher selectivity. The exception was encountered in the reaction of 3-bromopyridinium bis(methoxycarbonyl)methylide (1g) that lost bromo substituent in refluxing toluene to give 1,3-dimethoxycarbonylindolizine in 86 % yield, thus indicating that bromo substituent is activated by ylide structure. The reaction of (1g) with (2) in refluxing benzene produced the 8- and 6-isomer (3g and 4g) along with the debrominated indolizine in the ratio of 30 : 38 : 32 respectively. The slightly predominant formation of the 6-isomer is presumably ascribed to steric hindrance by bromo substituent. The reason for the lower site selectivity of the bis(methoxycarbonyl)methylides compared with that of the dicyanomethylides is not yet clear.

In conclusion, the site selectivity can be rationalized, to some extent, by dipole-dipole interactions, although the disadvantage inherent in this explanation is lack of quantitative nature.

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