ON THE REACTIVITY OF 5(4H)-OXAZOLONES WITH AMINES

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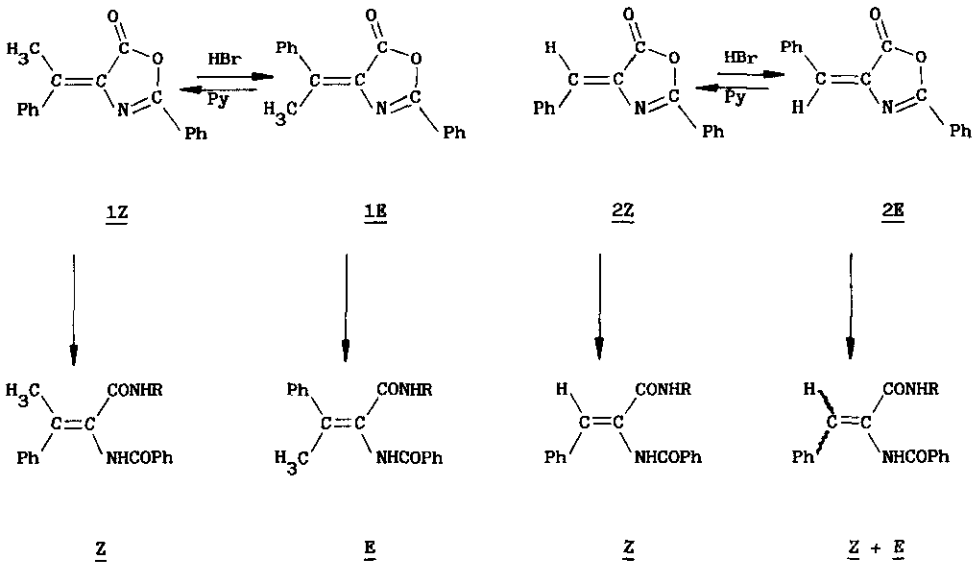
Abstract ——— Reactions of (Z/E)-2-phenyl-4-(α-arylethylidene)-5(4H)-oxazolones and Z-2-phenyl-4-arylmethylene-5(4H)-oxazolones with nucleophiles occur with retention of the exocyclic double bond geometry, whereas reactions of E-2-phenyl-4-arylmethylene-5(4H)-oxazolones with some nucleophiles occur with total or partial isomerization. Structural calculations, MMPI and AM1, on model compounds reveal that the methyl group does not essentially affect the phenyl ring-double bond planarity. Application of the Klopman-Salem equation to the reaction of E-2-phenyl-4-benzylidene-5(4H)-oxazolone with different amines, calculated by MNDO, points to a reversible nucleophilic attack at the exocyclic carbon of this 5(4H)-oxazolone as a possible explanation of this behaviour. As Z-2-phenyl-4-benzylidene-5(4H)-oxazolone is more stable than the E-isomer, the opening reactions of the Z-compound occur without isomerization.

A considerable interest has been shown in the synthesis and reactivity of α,β-dehydroamino acid derivatives as they have been found in small peptides with antimicrobial activity[1]. Moreover, they are one of the best precursors of optically-active α-amino acid derivatives obtained by asymmetric hydrogenation[2]. As previously reported, some of these α,β-dehydroamino acid derivatives, acids and esters, can usually be obtained by stereospecific opening of the corresponding Z- or E-5(4H)-oxazolones obtained by standard procedures[3]. We have been working for several years on the synthesis of (Z/E)-2-phenyl-4-(α-arylethylidene)-5(4H)-oxazolones[4] (1) and we have shown that in all cases these compounds can be stereospecifically opened to yield the corresponding (Z/E)-2-benzamido-3-aryl-2-butenoic acids, esters and amides[5].

Nevertheless, when these synthetic procedures were tried on (Z/E)-2-phenyl-4-arylmethylene-5(4H)-oxazolones (2), we found that the stereochemistry of the resultant products depended on the

stereochemistry of the 5(4H)-oxazolone and the nucleophile used[6]. Now we report our last results and a first attempt at rationalization.

As we have previously reported[5], hydrolysis and metanolysis of compounds 1 and 2 occur with retention of configuration to afford the (Z/E)-2-benzamido-3-phenyl-2-propenoic(or butenoic) acids and their corresponding methyl esters. Nevertheless, aminolysis of compounds 1 and 2, which is an important synthetic route to dehydrodipeptide derivatives and heterocyclic compounds[6], occurs in a different way depending on the stereochemistry and substitution of the double bond. That is to say, aminolysis of 1Z, 1E and 2Z occurs with retention of the double bond geometry in all cases, whereas *aminolysis of 2E occurs with total or partial isomerization* to give a mixture of Z- and E-2-benzamido-3-phenylpropenecarboxamides (Scheme 1).



SCHEME 1

Geometric study

These results showed that a slight structural difference between 1E and 2E (the presence of a methyl group) seemed to be of great importance in determining the final products. We initially thought that *this rather different behaviour might be attributable to geometrical differences* between the compounds leading to a lack of phenyl ring-double bond coplanarity in 1. Since no experimental data are yet available, theoretical calculations are the best way of estimating the molecular geometry of these compounds.

MNDO calculations[7] with all geometry, except phenyl rings, optimized on compounds 1 and 2 gave phenyl rings almost perpendicular to the double bond (Fig. 1), which is in strong contrast with the planar structure of Z-2-methyl-4-benzylidene-5(4H)-oxazolone 3 recently determined by X-ray diffraction[8].

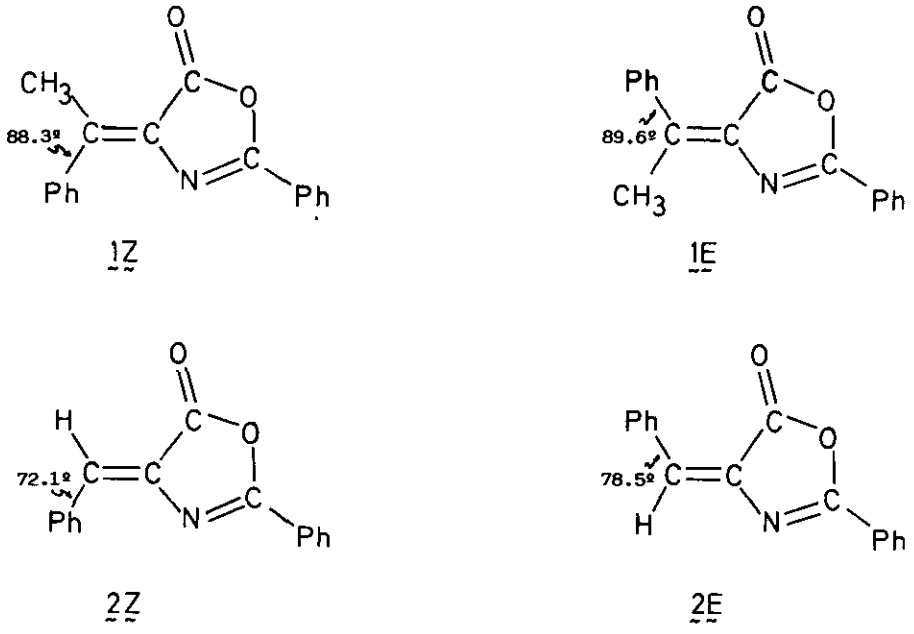
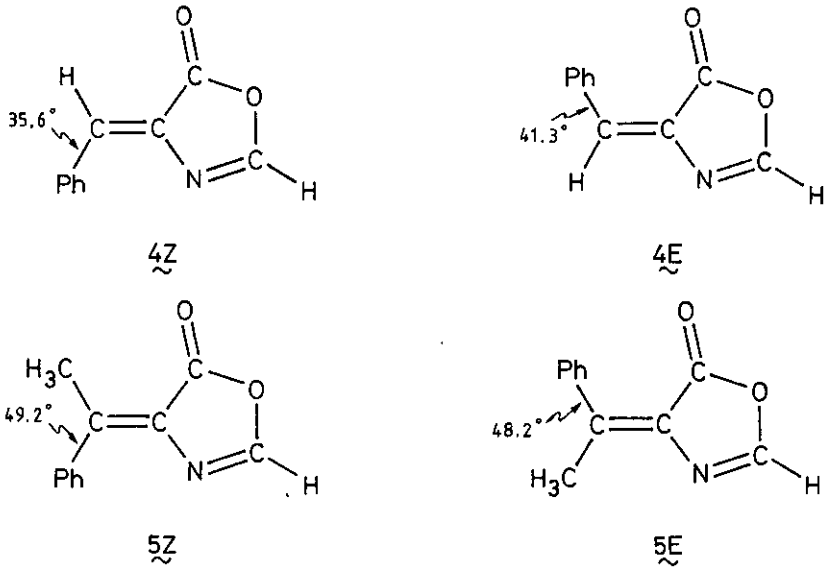


FIGURE 1

The lack of planarity may be due to the known MNDO tendency to overestimate short non-bonded contacts. Recent modification of MNDO approaches by Dewar[9] led to AM1 program where short contacts are better evaluated. AM1 calculations[10], keeping the phenyl ring as a rigid unit on model compounds 4 and 5, led to non-planar structures, although the deviation from planarity was smaller (Fig. 2). Finally MMPI calculations[11] were carried out on different model compounds 6 and 7[12]. Geometrical values obtained under full optimization using this empirical method were more in accordance with the experimental observed planarity for 3 (Fig. 3).

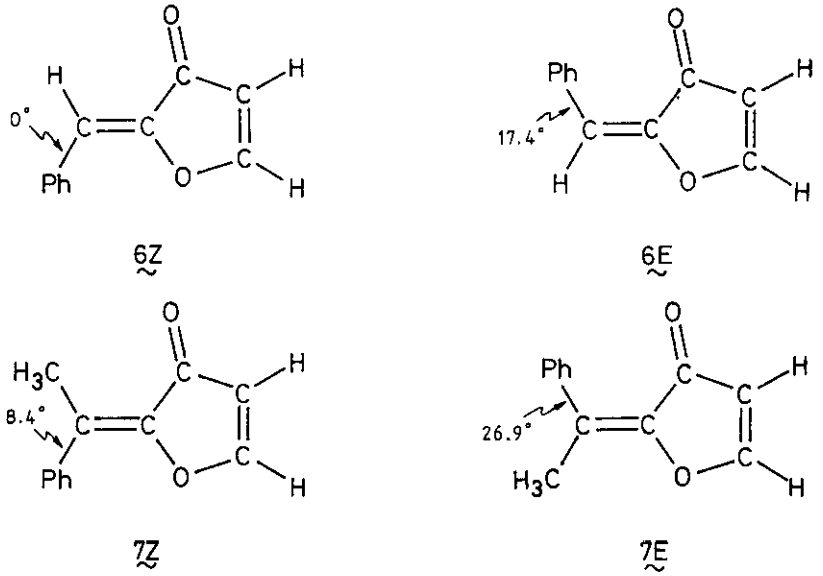
The obtained results point out that the diverse observed behaviour cannot be attributed to geometrical differences. According to MMPI calculations, all the compounds studied should be planar or quasi-planar. Consequently, MNDO calculations[7] were repeated on 1 and 2 but now forcing the planarity of the whole system. In both cases, MNDO with optimized geometry and with enforced planarity, the results showed very similar features regarding electronic properties of 1 and 2



4Z 4E

5Z 5E

Figure 2



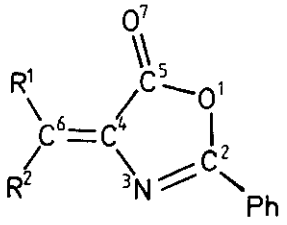
6Z 6E

7Z 7E

Figure 3

(Table 1), so that the differences between 1 and 2 and between 2Z and 2E cannot really be put down to some electronic effect. In summary, it is not easy to account for their different behaviour towards nucleophiles.

Table 1. Electronic properties of 5(4H)-oxazolones 1 and 2 as calculated by MNDO.



					Squares of the atomic coefficients			
R_1	R_2	Compound	$E_{LUMO}(ev)^a$	$E_{LUMO}(ev)^b$	C_5^a	C_6^a	C_5^b	C_6^b
CH_3	Ph	1Z	-0.980	-1.380	0.088	0.372	0.046	0.257
Ph	CH_3	1E	-0.940	-1.360	0.084	0.367	0.049	0.258
H	Ph	2Z	-0.950	-1.310	0.086	0.358	0.048	0.253
Ph	H	2E	-0.890	-1.280	0.088	0.364	0.053	0.257

			Atomic Charges			
R_1	R_2	Compound	C_5^a	C_6^a	C_5^b	C_6^b
CH_3	Ph	1Z	0.350	0.073	0.347	0.087
Ph	CH_3	1E	0.351	0.075	0.362	0.096
H	Ph	2Z	0.349	0.113	0.350	0.111
Ph	H	2E	0.353	0.114	0.367	0.119

a) All geometry, except phenyl rings, optimized

b) Enforced planarity

Quantitative study

When compound 2E reacted with several amines as nucleophiles different degrees of isomerization of its exocyclic double bond from E to Z were determined. The 5(4H)-oxazolone 2E has three reactive sites towards nucleophiles: C-2, C-5 and C-6. Reaction at C-2 was discarded, from considerations based on the present work (no experimental observation of products coming from C-2 attack) and

also from those of Suh et al.[13] where the attack at C-2 occurred only in acidic media. In our reaction conditions only attack on C-5 and C-6 are possible, and obviously the isomerization can only arise from the attack of the nucleophile at C-6. This raises the typical problem of an ambident electrophile reacting with nucleophiles. The importance of the frontier molecular orbital approach in solving such problems has been clearly shown[14], and the qualitative use of the Klopman-Salem equation is widespread. However, not many reports have appeared in the organic literature in which this equation is used in a quantitative way.

Table 2 contains the energy and atomic coefficients for the HOMO, and for the effective HOMO[15], molecular orbital having lone pair character, as well as the N atomic charge for the series of N-nucleophiles used.

Quantification of the Klopman-Salem equation for the nucleophilic attacks at C-5 and C-6 of the planar 5(4H)-oxazolone 2E in benzene (ε = 2.28) led to the results shown in Table 3. As can be seen, the reaction seemed to be governed by charge in all cases. Moreover, in all cases reaction should take place at C-5 while experimentally an initial partial or total isomerization from 2E to 2Z (attack at C-6 followed by reaction at C-5 and opening) was observed. Thus, theoretical calculation did not agree with experiment. However, when $\Delta E_5 - \Delta E_6$ is compared with the percentage of isomerization, a qualitative correlation was observed: the smaller the energy difference the larger the percentage of isomerization. As was to be expected in view of the table 1, quantification of the Klopman-Salem equation for the nucleophilic attacks at C-5 and C-6 of the 5(4H)-oxazolone 2E with optimized geometry led to very similar resuls, and the qualitative order for $\Delta E_5 - \Delta E_6$ is maintained.

Table 2. Energy and atomic coeficient of N atom at HOMO and effective HOMO, as well as N atomic charge, as calculated by MNDO.

Nucleophile	E_{HOMO}(ev)	C_{HOMO}	E_{HOMO*}(ev)	C_{HOMO*}	q_N
$PhCH_2NH_2$	-9.48	-0.127	-10.47	-0.542	-0.283
p-CH_3O-Ph-NH_2	-7.92	0.452	-10.60	-0.566	-0.384
p-CH_3-Ph-NH_2	-8.15	0.483	-11.04	0.588	-0.386
Ph-NH_2	-8.21	-0.500	-11.22	-0.611	-0.382
p-Cl-Ph-NH_2	-8.50	-0.486	-11.23	0.551	-0.375

Probably, some paramenters were badly considered when Klopman-Salem equation was quantitatively used. The dielectric constant introduced in the coulombic contribution (ε = 2.28 for benzene)

may have been underestimated since the "effective ε" should have been used. Obviously an increased ε value would decrease the coulombic contribution in the Klopman-Salem equation, although in order to justify a preferential attack on C-6 an extremely high value for ε is required. These results suggest that the cause of the isomerization may be a reversible attack of the nucleophile at C-6; this attack should be more hindered for 1 because of the methyl group[16]. This suggestion is in agreement with the fact that with harder nucleophiles such as CH_3O^- or HO^-, which must show a greater preference for C-5 attack, the reaction is stereospecific with all 5(4H)-oxazolones.

Table 3. Energetic terms of Klopman-Salem equation for the nucleophilic attack at C-5 and C-6 of 2E, as well as experimental percentage of isomerization.

	C_6			C_5				
Nucleophile	Coulomb. Contrib.	Orbital Contrib.	ΔE_6(ev)	Coulomb. Contrib.	Orbital Contrib.	ΔE_5(ev)	$\Delta E_5-\Delta E_6$	% Isom.
$PhCH_2NH_2$	-0.211	-0.023	-0.234	-0.651	-0.005	-0.656	-0.422	100
p-CH_3O-Ph-NH_2	-0.286	-0.024	-0.310	-0.881	-0.005	-0.886	-0.576	85
p-CH_3-Ph-NH_2	-0.287	-0.025	-0.312	-0.886	-0.005	-0.891	-0.579	80
Ph-NH_2	-0.284	-0.027	-0.311	-0.877	-0.006	-0.883	-0.572	55
p-Cl-Ph-NH_2	-0.279	-0.022	-0.301	-0.861	-0.004	-0.865	-0.564	40

Thermodynamic considerations

When the reactions were carried out on 2Z the stereochemistry of the exocyclic double bond was always maintained. The different behaviour between 2Z and 2E can be explained by the different stability of these compounds, which greatly favours the Z-isomer under the equilibrium conditions given by a reversible attack of the nucleophile at C-6. Table 4 contains the relative heats of formation for 2Z and 2E depending on the theoretical method employed. These resuls are in accordance with the fact that under thermal conditions only 2Z is obtained. The isomerization of 2Z into 2E can be achieved by treatment with HBr; it has been established, moreover, that this isomerization is radical-initiated[17].

Table 4. Relative heat of formation (Kcal/mol) for 2Z and 2E.

Compound	MNDO[a]	AM_1[b]	MMPI[c]
2Z	0.00	0.00	0.00
2E	3.69	5.15	7.11

a) Calculations carried out on 2Z and 2E with enforced planarity

b) Calculations carried out on 4Z and 4E with enforced planarity

c) Calculations carried out on 6Z and 6E on full optimization

EXPERIMENTAL

Nmr spectra were recorded on a Bruker WP-80-CW Spectrometer. 1Z and 2Z were synthesized by standard procedures from the carbonyl compound and hippuric acid[4]. Products 1E and 2E were obtained from 1Z and 2Z using the appropriate isomerization procedures[4]. In all cases the 5(4H)-oxazolone and the corresponding amine were refluxed in benzene until completion (TLC) and the resulting mixture was treated as usual[5].

Aminolysis of 5(4H)-oxazolones:

A solution of the corresponding 5(4H)-oxazolone (3 mmol) and the amine (9 mmol) in anhydrous benzene (40 ml) is heated at reflux temperature until completion (TLC) The solution is cooled and, if a precipitate appears, it is filtered, washed with anhydrous benzene (10 ml) and dried. The benzene solution is washed with diluted hydrochloric acid (15 ml), then with saturated sodium hydrogen carbonate (25 ml), is dried with sodium sulfate and is evaporated under reduced pressure and the product is gathered with the above mentioned precipitate. The isomerization ratio was determined by ^{1}H-nmr integration of the amide proton in the expanded spectra.

Methods used in theoretical calculations:

Electronic structures of the nucleophiles and 1 and 2 were calculated by the SCF semiempirical molecular orbital method MNDO. Measurements of ΔE from the Klopman-Salem equation were made taking 2.28 as "effective ϵ" for benzene. The resonance integral, β_{C-N} was taken as the geometric average of individual β values[18], and finally considering $\beta_C = 1$.

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