REGIOSELECTIVITY IN THE 1,3-DIPOLAR CYCLOADDITION REACTION OF DIAZOMETHANE TO 7-OXANORBORNENE DERIVATIVES

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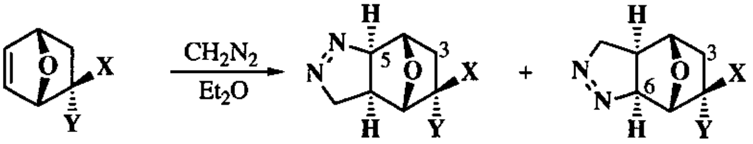
Dedicated to Prof. Edward C. Taylor

Abstract -The regioselectivity of the 1,3-dipolar cycloaddition reaction of diazomethane to 7-oxabicyclo[2.2.1]hept-5-ene derivatives substituted on C-2 is discussed. The observed ratio of regioisomers depends upon the nature of the substituents on C-2 and may be accounted for in terms of TS asyncrony for concerted processes.

The regioselectivity of electrophilic additions to bicyclo[2.2.1]hept-5-ene systems is controlled by the nature of the substituents at C-2.[1] On the other hand, Diels-Alder[2] and 1,3-dipolar cycloaddition reactions of nitrile betaines[3] to 7-oxabicyclo[2.2.1]hept-5-ene derivatives[4] displayed only moderate regioselectivity. In theses last cases kinetic parameters indicate a concerted mechanism. However, the cycloadditions of diazonium betaines with oxanorbornenic compounds are unprecedent in the literature.[5] In this report we wish account for our finding in this field.

Diazomethane reacts with oxanorbornenic derivatives (1a) and (1b) affording adducts (2) and (3) in quantitative yield.[6] Isomeric ratios were determined by integration of the 360 MHz ^{1}H-nmr spectra of the crude reaction mixtures. No isomer from *endo* face attack to the carbon-carbon double bond could be detected.[7]



1a X=CN, Y=OAc
1b X,Y=OCH_2CH_2O

2a (25)
2b (45)

3a (75)
3b (55)

All attemps to carry out the cycloaddition of diazomethane with the related 7-oxabicyclo[2.2.1]hept-5-ene-2-one led to inseparable mixtures formed by products of homologation and/or cycloaddition. It has been reported that the reaction between diazomethane and norbornenic ketones leads to cycloaddition products when a mixture of MeOH-Et_2O is used as a solvent, at -25°C,[8] and Adam *et al.* have prepared these adducts in CCl_4 at 20°C.[9] Homologation procedures of the saturated 7-oxanorbornanone employing diazomethane have been described.[10] In our case, all efforts to obtain exclusively cycloadditions products in the conditions reported for norbornenic ketones were fruitless. Nevertheless, products formally arising from cycloaddition of diazomethane to the double bond of 7-oxabicyclo[2.2.1]hept-5-ene-2-one may be obtained by treatment of derivatives (2a) and (3a) with MeONa/MeOH-formalin.[11]

Adducts (2) and (3) were separated by fractional crystallization (EtOH) of the reaction crude mixture and their structures were determined by NOE experiments in their 360 MHz ^1H-nmr spectra. All signals for both regioisomers were assigned in this fashion.[12] Ratio of regioisomers was evaluated by integration of the signals corresponding to the H-3 *endo* protons.

Table 1

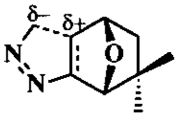
FMO's energies and coefficients for 1a and 1b

Compound	ε(HOMO)	ε(LUMO)	C_5HO	C_6HO	C_5LU	C_6LU
1a	-7.97eV	7.80eV	0.564	0.561	-0.749	0.716
1b	-7.37eV	8.09eV	0.410	0.383	0.775	-0.766
			C_{CH2}HO	C_NHO	C_{CH2}LU	C_NLU
Diazomethane	-6.75eV	7.86eV	-0.74	-0.659	0.662	0.612

The PMO theory provides a qualitative answer to regioselectivity problems in 1,3-dipolar cycloadditions.[13] Using MNDO[14] optimised geometries we have calculated the *ab initio* STO-3G[15] MO's of 2-*endo*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile (1, X=CN, Y=OH a reasonable model for 1a), (1b) and diazomethane[16] (Table 1).

The observed regioselectivity is qualitatively in agreement with a HOMO-dipole controlled reaction.[17] However, the differences in regioselectivity founded between (1a) and (1b) are not explained by this simple PMO's approach. Inspection of the energies and coefficients for both HO-LU interactions indicates that the regioselectivity should be very similar for both compounds (1a) and (1b).

Diazomethane is a good example of ambivalence of 1,3-dipoles,[18] possesing the nucleophilic terminus on the carbon atom and the electrophilic site on the terminal nitrogen. In terms of asincronicity of TS of 1,3-dipolar cycloaddition reactions, significant contribution of structure (4) is then possible.



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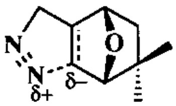

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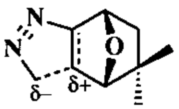

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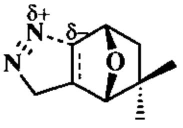

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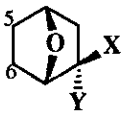
MNDO calculations[14] of model cations and anions in the 7-oxanorbornene system (Table 2) indicate that a homoconjugated ethylenedioxy functionality stabilizes both positive and negative charges developing on C-6 (structures 5 and 6).

Table 2

MNDO calculations of heats of formation of model cations and anions (Kcal/mol)



		Cation (ΔH^o_f)		Anion (ΔH^o_f)	
X	Y	C_5	C_6	C_5	C_6
F	CN	204.7	204.6	-26.6	-32.3
Cl	CN	238.7	239.3	6.74	1.21
OCH_2CH_2O		115.6	111.9	-89.8	-92.4

The contributions of these structures to the nature of the transition state do not modify the regioselectivity predicted by application of the PMO theory. On the other hand, electron deficient groups (F, Cl, CN) on C-2 stabilize a negative charge on C-6.

Thus, an increased contribution of structure (5) to the description of TS in the case of (1a) could be responsible for the difference in regioselectivity observed. In conclusion, the reaction of diazomethane and 7-oxanorbornenic derivatives is, at least in part, controlled by remote substitution on C-2 in the bicyclic sistem.

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12. For instance, isomer 3a: mp 153-155 °C; ir, (KBr) ν_{max}, 2270, 1740; ^{1}H-nmr ($CDCl_3$), δ 1.91 (1H, d, J_{xn} 15.1 Hz, H-3n), 2.23 (3H, s, CH_3), 2.25 (1H, ddd, $J_{5,6}$ 7.5 Hz, $J_{5,\alpha}$ 9.6 Hz, $J_{5,\beta}$ 3.6 Hz, H-5), 2.71 (1H, dd, J_{xn} 15.1 Hz, $J_{x,4}$ 6.0 Hz, H-3x), 4.41 (1H, d, $J_{x,4}$ 6.0 Hz, H-4), 4.41 (1H, ddd, $J_{\beta,\alpha}$, 18.3 Hz, $J_{\beta,5}$ 3.5 Hz, $J_{\beta;6}$ 2.7 Hz, H-β), 4.68 (1H, ddd, $J_{\alpha,\beta}$, 18.3 Hz, $J_{\alpha,5}$ 9.6 Hz, $J_{\alpha,6}$ 1.2 Hz, H-α), 5.23 (1H, ddd, $J_{5,6}$ 7.5 Hz, $J_{6,\alpha}$ 1.2 Hz, $J_{6,\beta}$ 2.7 Hz, H-6), 5.38 (1H, s H-1); ^{13}C-nmr ($CDCl_3$), δ 20.3, 38.6, 43.3, 73.4, 81.5, 82.2, 83.0, 90.5, 117.6, 168.8. Anal. Calcd for $C_{10}H_{11}O_3N_3$, C, 54.30; H, 4.98; N, 19.00. Found, C, 54.26; H, 4.77; N, 18.78. Isomer 2a: mp 122-123 °C; ir, (KBr) ν_{max}, 2250, 1735; ^{1}H-nmr ($CDCl_3$), δ 2.09 (1H, d, J_{xn} 15.1 Hz, H-3n), 2.18 (3H, s, CH_3), 2.46 (1H, ddd, $J_{5,6}$ 7.5 Hz, $J_{6,\alpha}$ 9.6 Hz, $J_{6,\beta}$ 3.6 Hz, H-6), 2.82 (1H, dd, J_{xn} 15.1 Hz, $J_{x,4}$ 6.0 Hz, H-3x), 4.41 (1H, ddd, $J_{\beta,\alpha}$, 18.3 Hz, $J_{\beta,6}$ 3.6 Hz, $J_{\beta,5}$ 2.7 Hz, H-β), 4.68 (1H, ddd, $J_{\alpha,\beta}$, 18.3 Hz, $J_{\alpha,6}$ 9.6 Hz, $J_{\alpha,5}$ 1.2 Hz, H-α), 4.79 (1H, s H-1), 5.00 (1H, ddd, $J_{5,6}$ 7.5 Hz, $J_{5,\alpha}$ 1.2 Hz, $J_{5,\beta}$ 2.7 Hz, H-5), 5.30 (1H, d, $J_{x,4}$ 6.0 Hz, H-4), ; ^{13}C-nmr ($CDCl_3$), δ 20.4 (q,^{1}J 133 Hz), 33.0 (d, ^{1}J 148 Hz), 42.0 (t, ^{1}J 140 Hz), 78.1 (d, ^{1}J 155 Hz), 82.0 (t, ^{1}J, 142 Hz), 85.8 (d, ^{1}J 175 Hz), 95.0 (d ^{1}J, 150 Hz), 117.8 (s), 168.8(s). Anal. Calcd. for $C_{10}H_{11}O_3N_3$, C, 54.30; H, 4.98; N, 19.00. Found, C, 54.20; H, 4.75; N, 18.80.

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