

APPLICATION OF THE MNDO METHOD IN PLANNING THE SYNTHESIS OF Δ^2 -1,2,3-TRIAZOLES

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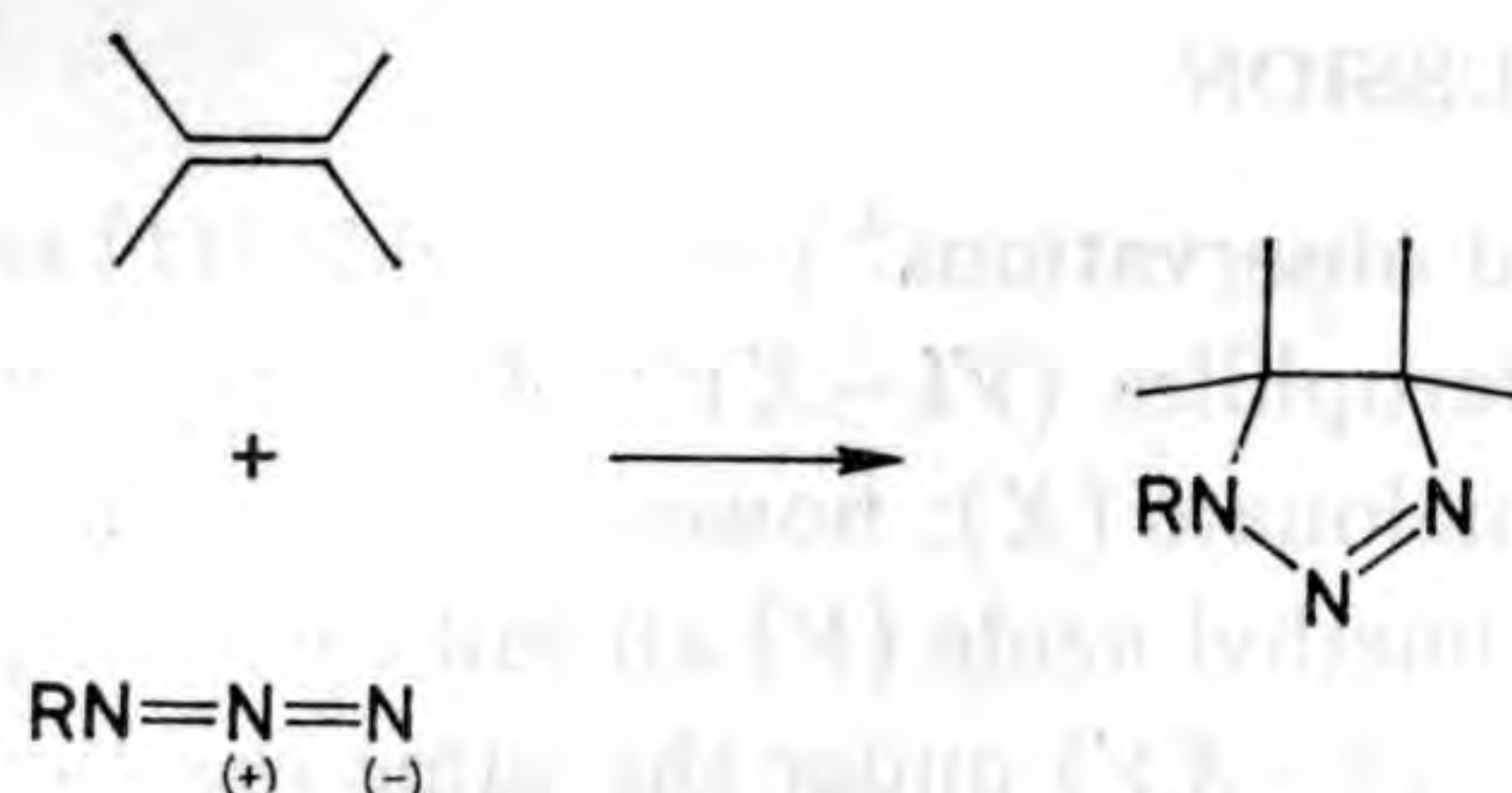
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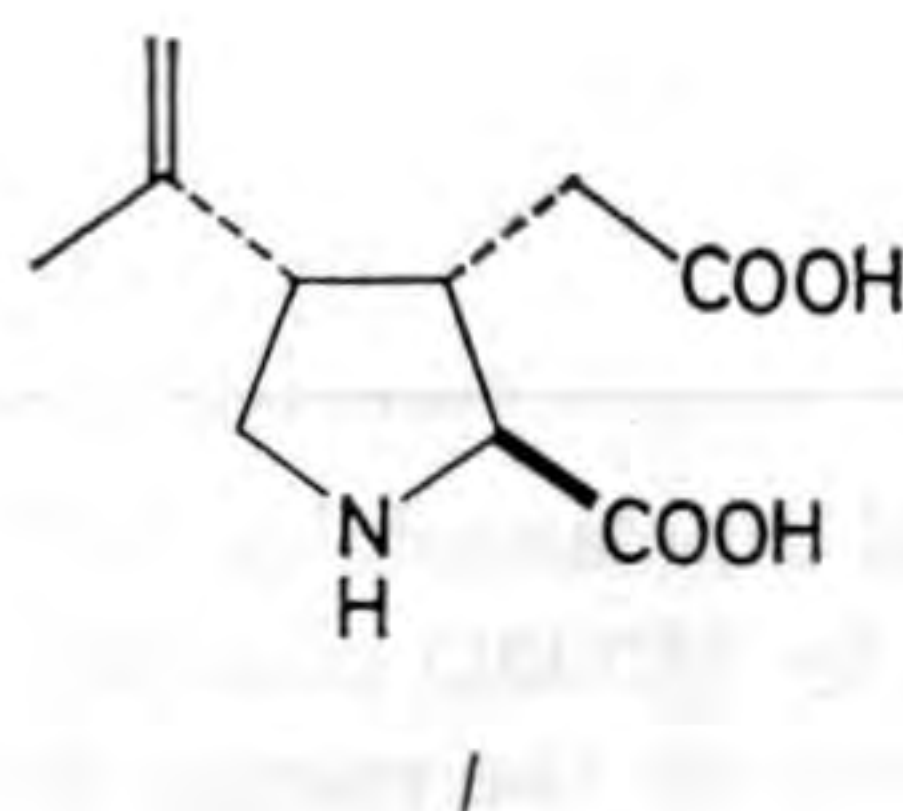
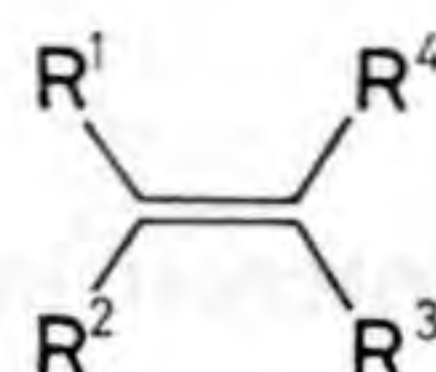
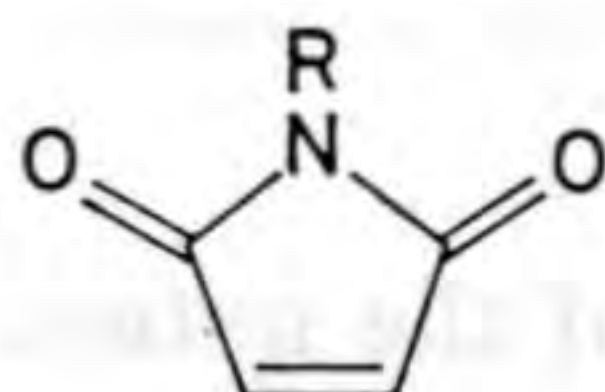
A study on the reactivity of several azides and dipolarophiles in $[3 + 2]$ cycloaddition reaction has been carried out and the results analyzed by MNDO calculations. In all cases it can be demonstrated that the reactivity is dependent not on the energy difference between the HOMO of one reactant and LUMO of the other but on the energy difference of corresponding chemically significant MOs.

As a part of our interest in the synthesis of the natural product kainic acid (*I*) we developed a strategy based on the $[3 + 2]$ cycloaddition reaction of an azomethine ylide and cyclopentenone^{1,2}. For this purpose we investigated the feasibility of cycloaddition reaction of several activated dipolarophiles with diazomethine ylides, generated by thermal decomposition of triazolines. Azomethine ylides have attracted considerable attention in recent years, and a number of new methods for their generation were developed³. However the most attractive method, because of its simplicity, involves extrusion of nitrogen from Δ^2 -1,2,3-triazolines. They are, in principle, easily derived by the way of a $[3 + 2]$ cycloaddition of an organic azide with suitable dipolarophile (Scheme 1).



SCHEME 1

Since our synthetic strategy requires that the substituent on the nitrogen ultimately becomes N-1 on pyrrolidine ring, substituent should (i) initially serve to activate the $[3 + 2]$ cycloaddition of the azide to cyclopentenone, (ii) serve as a protecting group during subsequent transformations, and (iii) be easily removed without degradation of the pyrrolidine ring, the choice of this substituent is crucial to the success of the strategy. The most attractive candidates for this role are thus substituents such as benzyl-, *p*-methoxybenzyl- or triphenylmethyl-, which should in principle satisfy our prerequisites. We have examined the reactions of benzyl azide (*III*), *p*-methoxybenzyl azide (*IV*) and triphenylmethyl azide (*V*) with a number of dipolarophiles (Table I), using the known reactions of phenyl azide (*II*) to provide a reference point.


 RN_3


- II*, $R = C_6H_5$
III, $R = CH_2C_6H_5$
IV, $R = p-CH_2C_6H_4OCH_3$
V, $R = C(C_6H_5)_3$

- VI*, $R = CH_3$
VII, $R = C_6H_5$

- VIII*, $R^1 = R^2 = H$; $R^3 = R^4 = COOC_2H_5$
IX, $R^1 = OC_2H_5$; $R^2 = H$; $R^3 = R^4 = COOC_2H_5$
X, $R^1 = SC_2H_5$; $R^2 = H$; $R^3 = R^4 = COOC_2H_5$
XI, $R^1 = C_6H_5$; $R^2 = H$; $R^3 = R^4 = COOC_2H_5$
XII, $R^1 = CN$; $R^2 = H$; $R^3 = R^4 = COOC_2H_5$
XIII, $R^1 = R^2 = R^3 = H$; $R^4 = COOCH_3$
XIV, $R^1 = R^2 = H$; $R^3 = CH_3$; $R^4 = COOCH_3$
XV, $R^1 = R^2 = R^3 = H$; $R^4 = OCOCH_3$
XVI, $R^1 = SC_6H_5$; $R^2 = H$; $R^3 = R^4 = COOC_2H_5$

RESULTS AND DISCUSSION

In accord with published observations⁴ phenyl azide (*II*) readily undergoes reactions with most of the dipolarophiles (*VI–XV*) (Table I), the notable exception being the *S*-ethyl methylene malonate (*X*); however, benzyl azide (*III*), *p*-methoxybenzyl azide (*IV*) and triphenylmethyl azide (*V*) all fail to undergo cycloaddition reactions with the dipolarophiles (*VI–XV*) under the same reaction conditions.

The similar problem was theoretically discussed by Sustmann and Trill⁵. They have discussed reactivity of substituted phenyl azides in terms of frontier molecular

orbital calculations. We found difficult to rationalize our results by the extrapolation of their ideas and we sought an explanation.

Energy values for the HOMOs and LUMOs and their coefficients were calculated by the MNDO method for a number of azides and dipolarophiles. As the complexity of these calculations increases with the size of groups attached to the carbon-carbon double bond, these calculations were only performed on a limited number of dipolarophiles (Fig. 1).

For the $[3 + 2]$ cycloaddition, variation in the rate of reaction is mainly dependent on the third term in perturbational equation⁶⁻⁸, i.e. on a second order energy term:

$$E'' = \frac{(H'_{ij})^2}{E_i - E_j},$$

where H'_{ij} is the gain in energy arising from overlap of the orbitals Φ_i and Φ_j of two reacting molecules. E_i and E_j are the corresponding orbital energies.

In most cases the contribution from the eigenvector coefficients in the numerator is assumed constant, i.e. independent on the structure of the 1,3-dipole and dipolarophile⁹. Generally, the feasibility of a given reaction is strongly dependent on the energy difference in the denominator; the lower the difference, the higher the reaction rate.

TABLE I

Possible combinations for cycloaddition of azides with dipolarophiles studied. Successful syntheses are marked by a "plus" sign (+)

Dipolarophiles	Azides			
	<i>II</i>	<i>III</i>	<i>IV</i>	<i>V</i>
<i>VI</i>				
<i>VII</i>	+			
<i>VIII</i>				
<i>IX</i>				
<i>X</i>				
<i>XI</i>	+			+
<i>XII</i>	+	+		
<i>XIII</i>	+			
<i>XIV</i>	+			
<i>XV</i>				

^a Results reported in this work; ^b ref. 17; ^c ref. 18; ^d ref. 19.

On the basis of calculated values for frontier orbitals it seems probable that the azide–dipolarophile cycloaddition proceeds through an interaction of HOMO azide and LUMO dipolarophile. When these calculated results are presented using appropriate scaling of values, Fig. 1 is obtained.

It would appear that these reactions exhibit a feature in that the energy difference between interacting orbitals is not critical, but MO coefficients are. In a number of cases the difference in energies between HOMO (azide) and LUMO (dipolarophile) is small and the formation of triazolines is expected to take place. It is, however, evident that the small coefficient on azide nitrogens in the case of benzyl azide (*III*), *p*-methoxy benzyl azide (*IV*) and triphenylmethyl azide (*V*) means that cycloaddition reactions with strongly activated dipolarophiles cannot take place even when the difference in energies for HOMO (azide) LUMO (dipolarophile) is relatively small. In these azides the HOMO and/or LUMO orbital density is not located at $-N_3$ group and it cannot be expected to contribute to cycloaddition reactivity.

Recently it was reported that if the frontier orbitals do not have large coefficients on atoms involved in metathesis, then other chemically significant orbitals (lower

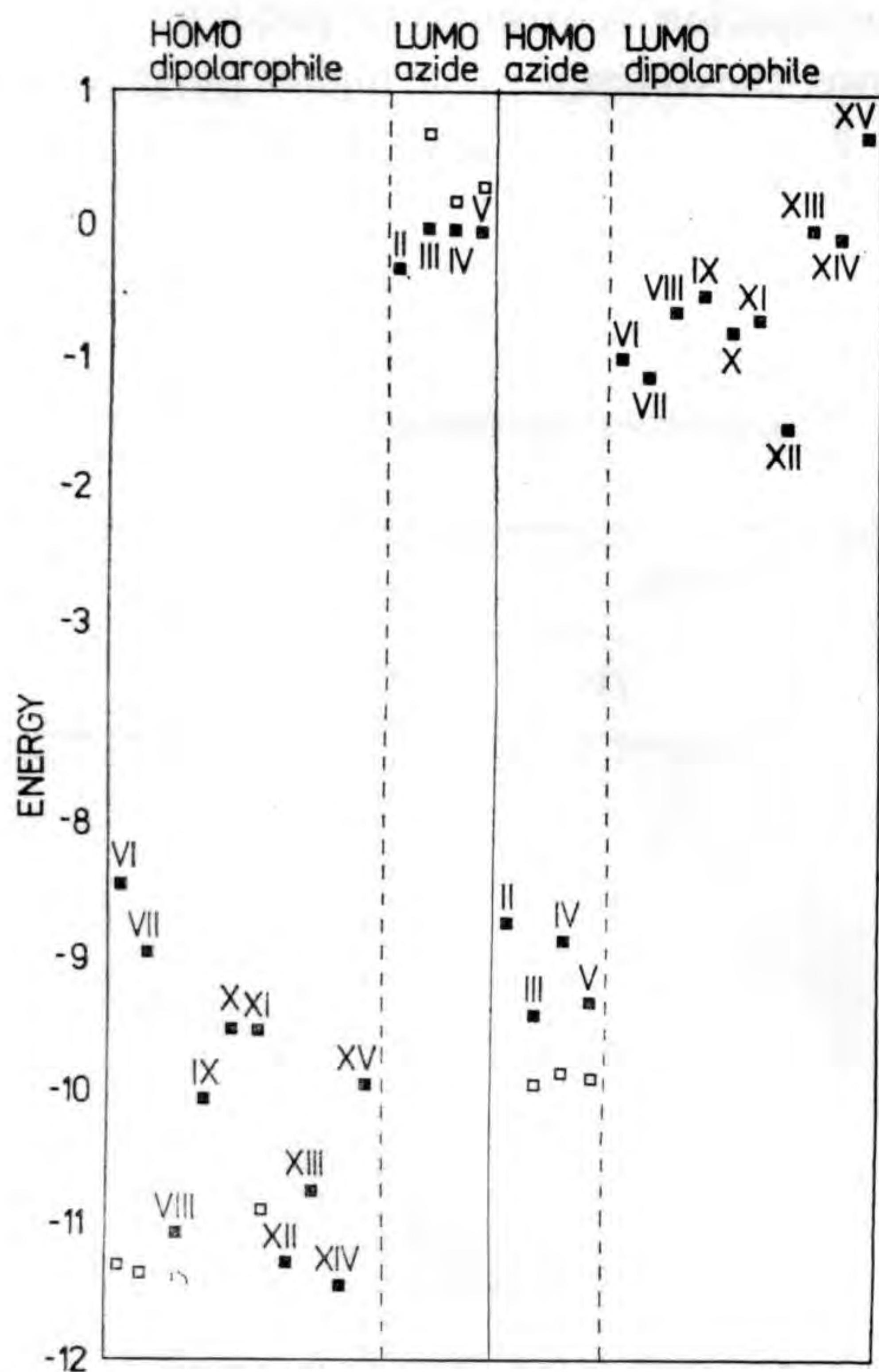


FIG. 1

Energy diagram of HOMO and LUMO levels (filled rectangles) and chemically significant molecular orbitals (empty rectangles) for azides and dipolarophiles. Labels correspond to those in Table I

than HOMO and/or higher than LUMO) that do, should be sought¹⁰. Chemically significant orbitals are MOs with large AO coefficients at centers involved in meta-thesis. If frontier orbitals do not satisfy this prerequisite then HOMO – 1 or HOMO – 2 and/or LUMO + 1 or LUMO + 2 should be taken in the consideration.

We found that our results can be easily explained when the energies of chemically significant orbitals are considered. On the basis of energy difference there is complete agreement between the theoretical and the experimental findings.

These observations clearly suggest that when planning the azide–dipolarophile cycloaddition reactions, the energies of chemically significant orbitals should be examined.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Infrared spectra were recorded by using Perkin–Elmer model 457 grating spectrophotometer. Proton NMR spectra (80 MHz) were obtained with a Varian FT-80A, with tetramethylsilane as internal standard. Mass spectra were taken with Finningan model 8230 (70 eV) mass spectrometer. TLC was carried out using precoated silica plates Kieselgel 60 F₂₅₄, Merck.

Preparation of *p*-Methoxy Benzyl Azide (IV)

p-Methoxy benzyl chloride (4.2 g, 0.027 mol) and sodium azide (1.74 g, 0.027 mol) were dissolved in anhydrous dimethylformamide (40 ml) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water (400 ml), extracted with ether (3 × 50 ml), dried (Na₂SO₄) and the solvent removed under reduced pressure (temperature below 20°C) yielding 3.8 g (87%) of the title compound. IR spectrum: $\nu_{\max}$ 2 980, 2 080, 1 600 and 1 580 cm^{–1} (ref.¹¹).

Preparation of Phenyl Azide (II)

A mixture of conc. HCl (55.5 ml) and water (300 ml) was stirred in an ice salt bath. Phenyl hydrazine (35.5 g, 0.38 mol) was added dropwise over a period of 30 min. The reaction mixture was cooled at 0°C, ether (100 ml) was added and the solution of sodium nitrite (25.0 g, 0.36 mol) in water (30 ml) was added dropwise at such a rate that the temperature never rose above 5°C. The reaction mixture was stirred at room temperature for 2 h. The ethereal layer was separated and the water layer extracted with ether (2 × 100 ml). Combined ethereal layers were dried (MgSO₄) and the solvent removed under reduced pressure at room temperature. Distillation of the residue in vacuo gave the title compound, 29.7 g (76%). B.p. 32°C/2 torr (ref.¹² 41–43°C/5 torr). IR spectrum: $\nu_{\max}$ 3 000, 2 100, 1 600, 1 500, 1 280, 810 and 760 cm^{–1}.

Preparation of Benzyl Azide (III)

To a solution of benzyl chloride (54.0 g, 0.38 mol) in acetone (300 ml) a solution of sodium azide (25.0 g, 0.38 mol) in water was added. The reaction mixture was stirred at room temperature for 2 h, then poured into water (1 000 ml). The organic layer was separated and dried (MgSO₄). Title compound 41 g (73%) was obtained¹³. IR spectrum: $\nu_{\max}$ 3 000, 2 100, 1 600 and 1 500 cm^{–1}.

Preparation of Diethyl Ethoxy Methylene Malonate (IX)

Triethyl orthoformate (100.0 g, 0.67 mol), acetic anhydride (126.0 g, 1.23 mol), diethyl malonate (96.0 g, 0.60 mol) and a catalytic amount of zinc chloride were placed in a three necked flask fitted with a gas inlet tube, a thermometer and a Vigreux column fitted with a still head and a condenser. The contents of the flask were agitated with an air stream during five minutes and heated as follows: 102–115°C for 2.5 h, 115–127°C for 7 h (after eight hours of heating, additional 20.0 g (0.135 mol) of triethyl orthoformate and 25.0 g (0.41 mol) of acetic anhydride was added), and heating was continued at 127–145°C for 2 h and 145–155°C for 2 h. The contents of the flask were filtered and distilled under reduced pressure. Diethyl malonate (19.4 g) was recovered (b.p. 80°C/3 torr) and 32 g (30.8%) of the title compound was obtained, b.p. 107–109°C/0.3 torr (ref.¹⁴ 108–110°C/0.25 torr). IR spectrum: $\nu_{\max}$ 2 980, 1 715, 1 625 and 1 090 cm^{-1} . ¹H NMR spectrum (CDCl_3): 7.60 s, 1 H; 4.20 m, 6 H; 1.35 m, 9 H.

Preparation of Diethyl Thiophenoxy Methylene Malonate (XVI)

Ethoxymethylene malonate (5.0 g, 0.023 mol), thiophenol (5.09 g, 0.046 mol) and a catalytic amount of *p*-toluene sulfonic acid were dissolved in toluene (20 ml) and heated so that the ethanol formed during the reaction was distilled off. The reaction mixture was washed with sodium hydroxide (10 ml of 1M solution) and water (50 ml). The organic layer was separated and dried (Na_2SO_4). Concentration of the resultant solution and distillation in vacuo gave the title compound (4.2 g, 65%), b.p. 172–175°C/0.5 torr. IR spectrum: $\nu_{\max}$ 3 000, 1 720, 1 630, 1 300 and 840 cm^{-1} . ¹H NMR spectrum (CDCl_3): 8.32 s, 1 H; 7.40 m, 5 H; 4.30 m, 4 H; 1.35 m, 6 H. Mass spectrum: found M^+ 280.0777, $\text{C}_{14}\text{H}_{16}\text{O}_4\text{S}$ requires 280.0770.

Preparation of Diethyl Benzalmalonate (XI)

Diethyl malonate (50.0 g, 0.312 mol), benzaldehyde (38.0 g, 0.358 mol) and piperidine (4 ml) were dissolved in benzene (100 ml) and heated to reflux for 18 h. Water formed during the reaction was collected in a Dean and Stark assembly. The reaction mixture was washed with water (50 ml), hydrochloric acid (50 ml of 1M solution) and saturated sodium bicarbonate (50 ml). Combined organic layers were dried (MgSO_4). The solvent was removed under reduced pressure and the residue distilled in vacuo yielding the title compound (64.3 g, 83%), b.p. 125°C/0.1 torr (ref.¹⁵ 142–144°C/2 torr). IR spectrum: $\nu_{\max}$ 2 980, 1 715, 1 630 and 1 060 cm^{-1} . ¹H NMR spectrum (CDCl_3): 7.70 s, 1 H; 7.40 m, 5 H; 4.30 q, 4 H; 1.32 m, 6 H.

General Procedure for the Synthesis of Triazolines

The azide–dipolarophile cycloaddition reactions were carried out following the procedure described by Texier¹⁶. An equimolar mixture of the azide and the dipolarophile were heated at 60°C without solvent for three weeks. In those instances when reaction took place, the triazoline crystallized on trituration with methanol. All products were identified on the basis of their spectroscopic properties and elemental analysis and by comparison of analytical data with literature values. A reaction was adjudged not to have occurred when no discernable products could be detected by thin layer chromatography. The data are given only for the cycloadducts that are not previously reported.

1-(4-Methoxybenzyl)-4,4-bis(ethoxycarbonyl)-5-phenylthio- Δ^2 -1,2,3-triazoline: m.p. 79–80°C; IR spectrum: $\nu_{\max}$ 2 950, 1 730, 1 600 and 1 110 cm^{-1} . ¹H NMR spectrum (CDCl_3): 7.35 s, 5 H; 6.95 AA'BB' q, 4 H; 5.40 s, 1 H; 5.00 AB q, 2 H; 4.20 m, 4 H; 3.70 s, 3 H; 1.30 m, 6 H. For $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5\text{S}$ (443.5) calculated: 59.59% C; 5.64% H; 9.48% N; found: 59.37% C; 5.55% H; 9.37% N.

1-(4-Methoxybenzyl)-4,4-bis(ethoxycarbonyl)-5-phenyl- Δ^2 -1,2,3-triazoline: m.p. 68°C; IR spectrum: $\nu_{\max}$ 2 980, 1 730, 1 600 and 1 120 cm^{-1} . ^1H NMR spectrum (CDCl_3): 7.25 m, 5 H; 6.80 AA'BB' q, 4 H; 5.05 s, 1 H; 4.70 AB q, 2 H; 4.30 m, 2 H; 3.80 s, 3 H; 3.70 m, 2 H; 1.30 t, 3 H; 0.80 t, 3 H. M/e 121 (base peak). Found M^+ 411.1754, $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5$ requires 411.1794. For $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_5$ (411.2) calculated: 64.23% C; 6.08% H; 10.22% N; found: 64.15% C; 6.16% H; 10.22% N.

1,5-Diphenyl-4,4-bis(ethoxycarbonyl)- Δ^2 -1,2,3-triazoline: m.p. 94–96°C; IR spectrum: $\nu_{\max}$ 2 990, 1 740, 1 600 and 1 150 cm^{-1} ; ^1H NMR spectrum (CDCl_3): 7.30 m, 1 H; 5.90 s, 1 H; 4.40 m, 2 H; 3.70 m, 2 H; 1.32 t, 3 H; 0.85 t, 3 H. M/e 180 (base peak), 339 ($M^+ - \text{N}_2$). Found $M^+ - \text{N}_2$ 339.1473, $\text{C}_{20}\text{H}_{21}\text{NO}_4$ requires 339.1471.

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REFERENCES

1. Husinec S., Porter A. E. A., Roberts J. S., Strachan C. H.: J. Chem. Soc., Perkin Trans. 1 1984, 2517.
2. Husinec S., Porter A. E. A., Strachan C. H.: Collect. Czech. Chem. Commun. 52, 207 (1987).
3. Padwa A., Casdoske J. R., Haffmans G., Rebello H.: J. Org. Chem. 52, 1027 (1987); Joucla M., Martier J.: Tetrahedron Lett. 1987, 2973; DeShong P., Kell D. A., Sidler D. R.: J. Org. Chem. 50, 2309 (1985); Grigg R., Kemp J., Warrock W. J.: J. Chem. Soc., Perkin Trans. 1 1987, 2275.
4. Klopman G.: J. Am. Chem. Soc. 90, 223 (1968).
5. Sustmann R., Trill H.: Angew. Chem. 87, 887 (1972).
6. Salem L.: J. Am. Chem. Soc. 90, 543, 553 (1968).
7. Fleming I.: *Frontier Orbitals and Organic Chemical Reactions*. Wiley, London 1976.
8. Gothard H., Boehm F. R.: Chem. Ber. 119, 3158 (1986).
9. Sustmann R.: Pure Appl. Chem. 40, 569 (1971).
10. Modro T. A., Rzepa H. S., Symes J.: J. Chem. Soc., Perkin Trans. 2 1987, 767; Dunn P. J., Rzepa H. S.: J. Chem. Soc., Perkin Trans. 2 1987, 1669.
11. Buckle D. R., Rockell C. J. M.: J. Chem. Soc., Perkin Trans. 1 1982, 627.
12. Fieser L. F., Fieser M.: *Reagents for Organic Synthesis*. Wiley, London 1967.
13. Curtius R., Eherhart G.: Chem. Ber. 55, 1565 (1922).
14. Parham W. E., Reed L. J.: Org. Synth., Coll. Vol. 3, 395 (1955).
15. Allen C. F., Sprangler F. W.: Org. Synth., Coll. Vol. 3, 377 (1955).
16. Texier F., Carrie R.: Bull. Soc. Chim. Fr. 1971, 4119.
17. Ouali M. S., Vaultier M., Carrié R.: Tetrahedron 36, 1821 (1980).
18. Mustafa A., Abdel Dayem Zayed S. M., Khattab S.: J. Am. Chem. Soc. 78, 145 (1956).
19. Sziemies G., Huisgen R.: Chem. Ber. 89, 491 (1966).