Effect of Substituents on the Reactivity of a Double Bond towards $[_{\pi}4_s + _{\pi}2_s]$ and Epoxidation Reactions : A Chemical Manifestation of Orbital Interactions through Space

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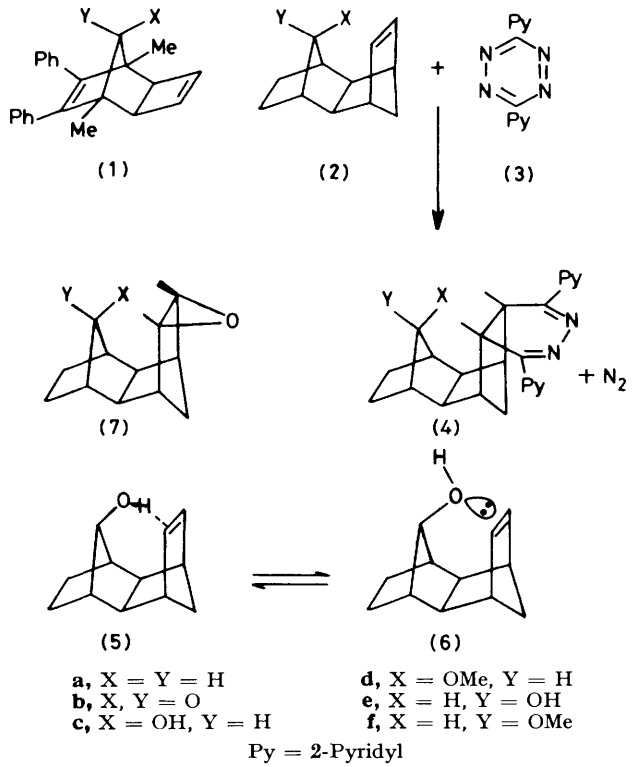
Summary Substitutents have a profound effect on the rates of reaction of (**2**) with the *s*-tetrazine (**3**) and *m*-chloroperbenzoic acid; these observations are interpreted in terms of orbital interactions through space.

WE have reported that the reactivity of the cyclobutene double bond of (**1**) in the $[_{\pi}4_s + _{\pi}2_s]$ reaction with the tetrazine (**3**) is markedly influenced by the nature of remote substituents (**1a**—**d**).[1] The epoxidations of (**1a**—**c**) appeared to be affected in a similar manner.[2] Using a frontier molecular orbital (FMO) model, Paddon-Row has explained these results in terms of orbital interactions through space (OITS) operating between the substituents and the double bond.[3] Thus for a HOMO (**1**)—LUMO (reagent) controlled reaction, which is the case for the reactions of (**2**) with *s*-tetrazines and peracids, anti-bonding admixture of a *syn* oxygen non-bonding orbital into the π cyclobutene MO of (**1d**) causes a narrowing of the HOMO (**1**)—LUMO (reagent) energy gap with a resulting rate enhancement. However bonding admixture of the π^* MO of the carbonyl group of (**1b**) into the π MO widens the energy gap and the rate is retarded.



a, X = Y = H; **b**, X, Y = O; **c**, X = OH, Y = H; **d**, X = OMe, Y = H; **e**, X = H, Y = OH; **f**, X = H, Y = OMe

Py = 2-Pyridyl

Although reports by other workers[4] have since appeared which tend to substantiate the FMO model, a more stringent test is provided by the series of compounds (**2a**—**f**). In this case the substituents are separated by an additional σ bond compared with (**1**) (thereby minimising substituent inductive effects), and the *syn* substituents are spatially closer to the double bond [*ca.* 1·8 Å in (**2c**)]† compared with (**1**) [*ca.* 2·5 Å in (**1c**)]†.

Compounds (**2b**) and (**2e**) were prepared according to literature procedures.[5] The *syn* alcohol (**2c**) could be isolated from $LiAlH_4$ reduction of (**2b**) followed by chromatography under basic conditions.‡§ The ethers, (**2d**) and (**2f**), were prepared from the corresponding alcohols (NaH–dioxan–MeI).

The $[_{\pi}4_s + _{\pi}2_s]$ reaction between (**2**) and the *s*-tetrazine (**3**) led to the quantitative formation of the adducts (**4**) at room temperature. The second order rate constants for this reaction in Me_2SO and $CHCl_3$ solvents are presented in the Table.

The observed rate sequence (**2d**) > (**2a**) > (**2b**) in either solvent is in complete agreement with prediction.[3] The *syn* methoxy compound (**2d**) is 257 times more reactive (in $CHCl_3$) than the ketone (**2b**) despite the severe steric interactions which must be present in the transition state for the formation of (**4d**). That the activation enthalpy for the ketone reaction is some 19 kJ mol^{-1} higher than that for the *syn* methoxy compound (Table) provides further confirmation of the operation of OITS.

The rate data for the *anti* alcohol (**2e**) and methoxy (**2f**) compounds are comparable with those for the parent molecule (**2a**) and indicate therefore that inductive effects are negligible. Indeed, the activation enthalpy for the reaction of (**2f**) is lower than that for (**2a**).¶

† Estimated from Dreiding models. Steric interactions in (**2c**) should increase this separation.

‡ All new compounds gave satisfactory combustion and spectral data.

§ The presence of trace quantities of acid caused the rapid formation of the isomeric bridged ether (addition of OH, across the double bond) (ref. 5). The ease of this reaction convincingly demonstrates the close proximity of the hydroxy group to the double bond.

¶ A $-I$ group such as methoxy would be expected to lower the π MO energy of the double bond resulting in an increase in $\Delta H^{\ddagger}$.

TABLE. Kinetic data for the reactions of (**2**) with the *s*-tetrazine (**3**) and *m*-chloroperbenzoic acid (MCPBA)

Compound	Tetrazine reaction				Epoxidation with MCPBA
	$10^3k(Me_2SO)$[a]	$10^3k(CHCl_3)$[a]	$\Delta H^{\ddagger}$ (Me_2SO)[b,c]	$\Delta S^{\ddagger}$ (Me_2SO)[b,d]	k_{rel}[e]
(**2a**)	12·57	12·86	41·9	−122	1
(**2b**)	1·83	0·3	50·4	−112	0·04
(**2c**)	459	0·92	—	—	—
(**2d**)	108·2	77·2	31·5	−135	13·2
(**2e**)	12·88	5·14	—	—	—
(**2f**)	4·52	4·82	37·7	−144	0·36

[a] Second order kinetics (1 $mol^{-1}s^{-1}$) were obtained spectrophotometrically (550 nm) at 28·8 °C. [b] Obtained from four kinetic measurements over *ca.* 20 °C range. [c] kJ mol^{-1}. [d] J K^{-1} mol^{-1} [e] Relative rate measurements (CH_2Cl_2 solvent) were obtained from competition studies at 22 °C. Concentrations of compounds were determined by ^1H n.m.r. measurements.

The *syn* alcohol (**2c**) shows an impressive kinetic dependence on the solvent, the reaction being some 500 times faster in Me_2SO. The corresponding alcohol (**1c**) behaves similarly[1a] and this solvent effect is due to the different conformations adopted by the OH group in the two solvents. In weak or non-hydrogen bonding solvents (CCl_4, $CDCl_3$) (**2c**) exists exclusively in the intramolecular hydrogen bonding conformation (**5**).** The π MO energy will be depressed[6] which explains why (**2c**) is less reactive than (**2a**) in $CHCl_3$. However in strong donor solvents (Me_2SO) intermolecular hydrogen bonding stabilises the conformation (**6**), which is identical with that of the methoxy compound (**2d**). The similarity in rates of these two compounds in Me_2SO is thereby explained.

The relative rate constants for the formation of the epoxides (**7**)‡ using *m*-chloroperbenzoic acid are also reported (Table). Again the rate sequence agrees with prediction, the *syn* methoxy compound (**2d**) showing a rate enhancement of 330 compared with the ketone (**2b**).

We thank the Australian Research Grants Committee for generous support.

(*Received*, 19*th December* 1977; *Com.* 1285.)

** A single OH stretching vibration for (**2c**) is observed at 3554 cm^{-1} (CCl_4). Compared with the corresponding vibration of the *anti* alcohol (**2e**) (3631 cm^{-1}; $\Delta\nu$ = 77 cm^{-1}), the intramolecular hydrogen bond is unusually strong.

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