Kinetics and mechanism of the reaction of substituted 4-pyrimidine carboxylic acids with diazodiphenylmethane in dimethylformamide

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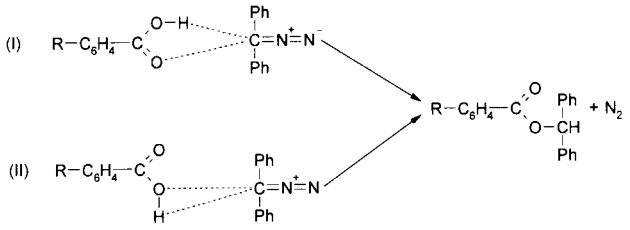
Correlation of the data for the reaction of 11 substituted 4-pyrimidine carboxylic acids with diazodiphenylmethane (DDM) in dimethylformamide (DMF) with calculated atomic charges on the carboxylic group showed that the reaction in this solvent may proceed *via* a concerted transition state.

The reaction of carboxylic acids with diazodiphenylmethane has been widely used in numerous structure-activity studies. The mechanism of this reaction has been thoroughly investigated, starting with the original works of Roberts *et al.*,[1] who proposed two variants with concerted transition states (Scheme 1).



Scheme 1 Concerted five (I) and three (II) member transition states for the esterification of carboxylic acids with DDM

Later the same authors[2] proposed a mechanism involving rate determining proton transfer from the undissociated acid to the diazo carbon and the formation of an ion-pair intermediate (Scheme 2). This second concept was further corroborated by other investigatiors[3,4] for both protic and aprotic solvents, and has been more or less generally accepted. Recently, Eliason[5] proposed a different reaction pathway for the acid catalysed decomposition of DDM, comprising a rate limiting formation of an encumbered diphenylcarbene, which consequently yielded as products, for chloroacetic acid, the corresponding ester, benzhydrol and benzophenone in comparable quantities. The author believes that this mechanism is applicable to the reaction of DDM with other carboxylic acids as well. Our own studies of substituted effects in heterocyclic acids using the reaction with DDM also included the reaction in DMF.[6–8]

$$RCO_2H + Ph_2CN_2 \xrightarrow{\text{slow}} RCO_2^-PhCN_2H^+$$

$$RCO_2^-PhCN_2H^+ \xrightarrow{\text{fast}} RCO_2^-Ph_2CH^+ + N_2$$

$$RCO_2^-Ph_2CH^+ \xrightarrow{\text{fast}} RCO_2CHPh_2$$

Scheme 2 Mechanism of the reaction of carboxylic acid with DDM proceeding *via* the formation of ion pair intermediate in the rate determining step

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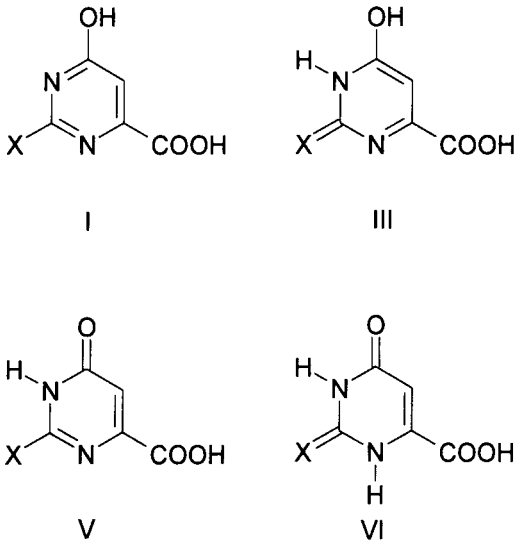
In the present work we investigated the reactivity of series of 4-pyrimidine carboxylic acids with DDM in DMF at 30°C (Table 1, Full text) and also for 2,6-dihydroxy-4-pyrimidine carboxylic acids, at three other temperatures for the calculation of activation parameters (Table 2. Full text).

For the investigated series of 4-pyrimidine carboxylic acids there are ten possible tautometric forms given in Scheme 3 (Full text). The most stable calculated isomeric structures in DMF are as follows: I, III, V, VI

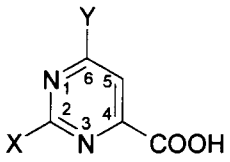


Scheme 3 (In part) Most stable isomers of substituted 4-pyrimidine carboxylic acids in DMF. The most stable calculated tautomers (for each particular acid) are given in Table 3.

Even with the most stable tautomers taken into account, it was not possible to correlate the obtained rate with Hammett type and related parameters. Therefore, we tried to find an alternative method for the quantitative structure reactivity correlation of the investigated compounds. There are reports in the literature on the use of calculated electrostatic charges on carboxylic hydrogen for the estimation of pK_a values of carboxylic acids. Correlation have been made with charges on carboxylic hydrogen, with the charge difference between O and H in carboxylic OH and with the overall charge on carboxylic acid group. Most reports use AM1 and PM3 semi-empirical methods.[9,10]

We believed that a linear free energy relationship in the form of equation (1) where Q denotes a charge on any atom of the carboxylic acid group or alternatively the overall charge of

Table 3 Most stable tautomers for various 2,6-disubstituted-4-pyrimidine carboxylic acids, as calculated by AM1 semiempirical MO method, including solvation effects of DMF (the structures of respective tautomeric forms are given in Scheme 3).



	N (1)	N (3)	X	Y	most stable tautomer in vacuum	most stable tautomer in DMF
1			SCH_3	OH	I	V
2			H	OH	V	V
3			H	H	I	I
4			Cl	CH_3	I	I
5			OH	CH_3	II	III
6	CH_3	H	= O	= O	VI	VI
7			OH	OH	VI	VI
8	CH_3	CH_3	= O	= O	VI	VI
9			SH	OH	VI	VI
10			Cl	Cl	I	I
11			CH_3	OH	I	V

that group should be applicable for correlation of the rate data for 4-pyrimidine carboxylic acids.

$$\log (k_2) = AQ + B \quad (1)$$

In this work atomic charges in the most stable tautomers of 4-pyrimidine carboxylic acids were calculated for all atoms of the carboxylic group. These data are given in Table 4. in the full text, together with the adapted composite charges Q obtained as a weighed sum of charges, according to equation (2), calculated by multiple regression analysis:

$$Q = Cq_h + D_{qo^-} + E\,q_c + F\,q_{o=} \quad (2)$$

with parameters $C = 1.00 \pm 0.231$, $D = 0.06 \pm 0.184$, $E = 0.32 \pm$, 0.137 $F = 1.44 \pm 0.096$.

A straightforward correlation of log (k_2) values with charges on the carboxylic hydrogen (q_h) according to equation (1) was very satisfactory, having the regression coefficient $r = 0.9606$, $n = 11$, $s = 0.001$ (Fig. 1, left).

In the linear regression between log (k_2) and Q the correlation is highly improved fitting the equation (1) with the regression coefficient $r = 0.9974$, $n = 11$, s = 0.002 ($A = 0.0254 \pm 0.0011$, $B = -0.1868 \pm 0.019$) and it is also given in Fig. 1, right.

The excellent correlation with Q could be used to interpret the relative importance of particular atomic charges as an indication of the mechanism which is taking place. The fairly good correlation of log (k_2) values with q_h point to the mechanism outlined in Scheme 2. However, the excellent correlation with Q as well as the high negative entropy of activation (–104.0 J/mol) suggests that the interaction with oxygen must be taken into account, particularly as the only products of the reaction were the corresponding esters. Furthermore, the important contribution of $q_{o=}$ to Q indicated that the transition state for this reaction should resemble to a considerable extent structure (1) in Scheme 1.

Techniques used: UV, IR, MNDO, AM1 and PM3 semiempirical MO calculation.

Tables: 4

Schemes: 3

Figure: 1

References: 23

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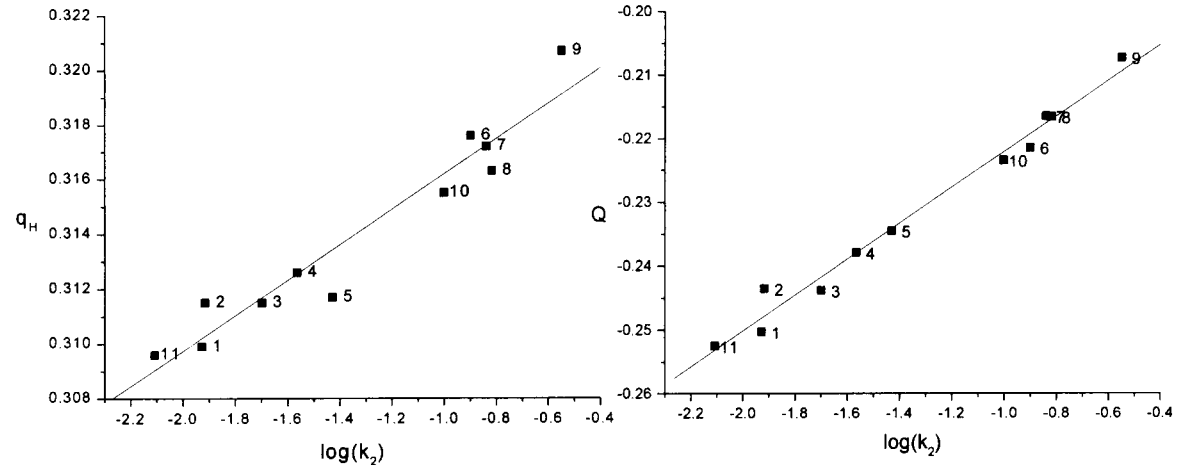

Fig. 1 Left: Correlation of the log (k_2) values with calculated charges on carboxylic hydrogen (q_H): Right: the same correlation of log k_2 with derived charges (Q) according to the equation (2).