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KINETIC AND MECHANISM OF THE REACTION OF SUBSTITUTED 4-PYRIMIDINE CARBOXYLIC ACIDS WITH DIAZODIPHENYLMETHANE IN DIMETHYLFORMAMIDE

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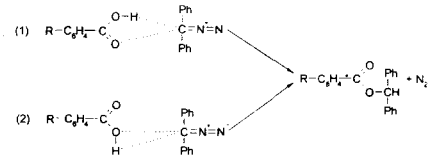
Introduction

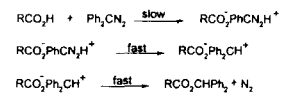
The mechanism of the reaction of carboxylic acids with DDM has been thoroughly investigated by several authors, starting with original work of Roberts and his coworkers[1] who proposed two variants of concerted transition states (Scheme 1), where, alternatively, proton transfer occurs simultaneously with the attack of either carbonyl or hydroxyl oxygen on the diazo carbon.



Transitions state

Scheme 1. Concerted five (1) and three (2) membered transition states for the esterification of carboxylic acids with DDM

Soon after, the same authors[2] proposed a mechanism involving the 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 authors[3,4] in both protic and aprotic solvents.



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

It is interesting to note that after many years of the general acceptance of the widely cited mechanism given in Scheme 2, a proposal of a quite different reaction pathway has been put forward recently. Eliason[5] investigated the acid catalyzed decomposition of DDM in near anhydrous dimethylsulfoxide (DMSO), involving the rate-determining formation of an encumbered carbene, which, for the reaction of chloroacetic acid with DDM, gives as products the corresponding ester, benzhydrol and benzophenone in comparable quantities. The author believes that this mechanism is applicable to the reaction of DDM at low concentration of carboxylic acids in other solvents as well.

Despite the complication of the parallel reaction of esterification in hydroxylic solvents, reaction of carboxylic acids with DDM has been widely used in numerous structure-activity studies. Our own studies of substituent effect in heterocyclic carboxylic acids using the reaction with DDM also included the reaction in DMF[6-8] and the obtained linear free energy correlations were satisfactory.

There are reports on the use of calculated electrostatic charges on carboxylic hydrogen for the estimation of pK_a values of carboxylic acids. Various approaches could be found in the literature. Correlation have been made with charges on carboxylic hydrogen as well as with the overall charge on COOH group. Most of the mentioned reports comprise AM1 and PM3 semiempirical MO methods[9,10].

In this present study we tried to obtain a better insight into the reaction of DDM with eleven 4-pyrimidine carboxylic acids in dimethylformamide as a solvent by correlating the obtained rate data with calculated atomic charges on the carboxylic group in the same solvent.

Method of calculation

The MNDO procedure has proven to be reliable alternative for studying molecular properties in many previous studies[4,10]. The AM1 parametrization was used as a reliable method for atomic charges[8,11]. We used the MOPAC program package, Version 7.01. The optimized geometries of all molecules were obtained by the force field minima in vacuum according to the AM1 method. Several structures were calculated by PM3 method giving completely identical energy ordering of tautomers, a fact that was already reported[12]. The effect of dimethyl formamide (DMF) and ethanol as a solvent is simulated as a dielectric continuum with corresponding dielectric constant, using COSMO model implemented in MOPAC[13].

Results and Discussion

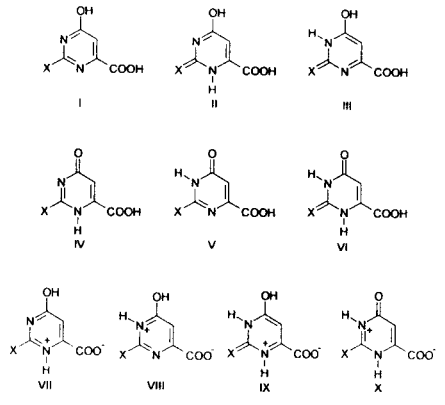
The reaction rates of 4-pyrimidine carboxylic acids with DDM in DMF were measured at equimolar concentration at 30 °C (Table 1) and also at three other temperatures for the calculation of the thermodynamic (activation) parameters (Table 2). However, it was not possible to correlate the obtained data with Hammett type and related LFER parameters.

In this work we aimed to find an alternative general scheme for the quantitative correlation of reactivity with the electronic structure of compounds. We believed that a

$$\log (k) = AQ + B \qquad (1)$$

linear free energy relationship in the form of equation (1), where Q denotes the charge on any atom of the carboxylic acid group or the overall charge of that group should be applicable for the correlation with the rate data of 4-pyrimidine carboxylic acids.

In the investigated 4-pyrimidine carboxylic acids tautomerism is possible, and all the possible tautomeric forms were calculated. Corresponding structures are given in Scheme 3.



Scheme 3. Possible tautomeric forms of substituted 4-pyrimidine carboxylic acids

Table 1. Rate data for the esterification of substituted 4-pyrimidine carboxylic acids with DDM in DMF at 30 °C

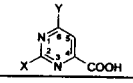
	Substitution	k_2 / dm^{3}mol^{-1}s^{-1}•10^{-2}	log (k_2)
1	2-SMe-6-OH	1.18	-1.928
2	6-OH	1.21	-1.917
3	H	2.00	-1.699
4	2-Cl-6-Me	2.72	-1.565
5	6-Me-2-OH	3.72	-1.429
6	1-Me-2,6-OH	12.6	-0.900
7	2,6-OH	14.5	-0.839
8	1,3-Me-2,6-OH	15.2	-0.818
9	2-SH-6-OH	28.2	-0.550
10	2,6-Cl	9.88	-1.001
11	2-Me-6-OH	0.78	-2.108

*The rate coefficients are reproducible cca ± 3%, of the mean, normally for 3 or 4 runs.

Table 2. Activation parameters for the esterification of 2,6-dihydroxy-4-pyrimidine carboxylic acids with DDM in DMF

log k_2				$\Delta_r H^{\neq}$ / kJ mol^{-1}	$\Delta_r S^{\neq}$ / J mol^{-1} K^{-1}
21 °C	30 °C	35 °C	45 °C		
-0.975	-0.839	-0.6383	-0.3565	47.3 ± 6.4	-104.0±1.2

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

The most stable tautomeric structures of eleven investigated acids in vacuum and DMF were found by semiempirical MO calculation using MNDO-AM1 procedure in the MOPAC package[15] and are given in Table 3.

If either of the mechanism given in Scheme 1 or Scheme 2 is assumed to be operative for the esterification of carboxylic acids with DDM, it should be expected that the main role will be played by the charges on hydrogen (Scheme 2) and also on ether hydroxylic or carbonyl oxygen (Scheme 1).

In Table 4 calculated charges on all the atoms of carboxylic group for the most stable tautomeric structures in DMF as a dielectric medium are given, together with the value of the adapted composite charge Q.

Table 4. Charges on all the atoms of carboxylic acids, calculated by MNDO-AM1 method, using a simulated dielectric continuum with dielectric constant 26.7 (DMF)

	log (k_2)	q_H	q_{O-}	q_C	$q_{O=}$	Q
2-SMe-6-OH	-1.928	0.3099	-0.3206	0.4432	-0.4720	-0.2503
6-OH	-1.917	0.3115	-0.3182	0.4401	-0.4678	-0.2435
H	-1.699	0.3115	-0.3193	0.4401	-0.468	-0.2438
2-Cl-6-Me	-1.565	0.3126	-0.318	0.4433	-0.4654	-0.2379
6-Me-2-OH	-1.429	0.3117	-0.3142	0.4352	-0.4608	-0.2345
1-Me-2,6-OH	-0.900	0.3176	-0.3216	0.4376	-0.4561	-0.2215
2,6-OH	-0.839	0.3172	-0.3234	0.4385	-0.4525	-0.2165
1,3-Me-2,6-OH	-0.818	0.3163	-0.3071	0.423	-0.4492	-0.2166
2-SH-6-OH	-0.550	0.3207	-0.3207	0.4427	-0.4496	-0.2073
2,6-Cl	-1.001	0.3155	-0.3158	0.4444	-0.4578	-0.2255
2-Me-6-OH	-2.108	0.3096	-0.3213	0.4436	-0.4734	-0.2525

According to the equation (2) with parameters C=1.00, D=0.06, E=0.32 and F=1.44

To distinguish between the above mechanistic possibilities we have done an analysis of the contribution of the partial charges on every atom of the carboxylic group of each acid to the composite charge Q, obtained as a weighted sum of charges according to equation (2), calculated by multiple regression analysis:

$$Q = C_{q_H} - D_{q_{O-}} - E_{q_C} + F_{q_{O=}} \qquad (2)$$

The calculated parameters are as follows: C = 1.00 ± 0.23, D = 0.06 ± 0.19, E = 0.32 ± 0.14 F = 1.44 ± 0.10, denoting the relative contribution of the atomic charges to the overall charge of the carboxylic group.

A straightforward correlation of log k_2 rate constants with charges on the carboxylic hydrogen (q_H) according to equation (1) was satisfactory having regression coefficient r = 0.9708 (Figure 1, Left), n = 11, s = 0.001

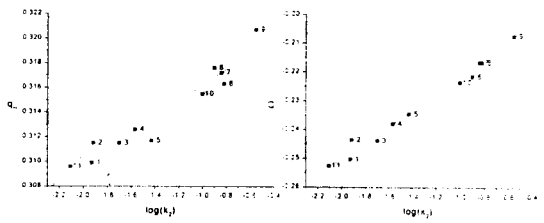


Figure 1. Left: Correlation of the log (k_2) values with calculated charges on carboxylic hydrogen (q_H); Right: the same correlation of log k_2 with derived charges (Q) according to the equation (2).

The linear regression between log (k_2) and composite charge Q is highly improved, fitting the equation (1) with regression coefficient 0.9911, n = 11, s = 0.002 (A = 0.0254 ± 0.0011, B = -0.1868 ± 0.019) which is also given in Figure 1, Right

Conclusion

The excellent correlation of log (k_2) with composite charge Q may 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, points to the mechanism outlined in Scheme 2. But, the excellent correlation with Q, as well as a highly negative entropy of activation (-104.0 J mol^{-1}) suggests that the interaction with oxygen must be taken into account, particularly as an ester was almost the only product of the reaction. The important contribution of q_{O-} to Q indicates that transition state for this reaction should resemble to a considerable extent to the structure (1) in Scheme 1.

The results presented in this paper show the strong dependence of log (k_2) values on atomic charges on carboxylic group, particularly on the charge on hydrogen. They are highly indicative, but not conclusive, regarding the preferred mechanistic intermediate. The presented approach should be tested on the greater number of measurement on the substrates of various structures, and on the reactions done in different solvents.

Experimental

Materials

Diazodiphenylmethane (DDM) was prepared by Smith and Howard's method[16], and stock solutions (ca. 0.06M) were stored in a refrigerator and diluted for use

Solvent

N,N-Dimethylformamide for ultraviolet spectroscopy ("Fluka") was used

Pyrimidine carboxylic acids

All acids used in this work were prepared by know methods[17,18,19,20,21] and had m.p.s. in agreement with those in the literature.

Rate measurements

Rate constants for the reaction of diazodiphenylmethane (DDM) with a series of substituted 4-pyrimidine carboxylic acids were determined by the spectroscopic method proposed by Roberts and his co-workers[22]. Absorbance measurements were performed at 525 nm with 1 cm cell in dimethylformamide (DMF) solution at 30 °C. A Shimadzu 160 A spectrophotometer was used. The reaction were studied as a second-order process, the concentration of acid being 0.006M and of DDM 0.006M. These values are given in Table 1.

References

1. J.D.Roberts, W.Watanabe and R.E.McMahon, *J. Am. Chem. Soc.* 1951, **73**, 760.
2. J.D.Roberts, W.Watanabe and R.E.McMahon, *J. Am. Chem. Soc.* 1951, **73**, 2521.
3. K.Bowden, A.Buckley, N.B.Chapman and J.Shorter, *J. Am. Chem. Soc.* 1964, 3370.
4. R.A.MoreO'Ferral, W.K.Kwok and S.I.Miller, *J. Am. Chem. Soc*, 1964, **86**, 5553.
5. R.Eliason, *Can. J. Chem.*, 1999, **77**, 744.
6. M.Radojković-Veličković, M.Mišić-Vuković and Đ.Dimitrijević, *Bull. Soc. Chim. Beograde*, 1980, **45**, 261.
7. M.Radojković-Veličković and M.Mišić-Vuković, *J. Chem. Soc. Perkin Trans. 2*, 1984, 1975; M.Mišić-Vuković, M.Radojković-Veličković and V.Jezdić, *J. Chem. Soc. Perkin Trans. 2*, 1996, 109.
8. B.Ž.Jovanović and M.Mišić-Vuković, *J. Serb. Chem. Soc.*, 1991, **56**, 461; M.Mišić-Vuković, S.Drmanić and B.Ž.Jovanović,*Heterocycles*, 1994, **37**, 1503.
9. C.Sella, A.Hocquet, D.Bauer, *J. Chem. Research (S)*, 1996, 480-481.
10. A.G.Cook, L.R.Weasner, S.L.Folk, *J. Org. Chem*, 1997, **62**, 7205.
11. Lj.S.Stevović, B.J.Drakulić, I.O.Juranić, S.Ž.Drmanić and B.Ž.Jovanović, *J. Serb Chem. Soc.*, 1998, **63(5)**, 359.
12. G.M.Anstead, P.R.Kym, *Steroids*, 1995, **60**, 383; D.Galanakis, I.A.Calder, C.R.Ganellin, C.S.Owen, P.M.Dunn, *J. Med. Chem.*, 1995, **38**, 3536, G.P.Ford, G.R.Griffin, *Chem. Biol. Interact.*, 1992, **1-2**, 19; J.Ruiz, M.Lopez, J.Mila, I.Tozoya, J.J.Lozano, R.Pouplana, *J. Comput. Aided Mol. Des.*, 1993, **7**, 183.
13. B.Song, R.K.O.Siegel and H.Siegel, *Chem. Eur. J.*, 1997, **3**, 29.
14. A.Klamt and G.Schürmann, *J. Chem. Soc. Perkin Trans. 2*, 1993, 799; D.O'Hagan and H.S.Rzepa, *J. Chem. Soc. Perkin Trans. 2*, 1994, 3.
15. R.C.Bingham, M.J.S.Dewar, D.H.Lo, *J. Am. Chem. Soc.*, 1975, **97**, 1285; (b) P.Bischof, *Croat. Chem. Acta*, 1980, **53**, 51; (c) M.J.S.Dewar, G.Ford, H.S.Rzepa, Y.Yamaguchi, *J. Mol. Struc.*, 1978, **43**, 1325; (d) J.J.P.Stewart, QCPE = 455; (e) H.S.Rzepa, W.A.Wylie, *J. Chem. Soc., Perkin Trans 2*, 1991, 939.
16. L.J.Smith and K.L.Howard, *Org. Synthesys*, 1955, **Coll. Vol. III**, 357.
17. H.Bredereck, W.Jentzsch, G.Morlock, *Ber.93*, 1960, 2405.
18. G.D.Daves, F.Baiocchi, R.K.Robins, G.C.Cheng, *J. Org. Chem.*, 1961, **26**, 2755.
19. H.Gershon, *J. Org. Chem*, 1962, 3507.
20. W.V.Curran and R.B.Angier, *J. Org. Chem.*, 1966, 201.
21. Z.Budešinský and R.Roubinek, *Collect. Czech. Chem. Commun.*, 1961, **26**, 2871.
22. J.D.Roberts, E.A.Mc Elhill and R.Armstrong, *J. Am. Chem. Soc.*, 1949, **71**, 2923.