

SHORT COMMUNICATION

Kinetics of the reaction of 5-substituted orotic acids with diazodiphenylmethane*

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Abstract: Rate constants for the reaction of eight 5-substituted orotic acids with diazodiphenylmethane (DDM) in dimethylformamide (DMF) were determined at 30 °C by the known spectrophotometric method. The determined rate constants were correlated with the equations:

$$\log k_2 = \alpha\sigma_1 + \beta\sigma_R + h$$

$$\log k_2 = \alpha\sigma_1 + \beta\sigma_R + \psi\nu + h$$

to detect the presence and investigate the influence of both electrical and steric substituent effects. The obtained results show that the electrical effect (the localized – field and delocalized – resonance) is predominant and that the steric effect, although present, is relatively small in this reaction.

Keywords: orotic acids, diazodiphenylmethane, reaction kinetics dimethylformamide.

INTRODUCTION

The importance of orotic acid in pyrimidine nucleotide synthesis has been well established.¹ Derivatives of orotic acid substituted at the 5-position, such as chloro, bromo and fluoro,^{2,3} have been shown to exhibit orotic acid antimetabolite activity. Only a few potent inhibitors of orotate phosphoribosyltransferase are known, such as methyl-5-azaorotate and 5-fluoroorotate.⁴

Generally speaking, 5-substituted uracils and their nucleoside and nucleotide derivatives function either as substrates, products, or inhibitors of certain enzymes which catalyzes the synthesis, degradation or interconversion of pyrimidine compounds.

It was to be expected that the investigation of the structure-activity relationships of 5-substituted uracils and specially orotic acids analogs should be an important contribution to a better understanding of their biological activity.⁵

* Dedicated to Professor Živorad Čeković on the occasion of his 70th birthday.

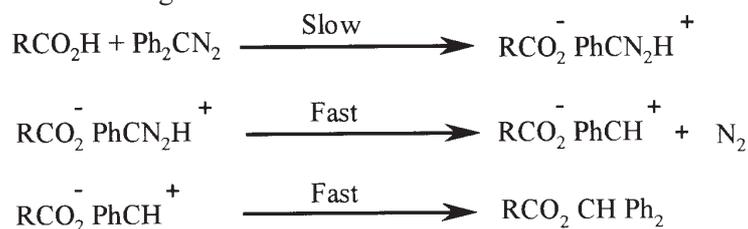
Serbian Chemical Society active member.

In connection with our study of the transmission of polar effects of substituents through the pyrimidine ring, in this paper our previous work⁶ is extended to the study of the reactivity of 5-substituted orotic acids in their reaction with diazodiphenylmethane (DDM) in dimethylformamide (DMF). The intention was to investigate the influence of the *ortho*-effect of substituents in position 5 of orotic acid, bearing in mind the therapeutic importance of orotic acid derivatives with a substituent in the position 5 of the pyrimidine nucleus.

For the reaction with DDM, if tautomerism of the examined acid is possible, it is most important to know the tautomeric form in the solvent used. However, although no specific information on the tautomerism of orotic acid (4-carboxy uracil) is available in the literature, all uracils, thymines and their derivatives have been observed to exist in the diketo form.⁷ Hence, it is very likely that orotic and 5-substituted orotic acids also predominately exist in this form (structure in Fig. 1) in solutions. In our previous investigation, it was found that this form was the most stable one in both vacuum and in dimethylformamide.⁶

RESULTS AND DISCUSSION

The reaction of carboxylic acids with DDM has been widely used in numerous structure-activity studies. Mechanism of the reaction of carboxylic acid with DDM in aprotic solvents⁶ is given in Scheme 1.



Scheme 1. Mechanism of the reaction of a carboxylic acid with DDM, proceeding *via* the formation of an ion pair intermediate in the rate determining step.

The rate determining step involves a proton-transfer from the carboxylic acid to DDM, to form the diphenylmethyldiazonium/carboxylate ion-pair, which rapidly reacts in the subsequent, product-determining step to give esters (or ethers in the case of alcoholic solvents).

The structures of the investigated 5-substituted orotic acids, as well as the values of the second order rate coefficients for their reaction with DDM in DMF at 30 °C are presented in Fig. 1 and Table I.

The rate data from Table I were analyzed using the Charton method.⁸ The rate constant were correlated with the following Eqs (1) and (2).

$$\log k_2 = \alpha\sigma_1 + \beta\sigma_R + h \quad (1)$$

$$\log k_2 = \alpha\sigma_1 + \beta\sigma_R + \psi\nu + h \quad (2)$$

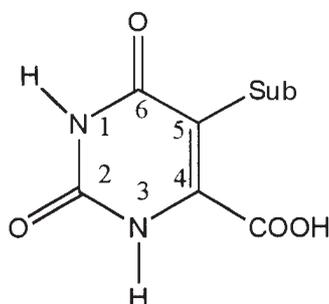


Fig. 1. Structure of the 5-substituted orotic acids.

TABLE I. Rate coefficients, $\log k_2/\text{dm}^3 \text{ mol}^{-1} \text{ min}^{-1}$, for the reaction of 5-substituted orotic acids with DDM in DMF at 30 °C

| Compound | -Sub | $k_2 / \text{dm}^3 \text{ mol}^{-1} \text{ min}^{-1}$ | $\log k_2$ |
|----------|--------------------------------|---|------------|
| 1 | -H | 8.700 | 0.9395 |
| 2 | -Cl | 18.024 | 1.2559 |
| 3 | -Br | 23.082 | 1.3633 |
| 4 | -I | 19.830 | 1.2973 |
| 5 | -NO ₂ | 52.956 | 1.7239 |
| 6 | NH ₂ | 4.092 | 0.6119 |
| 7 | -CH ₃ | 8.778 | 0.9434 |
| 8 | -C ₂ H ₅ | 8.598 | 0.9344 |

In Eqs. (1) and (2), σ_1 , σ_R and ν are inductive, resonance and steric substituent constants, respectively, and the values used were those compiled by Aslam *et al.*⁹ The regression coefficients are α , β and ψ , while h is the intercept.

The results from regression analysis by Eqs. (1) and (2) are expressed by the correlation given in Eqs. (3) and (4).

$$\log k_2 = 0.977 \sigma_1 + 0.677 \sigma_R + 1.010 \quad (3)$$

(±0.079) (±0.078) (±0.035)

$$n = 8 \quad R = 0.9991 \quad s d = 0.055 \quad F = 135.49$$

$$\log k_2 = 0.863 \sigma_1 + 0.639 \sigma_R + 0.107 \nu + 0.969 \quad (4)$$

(±0.114) (±0.079) (±0.081) (±0.045)

$$n = 8 \quad R = 0.994 \quad s d = 0.051 \quad F = 103.96$$

(n – number of points, R – correlation coefficient, $s d$ – standard deviation of the estimate, F – test for the significance of the regression).

According to Charton,⁸ if the intercept in Eq. (3), $h = 1.010$ is different from the experimentally observed value for the data point S=H, *i.e.*, $\log k_0 = 0.9395$, the

steric effect was operative in the investigated reaction. This leads to the conclusion that electrical effects alone are not sufficient to account for the *ortho*-substituent effects. Furthermore, the confidence level of ψ is greater than 90 % in Eq. (4), which confirms the above conclusion.

The regression coefficients of σ_1 , σ_R and ν are all positive, which shows that electron-withdrawing substituents accelerate the reaction and electron-releasing substituents retard it, which is in agreement with the proposed mechanism.

The positive regression coefficient for the steric term corresponds to the reaction being subject to steric acceleration by *ortho*-substituents.

The composition of the electrical effect, P_R was calculated using Eq. (5):

$$P_R = \frac{\beta 100}{\alpha + \beta} \quad (5)$$

The value of P_R was calculated to be 42.54 %. The values of P_R shows that the localized (inductive) effect is more dominant than the delocalized (resonance) effect.

The magnitude (percent) of the steric effect, P_S was calculated using Eq. (6).

$$P_S = \frac{|\psi| 100}{|\alpha| + |\beta| + |\psi|} \quad (6)$$

The magnitude of the steric effect was found to be 6.65 %, which shows that the steric effect, although present, is relatively small.

The magnitudes of α , β and ψ reveal that the reaction is more susceptible to the inductive effect (50.81 %), than to the resonance effect (42.54 %), and the contribution of the steric effect is 6.65 % only.

EXPERIMENTAL

Rate measurements: Rate constants for the reaction of the investigated acids with DDM were determined as reported previously, by the spectroscopic method of Roberts and his co-workers,¹⁰ using a Shimadzu 160 A spectrophotometer. The optical density measurements were performed at 525 nm with 1 cm cells at 30 ± 0.05 °C.

Three to five rate determinations were made for each acid and in every case the individual second-order rate constants agreed within 3 % of the mean.

Materials: DDM was prepared by the Smith and Howard method,¹¹ stock solution of *ca.* 0.06 mol dm⁻³ was stored in a refrigerator and diluted before use.

The solvent was *N,N*-dimethylformamide for ultraviolet spectroscopy (commercial product, Fluka).

Orotic acid, 5-amino and 5-iodoorotic acid were commercial products (Fluka and Sigma-Aldrich). The 5-chloro,¹² 5-bromo,¹³ 5-nitro,¹⁴ 5-methyl¹⁵ and 5-ethylorotic acid¹⁵ were prepared by the known methods and had m.ps. in agreements with those in the literature.

ИЗВОД

КИНЕТИКА РЕАКЦИЈЕ 5-СУПСТИТУИСАНИХ ОРОТИНСКИХ КИСЕЛИНА
СА ДИЗАОДИФЕНИЛМЕТАНОМ

БРАТИСЛАВ Ж. ЈОВАНОВИЋ, FATNI H. ASSALEH и АЛКЕСАНДАР Д. МАРИНКОВИЋ

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Константе брзине за реакцију осам 5-спституисаних оротинских киселина са диазодифенилметаном (DDM) одређене су на 30 °C у диметилформамиду (DMF) као растварачу, познатом спектрофотометријским методом. Константе брзина испитиваних реакција корелисане су следећим једначинама:

$$\log k_2 = \alpha\sigma_1 + \beta\sigma_R + h$$

$$\log k_2 = \alpha\sigma_1 + \beta\sigma_R + \psi\nu + h$$

са циљем да се одреде ефекти супституената. Добијени резултати указују на то да су електрични ефекти супституената (индуктивни и резонантни) преовлађујући, а да су стерни ефекти супституената, иако су присутни, у односу на њих релативно мали.

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