The rate of cyclization of 2′- and 4′-substituted diphenylamine-2-carboxylic acids in sulfuric acid as a function of the electronic properties of substituents

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The kinetic regularities of cyclization of 2′- and 4′-substituted diphenylamine-2-carboxylic acids in sulfuric acid were determined. The rate of cyclization of diphenylamine-2-carboxylic acids is linearly dependent on the nature of substituents in the *meta*-position relative to the reaction site in accordance with the two-parameter Hammett equation.

Key words: diphenylamine-2-carboxylic acids, acridones, cyclization, rate constant, Hammett equation.

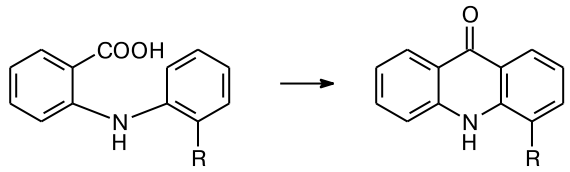
Cyclization of diphenylamine-2-carboxylic acids is a conventional approach to the synthesis of the corresponding practically important acridones. Of special interest are biologically active acridone derivatives, among which there are antimicrobial, antifungal, anticancer, and other agents.[1—7] In particular, acridoneacetic acid derivatives possess such pharmacological properties as low toxicity and the absence of allergenic, mutagenic, and embriotoxic effects that are required for the design of an "ideal" substance for inducing endogenic interferon.[8—14] The acridone fragment is also a part of many natural compounds.[15—19]

Cyclization of diphenylamine-2-carboxylic acids in sulfuric acid is the most available and common method for the preparation of the corresponding acridones bearing no amino and hydroxyl groups.[20—23] The quantitative effect of substituents in the aromatic ring on the rate of such a cyclization is poorly studied. It is known that cyclization in sulfuric acid proceeds most rapidly when the benzene ring bears electron-withdrawing substituents. For example, the reaction time at 100 °C is 15 min and 1 h for the cyclization of 2′-nitrodiphenylamine-2-carboxylic acid and diphenylamine-2,4′-dicarboxylic acid *vs.* 4—5 and 3—4 h for the cyclization of 2′-methyl- and 4′-methyldiphenylamine-2-carboxylic acids, respectively.[24,25]

In the present work. we studied the quantitative dependence of the cyclization rate of diphenylamine-2-carboxylic acids on the electronic properties of substituents.

Cyclization of the 2′-substituted diphenylamine-2-carboxylic acids **1a—e** affords the corresponding 4-substituted acridones **2a—e** (Scheme 1).

Scheme 1



1a—e **2a—e**

R = H (**a**), Me (**b**), COOH (**c**), NO_2 (**d**), Br (**e**)

To perform quantitative evaluation of this reaction, we determined the rate constants at different temperatures (Table 1).

As is seen from Table 1, the rate of cyclization of the nitro acid is considerably higher than those of diphenylamine-2-carboxylic acids with other substituents under study and decreases in the order NO_2 > Br > COOH > H > Me. The following regularitiy was observed: if the electron-withdrawing properties of a substituent increase, the rate of cyclization of the corresponding substrate **1** increases.

Upon cyclization of 4′-substituted diphenylamine-2-carboxylic acids **3b—d,f**, the 2-substituted acridones **4b—d,f** were produced (Scheme 2).

Cyclization of 4′-methoxydiphenylamine-2-carboxylic acid (**3f**) in sulfuric acid affords 2-methoxyacridone (**4f**) in a low yield due to fast side reactions resulting in the formation of the hydroxy derivatives of both the starting diphenylamine-2-carboxylic acid and acridone. The determined values for the rate constants of cyclization of the 4′-substituted derivatives **3b—d** are given in Table 2.

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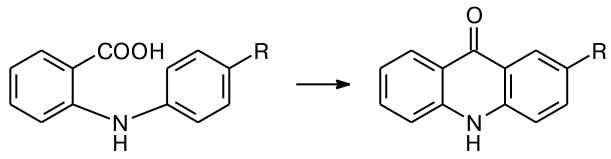
Table 1. The rate constant for the cyclization (k) of 2′-substituted diphenylamine-2-carboxylic acids **1a—e** in sulfuric acid as a function of their structures and temperature

Starting acid	$k \cdot 10^5/s^{-1}$ at different T/°C				
	60	70	80	90	100
1a	—	2.12±0.08	6.88±0.25	21.00±0.81	56.30±2.17
1b	—	1.43±0.05	6.09±0.24	17.29±0.69	55.42±2.21
1c	—	7.87±0.31	27.79±1.11	89.22±3.56	294.00±11.76
1d	15.43±6.17	42.77±1.71	113.70±4.55	246.6±9.86	—
1e	—	8.35±0.33	27.81±1.11	93.6±3.74	298.00±11.92

Scheme 2



3b—d,f **4b—d,f**

R = Me (**b**), COOH (**c**), NO_2 (**d**), OMe (**f**)

As is seen from Table 2, the regularities of the cyclization of 4′-substituted diphenylamine-2-carboxylic acids **3** are the same as those observed in the cyclization of 2′-substituted diphenylamine-2-carboxylic acids **1**, *i.e.*, the reaction rate increases with the enhancement of the electron-withdrawing properties of the substituent.

Thus, the reaction rate is defined to a large degree by the nature of the substituents in the aromatic ring and, when moving from the most electron-donating methyl group to the most electron-withdrawing nitro group, the reaction rate increases 15—30-fold.

The σρ-analysis[26] of the studied constants for the cyclization of 2′-substitued diphenylamine-2-carboxylic acids **1** at 70 °C shows that the effect of the group R on the rate constant is well described by the Hammett equation:

$$\log(k/s^{-1}) = 1.825\sigma + 0.280 \ (R^2 = 0.992), \quad (1)$$

which is reflected by the graph in Fig. 1.

The analogous dependencies was also obtained at 80 and 90 °C, which are described by Eqs (2) and (3), respectively.

$$\log(k/s^{-1}) = 1.640\sigma + 0.858 \ (R^2 = 0.994) \quad (2)$$

$$\log(k/s^{-1}) = 1.524\sigma + 1.351 \ (R^2 = 0.993) \quad (3)$$

The σρ-analysis of the rate constants for the cyclization of 4′-substituted diphenylamine-2-carboxylic acids **3** allowed us to establish that the effect of the group R on the rate constant is well described by the following equations:

$$\text{at 70 °C:} \quad \log(k/s^{-1}) = 2.477\sigma + 0.346 \ (R^2 = 0.991), \quad (4)$$

$$\text{at 80 °C:} \quad \log(k/s^{-1}) = 2.164\sigma + 0.914 \ (R^2 = 0.989), \quad (5)$$

$$\text{at 90 °C:} \quad \log(k/s^{-1}) = 2.028\sigma + 1.340 \ (R^2 = 0.992). \quad (6)$$

From the analysis of these functions, one can conclude that with the increase in the temperature the value of the sensitivity coefficient ρ decreases, which is evidence of a decrease in the dependence of the process rate on the properties of substituents. The value $\rho > 0$ indicates that the electron-withdrawing substituents favors the reactions. The enhancement of the electron-withdrawing properties of substituents results in the increase in the reaction rate.

Thus, it was established that when moving from the most electron-donating methyl substituent to the most electron-withdrawing nitro substituent the cyclization rates of compounds **1** and **3** increase 15-fold at 70 °C and 30-fold at 90 °C. The dependence of the rate constant on the substituent in the *meta*-position relative to the reaction site was evaluated quantitatively using the two-parameter Hammett equation and the constants of this equation were determined for the cyclization of 2′- and 4′-substituted diphenylamine-2-carboxylic acids in sulfuric acid at 70, 80, and 90 °C.

Table 2. The rate constant (k) for the cyclization of 4′-substituted diphenylamine-2-carboxylic acids **3b—d** in sulfuric acid as a function of their structures and temperature

Starting acid	$k \cdot 10^5/s^{-1}$ at different T/°C				
	60	70	80	90	100
3b	–	1.37±0.05	6.11±0.24	14.92±0.59	45.28±1.81
3c	7.51±0.30	22.31±0.89	61.28±2.45	142.8±5.71	–
3d	51.7±2.06	109.4±4.37	250.8±10.03	537.7±21.50	–

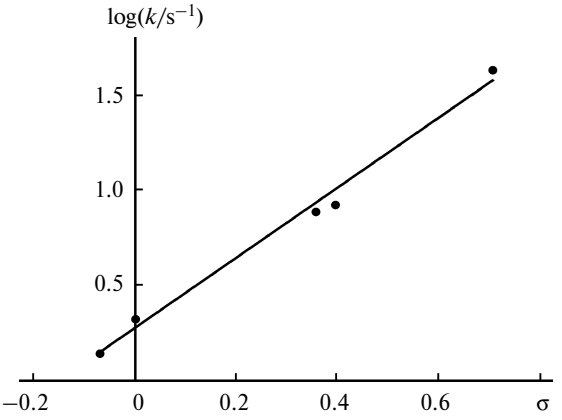


Fig. 1. The effect of the substituent in the aromatic ring of 2′-substitued diphenylamine-2-carboxylic acids **1** on the rate constant for the cyclization (k) at 70 °C; σ is the Hammet constant.[26]

The determined rate constants for the cyclization of diphenylamine-2-carboxylic acids in sulfuric acid allowed selection of optimal conditions (temperature and time) for the synthesis of acridones with different substituents and the resulted correlation dependences between the reactivities and structures of reagents make it possible to predict the reactivities of yet nonstudied diphenylamine-2-carboxylic acids in their cyclization in sulfuric acid.

Experimental

The starting diphenylamine-2-carboxylic acid (**1a**)[22], 2′-methyldiphenylamine-2-carboxylic acid (**1b**)[22], diphenylamine-2,2′-dicarboxylic acid (**1c**)[27], 2′-nitrodiphenylamine-2-carboxylic acid (**1d**)[24], 2′-bromodiphenylamine-2-carboxylic acid (**1e**)[22], 4′-methyldiphenylamine-2-carboxylic acid (**3b**)[22], diphenylamine-2,4′-dicarboxylic acid (**3c**)[27], 4′-nitrodiphenylamine-2-carboxylic acid (**3d**)[24], and 4′-methoxydiphenylamine-2-carboxylic acid (**3f**)[22] were prepared according to known procedures and purified by recrystallization from AcOH.

Cyclization of diphenylamine-2-carboxylic acids. A solution of diphenylamine-2-carboxylic acid **1a—e** or **3b—d**,**f** (0.1 mol) in sulfuric acid (0.75 mol) (d = 1.835 g cm^{-3}) was kept at a specified temperature (60, 70, 80, 90, or 100 °C), samples (0.050—0.100 g) being withdrawn from the reaction mixture at definite intervals. The quantitative determination of the starting compounds and reaction products in the reaction mixtures was performed by quantitative TLC using a Sorbfil densimeter according to the previously developed procedure.[28]

The required calculations, graph plotting, and statistical processing of the data obtained were performed using the Microsoft Office Excel 2007 program.

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