Determination of the activation parameters and the mechanism for atropisomerization of (*S*)-3-(2-chlorophenyl)-2-[2-(6-diethylaminomethylpyridin-2-yl)vinyl]-6-fluoroquinazolin-4(3*H*)-one †

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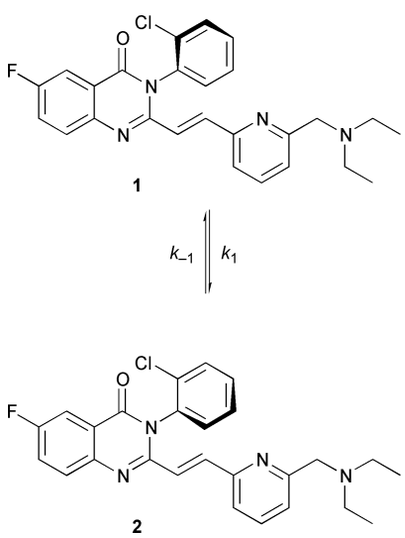
Values of $\Delta H^{\ddagger} = 111.6 \pm 0.3$ kJ mol^{-1} (26.7 ± 0.1 kcal mol^{-1}) and $\Delta S^{\ddagger} = -25.7 \pm 0.9$ J K^{-1} mol^{-1} (−6.1 ± 0.2 cal K^{-1} mol^{-1}) have been determined for the atropisomerization of (*S*)-3-(2-chlorophenyl)-2-[2-(6-diethylaminomethylpyridin-2-yl)vinyl]-6-fluoroquinazolin-4(3*H*)-one in decane. Based on molecular mechanics calculations in the literature and an observation that more polar solvent does not increase isomerization rate, it is proposed that the isomerization occurs *via* a planar non-ionic transition state in which the carbonyl oxygen and the 6-chloro substituent are coplanar with each other.

Introduction

Compounds containing quinazolinone ring systems exhibit a large variety of biological effects,[1] such as antiinflammatory,[2] antimalarial,[3] anticonvulsive[4] and hypotensive[5] activities. Once it was recognized that substituents at the 2 and 3 positions modulate the hypertensive and antiinflammatory activities,[5,6] a large number of 2-alkyl-3-arylquinazolin-4(3*H*)-ones were synthesized and screened to develop new drugs. However, in many of these studies it was not recognized that the 2-alkyl-3-arylquinazolin-4(3*H*)-ones were stereochemically analogous to the *ortho* substituted biphenyls and therefore isolatable rotational isomers might exist. The first observation of restricted internal rotation in the 3-aryl C–N bond was reported in 1975 based on ^{1}H NMR evidence.[7] Later it was shown that these types of atropisomers[8] are resolvable and stable at room temperature but racemize at elevated temperatures.[9]

We report here activation parameters for atropisomerization of (*S*)-3-(2-chlorophenyl)-2-[2-(6-diethylaminomethylpyridin-2-yl)vinyl]-6-fluoroquinazolin-4(3*H*)-one **1** (Scheme 1) and propose a mechanism for the process. It has been shown in the literature that the biological effects of atropisomers can be different[10] and because the atropisomers can interconvert during synthesis and formulation development, we determined the activation parameters in order to estimate the atropisomerization rate constants at different temperatures.



Scheme 1 Atropisomerization of 3-(2-chlorophenyl)-2-[2-(6-diethylaminomethylpyridin-2-yl)vinyl]-6-fluoroquinazolin-4(3*H*)-one (**1**).

Results and discussion

Detailed discussion about the synthesis and resolution is provided in a separate paper.[11] The enantiomers were separated by preparative HPLC chromatography and the achiral purity of the isomers was >98% based on reversed-phase HPLC chromatography. The kinetic experiments to determine activation parameters were performed as follows. To prepare a stock solution, approximately 2.5 mg of **1** were dissolved in 30 µl dichloromethane. The racemization reaction was immediately initiated by injecting 20 µl stock solution into 10 ml decane in a three-necked flask; the solution was vigorously stirred with a stirbar and was thermostatted beforehand for at least 15 minutes in an oil bath (Omega CN76000 temperature control unit). Before the first sample was taken, the isomerization reaction was allowed to proceed at least 0.2 half-lives in order to obtain samples containing at least 7% the other atropisomer **2**. The delay was necessary because the prerequisite for an accurate kinetic analysis was determination of the exact ratio between the two isomers. After an interval, a 150 µl sample was withdrawn with a syringe and was immediately discharged into a glass vial which was cooled in an ice-bath. The number of samples taken at each temperature varied between 12–16 and six different temperatures were used between 100 and 150 °C. Samples were analyzed by HPLC using a ChiralPac OD 4.6 × 50 mm column with a Hewlett Packard HP-1090 system. 5 µl samples were injected, eluted with 5% ethanol in hexane at flow rate 1.00 ml min^{-1} and monitored at 332 nm. The retention time for **1** was 2.3 min and for the other atropisomer **2**, 3.1 min. First order rate constants for the racemization, k_{obs}, were obtained from the plots of ln $(A - A_{\infty})$ against time. A is the peak area of **1** divided by the sum of peak areas of **1** and **2** in the HPLC chromatogram and A_{∞} is 0.5, because after racemiz-

† Electronic supplementary information (ESI) available: the kinetics for reactions of **1** and **2** at 100–150 °C. See http://www.rsc.org/suppdata/p2/b0/b010090k/

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Table 1 Observed first order rate constants for the racemization of **1** in decane

T/°C	k_{obs}/s^{-1}	s.d.
100	8.28×10^{-5}	0.02×10^{-5}
	8.55×10^{-5}	0.04×10^{-5}
110	2.20×10^{-4}	0.01×10^{-4}
	2.24×10^{-4}	0.01×10^{-4}
120	5.45×10^{-4}	0.02×10^{-4}
	5.48×10^{-4}	0.02×10^{-4}
130	1.30×10^{-3}	0.01×10^{-3}
	1.30×10^{-3}	0.01×10^{-3}
140	2.99×10^{-3}	0.02×10^{-3}
	3.10×10^{-3}	0.03×10^{-3}
150	6.61×10^{-3}	0.07×10^{-3}
	6.81×10^{-3}	0.08×10^{-3}

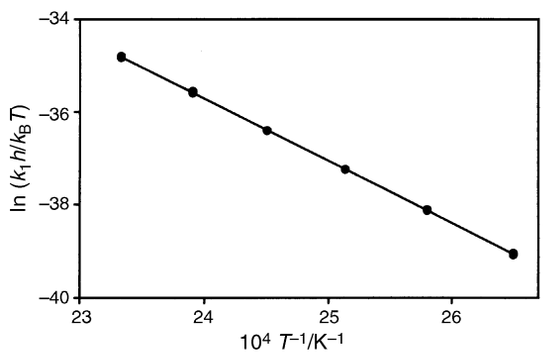
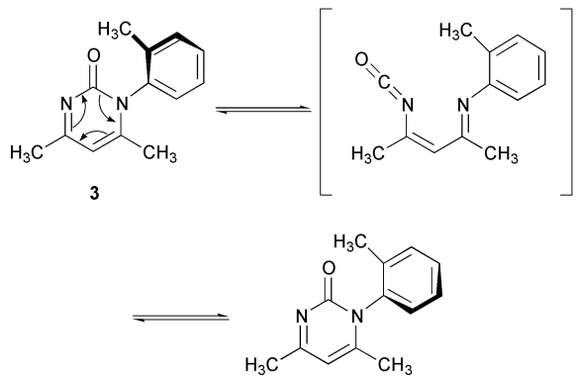


Fig. 1 Eyring plot for the atropisomerization of **1** in decane. Duplicate determinations at each temperature are plotted. The solid line represents equation $y = -1.34x - 3.09$, ($r^2 = 0.9999$) from the linear regression analysis.

ation a 1 : 1 ratio of **1** and **2** was measured. Reactions were monitored for between 3 and 5 half-lives and in every case good first-order kinetics were obtained. The rate constant values from these experiments are shown in Table 1.

The activation parameters were determined from the Eyring plot[12] shown in Fig. 1. The measured first-order rate constants, k_{obs}, represent the rate constants for racemization, which equal the sum of k_1 and k_{-1}, the rate constants for enantiomerization. Enantiomerization rate constants for the forward and reverse processes are numerically identical but have opposite signs. For construction of the Eyring plot, rate constants for the enantiomerization were used; these were obtained from the measured rate constant values by dividing them by a factor of two ($k_{obs} = k_1 + k_{-1}$; $k_1 = k_{-1}$; therefore $k_1 = k_{obs}/2$). The measurements shown at each temperature are duplicates. The value of activation enthalpy $\Delta H^{\ddagger} = 111.6 \pm 0.3$ kJ mol^{-1} (26.7 ± 0.1 kcal mol^{-1}) was calculated from the gradient and the value of activation entropy $\Delta S^{\ddagger} = -25.7 \pm 0.9$ J K^{-1} mol^{-1} (-6.1 ± 0.2 cal K^{-1} mol^{-1}) was obtained from the intercept after multiplying with the gas constant (R). Based on these numbers, the calculated values for the Gibbs energy of activation are $\Delta G^{\ddagger} = 118.6 \pm 0.3$ kJ mol^{-1} at 0 °C, $\Delta G^{\ddagger} = 119.3 \pm 0.3$ kJ mol^{-1} at 25 °C, $\Delta G^{\ddagger} = 119.6 \pm 0.3$ kJ mol^{-1} at 37 °C, and $\Delta G^{\ddagger} = 121.2 \pm 0.3$ kJ mol^{-1} at 100 °C. These values correspond to half-lives of 187 years, 2.8 years, 171 days, and 137 minutes for the atropisomerization at each temperature, respectively.

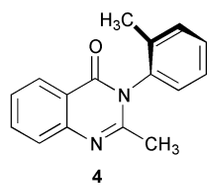
It is proposed in the literature that the atropisomerization of **3** and its sulfur analog 1-(2-methylphenyl)-4,6-dimethylpyrimidine-2(1*H*)-thione would occur *via* a ring opened intermediate as shown in Scheme 2.[9] In this mechanism the bond between N1 and C2 breaks in a 3,3-electrocyclic rearrangement, leading to isocyanate or isothiocyanate intermediates, respectively. The 6-methylphenyl ring is then free to rotate to give, when the pyrimidin-2-one ring recloses with the methyl behind the plane, the other atropisomer. This kind of isomerization mechanism cannot be operative in the case of **1** because it



Scheme 2 Literature mechanism for the racemization of **3**.[9]

requires breaking a C–N bond of an aromatic ring and forming a ketene intermediate in a concerted manner. Formation of such a high energy intermediate is most probably an energetically unfavorable reaction.[13]

We propose that **1** isomerizes with the same mechanism suggested for methaqualone **4** by rotating around the N–C



single bond *via* a planar non-ionic transition state.[9] Because the pyrimidin-2-one ring in **1** has two different *ortho*-substituents, opposite rotations of the 6-chlorophenyl ring lead to two different possibilities of isomerization. It is widely accepted that the steric factors almost entirely control the atropisomerization rate of the *ortho*-substituted biphenyls.[14] An application of this principle has been demonstrated in the molecular mechanics calculations of **3**.[15] It is shown that the repulsion between the bulkier methyl groups is much higher than the repulsion between the arylmethyl group and the smaller carbonyl oxygen. Therefore the rotation occurs *via* a transition state in which the carbonyl oxygen and the 6-methyl substituents are coplanar with each other. In the case of **1**, the situation must be similar because the pyridinylvinyl substituent is even bulkier than the methyl group in **3**.[16]

The proposed mechanism is consistent with the observed solvent effect. In addition to the rate constants measured in decane, kinetic experiments were also performed in 3-methylbutan-1-ol at 120 °C in order to study how solvent polarity affects the isomerization rate. The relative permittivity, ε, of decane is 1.99, whereas 3-methylbutan-1-ol is more polar, having $\varepsilon = 14.7$ at 25 °C.[17] From duplicate experiments, a rate constant $k = 1.79 \pm 0.01 \times 10^{-4}$ s^{-1} was measured in 3-methylbutan-1-ol, whereas $k = 5.47 \pm 0.03 \times 10^{-4}$ s^{-1} was obtained in decane at the same temperature. The fact that the observed rate constant is a factor of 3 *smaller in the more polar solvent* clearly demonstrates the non-ionic nature of the transition state of the isomerization and is consistent with the proposed mechanism.

If **1** and **3** both isomerize *via* the proposed mechanism, **1** should have a somewhat smaller Gibbs free energy value than **3** because the chloro substituent on the rotating aryl group is less bulky than the methyl group in **3**.[18] This is indeed the case. For **3** a value of $\Delta G^{\ddagger} = 126.8$ kJ mol^{-1} at 37 °C can be calculated from the published results.[15] The difference in the $\Delta G^{\ddagger}$ values indicates that **1** isomerizes 16 times faster than **3** at 37 °C. Furthermore, a value of $\Delta G^{\ddagger} = 131.6 \pm 0.4$ kJ mol^{-1} has been reported for methaqualone (**4**) in diphenyl ether at 135 °C.[10] This also corresponds to the reaction 16 times faster than **1** at the same temperature.

Experimental

Analytical and spectroscopic data for **1** and **2**.

For **1**; mp 139–140 °C (from EtOH–heptane); $[a]_D$ +43.2 (*c* 1 in MeOH); λ_{max}(MeCN : 0.2% HCOOH in H_2O = 20 : 80)/nm 210, 330; δ_H (400 MHz; $CDCl_3$) 1.24 (6 H, br s), 2.83 (4 H, br s), 4.00 (2 H, br s), 6.89 (1 H, d, *J* 15), 7.30 (1 H, m), 7.39–7.42 (1 H, m), 7.49–7.57 (4 H, m), 7.63–7.65 (1 H, m), 7.74–7.70 (1 H, m), 7.81–7.84 (1 H, m), 7.96 (1 H, d, *J* 15), 7.96 (1 H, m); *m*/*z* 463 ($M + H^+$); (**1**)·$MeSO_3H$ (Found: C, 57.81; H, 5.03; N, 9.96. $C_{27}H_{28}ClFN_4O_4S$ requires C, 58.01; H, 5.05; N, 10.02%).

For **2**; mp 139–141 °C (from EtOH–heptane); $[a]_D$ −43.5 (*c* 1 in MeOH); λ_{max}(MeCN : 0.2% HCOOH in H_2O = 20 : 80)/nm 210, 330; δ_H (400 MHz; $CDCl_3$) 1.04 (6 H, br s), 2.56 (4 H, br s), 3.69 (2 H, br s), 6.89 (1 H, d, *J* 15), 7.18 (1 H, m), 7.38–7.40 (2 H, m), 7.48–7.54 (3 H, m), 7.59–7.64 (2 H, m), 7.78–7.82 (1 H, m), 7.95 (1 H, d, *J* 15), 7.92–7.94 (1 H, m); *m*/*z* 463 ($M + H^+$).

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