Intermediates in the Paal-Knorr Synthesis of Pyrroles

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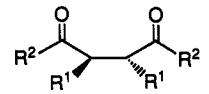
The mechanism of Paal-Knorr reaction between a 1,4-dicarbonyl compound and ammonia or a primary amine to form a pyrrole is explored. In aprotic solvents and in aqueous solutions near neutrality, *d,l* diastereomers of 3,4-dimethyl- and 3,4-diethyl-2,5-hexanediones (**1r** and **2r**) formed pyrroles 1.3–57.0 times faster than the corresponding meso diastereomers (**1m** and **2m**). This contradicts any intermediate, such as the enamine **15**, which does not remain saturated at *both* the 3- and 4-positions through the rate-determining step. The demonstrated stereoisomeric difference in reactivity coupled with the following results support the hemiaminal (**9**) as the intermediate undergoing cyclization in the rate-limiting step of the Paal-Knorr reaction: (1) The reaction rate was adversely affected by increase in the size of the alkyl substituents on the dione. (2) Racemic 2,3-dimethyl-1,4-diphenyl-1,4-butanedione (**3r**) was more reactive toward ammonium acetate (2.2:1) and 2-aminoethanol (11.2:1) than the meso isomer (**3m**), ruling out the involvement of the less substituted enamine **14**. (3) The relative rate of pyrrole formation of 1,4-diphenyl-1,4-butanedione (**5**) and its dimethoxy (**6**) and dinitro (**7**) derivatives (1:03:6) does not support cyclization of the imine (**11**) to the pyrrolinium ion (**12**). (4) The rates of reaction of 2,2,3,3-tetradeuterio-1,4-diphenyl-1,4-butanedione (**5D**) and perdeuterio-2,5-hexanedione (**4D**) were very close to those of unlabeled diketones, indicating the absence of a primary isotope effect in the reaction. (5) Neither the isomerization of the unreacted diastereomers of **1**, **2**, and **3** nor hydrogen exchange of **4D** and **5D** was detected during the reaction.

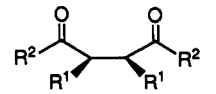
Introduction

A pyrrole ring is part of many important biological compounds.[1] The condensation of 1,4-dicarbonyl compounds with primary amines constitutes a very useful method for generating pyrroles. This reaction, known as the Paal-Knorr condensation,[2,3] is applicable to a wide variety of γ-dicarbonyl compounds and primary amines. In spite of its synthetic utility, the mechanism of the Paal-Knorr reaction is still not completely understood. Previously one of us reported[4] stereoisomer effects on the rate of the reaction, which were not addressed in the recently proposed mechanism,[5] and which have strong implications for the reaction mechanism.[6]

Although the reaction has been studied with various amines, the effect of substituents on the starting diketone has not received much attention. The neurotoxicity of hexane has been shown in our laboratory[7] and by others[8] to be caused by its metabolic oxidation to 2,5-hexanedione (**4**) and by the subsequent reaction of the diketone with amino groups of proteins. Our continuing interest in understanding the pathogenesis of hexane neurotoxicity has led us to the preparation of substituted 2,5-hexanediones and the measurement of their rates of pyrrole formation. Previously, the diastereomers of 3,4-dimethyl-2,5-hexanedione (**1r** and **1m**) were separated and the greater

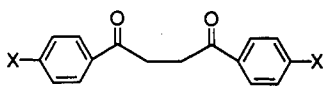


1r, $R^1 = R^2 = CH_3$
2r, $R^1 = C_2H_5$; $R^2 = CH_3$
3r, $R^1 = CH_3$; $R^2 = C_6H_5$



1m, $R^1 = R^2 = CH_3$
2m, $R^1 = C_2H_5$; $R^2 = CH_3$
3m, $R^1 = CH_3$; $R^2 = C_6H_5$

4, $R^1 = H$; $R^2 = CH_3$



5, X = H
6, X = OCH_3
7, X = NO_2

toxicity of the *d,l* over the meso diastereomer was attributed to its higher reactivity with primary amines.[9] The racemic pairs of other 3,4-dialkylhexane-2,5-diones were also found to react with benzylamine in cyclohexane more rapidly than their meso analogues.[4] This difference in stereoisomer reactivity can be expected to provide some insight into the mechanism of Paal-Knorr synthesis. Several intermediates (Scheme I) have been proposed for the reaction, although only one (**11**) has been detected in reactions involving **4** and a primary amine.[10] In this paper we describe several experiments specifically designed to differentiate the involvement of various intermediates and pathways. A mechanism consistent with our results as well as with observations reported previously is presented.

Results

A. Substituted 2,5-Hexanediones. The rates of pyrrole formation were first studied for the *d,l* (**1r** and **2r**) and meso (**1m** and **2m**) isomers of 3,4-dimethyl- and 3,4-diethyl-2,5-hexanediones. The dependence of the rate on the pH and the nature of primary amine was investigated.

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Scheme I

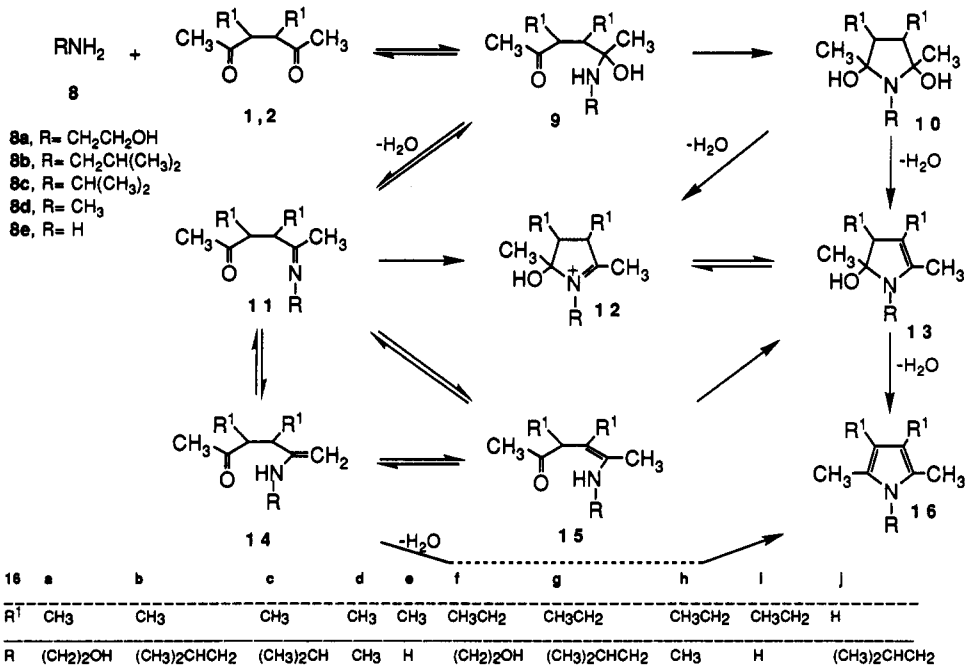

Table I. Second-Order Rate Constants for Pyrrole Formation in Chloroform

entry	diketone	amine	concn, mM[a]	product	$k \times 10^6$, M^{-1} s^{-1}
1	**1r**	**8e**	200	**16e**	341.1 ± 14.4
2	**1m**	**8e**	200	**16e**	266.0 ± 18.9
3	**1r**	**8d**	40	**16d**	2287.0 ± 66.3
4	**1m**	**8d**	40	**16d**	1219.0 ± 26.7
5	**1r**	**8b**	100	**16b**	981.6 ± 26.8
6	**1m**	**8b**	100	**16b**	38.77 ± 1.07
7	**1r**	**8c**	400	**16c**	60.77 ± 4.01
8	**1r**	**8c-Ac**	400	**16c**	151.5 ± 4.09
9	**2r**	**8e**	400	**16i**	84.71 ± 1.60
10	**2m**	**8e**	400	**16i**	52.29 ± 5.79
11	**2r**	**8d**	100	**16h**	213.6 ± 0.25
12	**2m**	**8d**	100	**16h**	120.9 ± 0.40
13	**2r**	**8b**	400	**16g**	157.4 ± 1.00
14	**2m**	**8b**	400	**16g**	2.760 ± 0.30

[a] The reactants were mixed at room temperature in equal concentrations with the initial values given.

Table II. Pseudo-First-Order Rate Constants for Pyrrole Formation in Aqueous Solution[a]

entry	diketone	amine	pH	product	$k \times 10^6$, s^{-1}
1	**1r**	**8a**	6.2	**16a**	2.808 ± 0.013
2	**1m**	**8a**	6.2	**16a**	1.259 ± 0.016
3	**1r**	**8a**	7.2	**16a**	9.002 ± 0.225
4	**1m**	**8a**	7.2	**16a**	3.650 ± 0.042
5	**1r**	**8a**	8.2	**16a**	106.6 ± 0.042
6	**1m**	**8a**	8.2	**16a**	44.22 ± 0.129
7	**1r**	**8b**	8.2	**16b**	4.760 ± 0.070
8	**1m**	**8b**	8.2	**16b**	1.519 ± 0.004
9	**1r**	**8c**	8.2	**16c**	0.286 ± 0.008
10	**1m**	**8c**	8.2	**16c**	–[b]
11	**2r**	**8a**	8.2	**16f**	14.12 ± 0.460
12	**2m**	**8a**	8.2	**16f**	2.325 ± 0.034
13	**1r**	**8a**	11.0	**16a**	524.9 ± 9.48
14	**1m**	**8a**	11.0	**16a**	223.3 ± 5.23
15	**2r**	**8a**	11.0	**16f**	177.4 ± 4.67
16	**2m**	**8a**	11.0	**16f**	30.30 ± 0.93

[a] The initial concentrations of the dione and amine were 0.5 and 10 mM, respectively. The reactions were followed at room temperature. [b] The rate was too low to be measured accurately.

In water solutions the reaction was followed spectrophotometrically and in nonaqueous solvents GC could be used to differentiate the isomers of diketones and the pyrroles formed. The reaction was very slow below pH 3 and was complicated by the furan formation. When **1** was treated with **8d** in 0.01 N HCl solution or with HCl salt of **8d** in methanol, only furan was detected. Therefore, earlier reports on the mechanism of the reaction in acidic solutions[11] must be viewed with caution. Self-condensation prevented studies in alkaline solutions.

The Paal–Knorr reaction was first-order with respect to the diketone under all conditions studied. The order with respect to the amine was also 1 in chloroform, ethanol, acetonitrile, and at pH 11, but the order was more than 1 at lower pH. When the reaction followed second-order kinetics, the amine and diketone were taken in equal concentrations and the observed rate constants are given in Table I. In order to compare reactions of diketones and amines in the pH range 6–11 and to study the slowly reacting ketones, the amine was taken in 20-fold excess. Under these conditions the disappearance of the γ-diketone followed a pseudo-first-order rate equation (Table II).

In both tables the higher reactivity of **1r** compared to **1m** can be seen; this difference was observed whether ammonia (entries 1 and 2 in Table I) or a primary amine was the other reactant. In accordance with earlier observations,[10,11] substitution at the 2 and more importantly at the 1 position of the amine reduced the rate of the reaction (entries 3, 5, and 7 in Table I and entries 5, 7, and 9 in Table II). This steric effect was felt more by the meso isomer than the racemic pair (Table I, entries 4 and 6). Adding acetic acid as a catalyst to reactions in nonaqueous solvent (entry 8 in Table I) or increasing the pH of the reaction solution in water accelerated the reaction. Increasing the chain length of substitution on hexanedione from methyl to ethyl slowed the rate of pyrrole formation (Table I, entries 3 and 11, and 5 and 13). With 2-aminoethanol, at pH 8.2, **1r** reacted 7.5 times faster than **2r**. However, the higher reactivity of **2r** compared to **2m** was again observed under various conditions (entries 9–14 of Table I and entries 11 and 12 of Table II).

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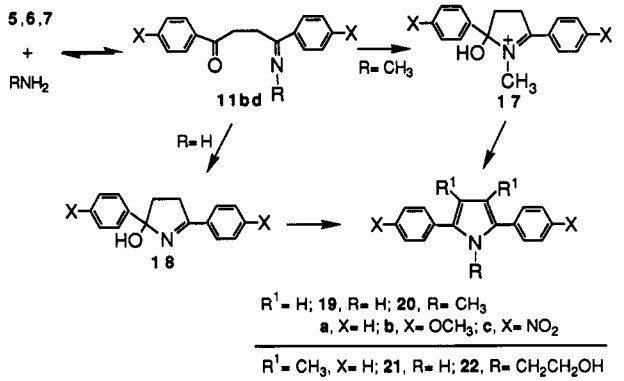
Table III. Comparison of the Rates of Pyrrole Formation for the Diastereomers of 2,3-Dimethyl-1,4-diphenyl-1,4-butanediones 3r and 3m[a]

diketone	amine	product	solvent	$k \times 10^6$, s^{-1}
3r	**8a**	**22**	benzene	18.39 ± 0.75
3m	**8a**	**22**	benzene	1.65 ± 0.06
3r	**8e**	**21**	ethanol	15.27 ± 0.42
3m	**8e**	**21**	ethanol	6.983 ± 0.21

[a] Pseudo-first-order rate constants were determined with 20 times excess of the amine; the initial concentration of **3** was 20 mM in benzene and 10 mM in ethanol.

Scheme II



B. 1,4-Diphenyl-1,4-butanedione and Its Derivatives. Our initial work was next extended to less reactive aromatic diketones. The diketones **3r** and **3m** were prepared by oxidative dimerization of propiophenone.[4] When the diastereomers were separated by column chromatography, the *d,l* pair (**3r**) was found to melt at 88–89 °C, very close to the value reported in the literature. Although the mp of the other isomer (102.5–103.5 °C) was much higher than the reported values (66–67 °C)[12,13] for the meso isomer, its mass spectrum was identical to that of the racemic mixture and it formed the same pyrroles as **3r**. Furthermore, the assignment of the higher melting isomer as meso was confirmed by ^{13}C NMR spectroscopy. In agreement with the previous observation,[4] the carbonyl ^{13}C chemical shift for the meso isomer was upfield (by 0.57 ppm) to that of the *d,l* isomers, while the 2,3-methyl groups were more shielded (by 1.96 ppm) in the *d,l* pair than in the meso isomer. Pyrrole formation was extremely slow with primary amines, but the reaction occurred readily in the presence of acetic acid. Since the product pyrroles exhibited UV maxima at wavelengths sufficiently removed from the λ_{max} of starting ketones, the reaction could be readily studied spectrophotometrically. The superior reactivity of the racemic pair (**3r**) over the meso (**3m**) was still observed (Table III).

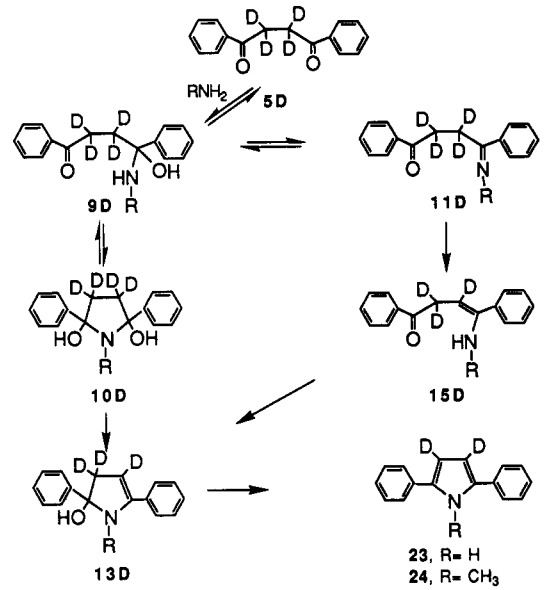
While the rate of the reaction is known to be positively influenced by the basicity of the amine,[11] the relation between the electron density of the carbonyl function and the rate has not been investigated. To fulfill that goal 1,4-diphenyl-1,4-butanedione (**5**) and its dimethoxy (**6**) and dinitro (**7**) derivatives were synthesized by oxidizing the enol ethers of the corresponding acetophenones.[14,15] The rates of reaction with ammonium acetate or methylamine–acetic acid (Scheme II) are compared in Table IV. In both instances the order of reactivity was **7** > **5** > **6**.

Table IV. The Effect of Para Substitution (X) on the Rate of Cyclization of 1,4-Diphenyl-1,4-butanedione[a]

entry	diketone (X)	amine	product	$k \times 10^6$, s^{-1}	relative rate
1	**5** (H)	**8e**	**19a**	1.808 ± 0.103	1.00
2	**6** (OCH_3)	**8e**	**19b**	0.7085 ± 0.026	0.39
3	**7** (NO_2)	**8e**	**19c**	6.823 ± 0.012	3.77
4	**5** (H)	**8d**	**20a**	2.852 ± 0.040	1.00
5	**6** (OCH_3)	**8d**	**20b**	0.7262 ± 0.080	0.25
6	**7** (NO_2)	**8d**	**20c**	23.75 ± 0.080	8.33

[a] The reactions were carried out at room temperature in 3:2 $CHCl_3$–EtOH starting with 8 mM of diketone and 160 mM of amine.

Scheme III



C. Deuterio Analogues. In order to determine whether a primary deuterium isotope effect was present in the Paal–Knorr reaction, 2,2,3,3-tetradeuterio-1,4-diphenyl-1,4-butanedione (**5D**) and 1,1,1,3,3,4,4,6,6,6-decadeuterio-2,5-hexanedione (**4D**)[16] were prepared from the corresponding unlabeled diketones by deuterium exchange under basic conditions. The rates of reaction of **5** and **5D** with ammonium acetate and methylamine–acetic acid (Scheme III) were compared (Table V). Diketone **5** produced pyrrole with ammonium acetate 21% faster than its deuterio analogue, while its reactivity with methylamine–acetic acid was slightly slower. The rates of pyrrole formation with **8b** for **4** and **4D** also did not differ appreciably in acetonitrile.

Discussion

As shown in Scheme I, the first step in the Paal–Knorr reaction is the addition of an amine to one of the carbonyl groups yielding the hemiaminal **9**. The hemiaminal can eliminate water to form the imine **11** which can tautomerize to the enamine **15**. Since the formation of hemiaminals and imines is known to be rapid and reversible,[17] the rate-limiting step must be the ring closure of **9**, **11**, or **15**, the formation of **15**, or the elimination of the diol **10**. In his discussion of Paal–Knorr synthesis, Sundberg[3] indicated the intermediacy of **10**, which must arise from the cyclization of the hemiaminal **9**. On the other hand, Ka-

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Table V. Deuterium Isotope Effect in Paal–Knorr Reaction of 4D and 5D[a,b]

diketone	amine	product	$k \times 10^6$	k_D/k_H
5	8e	19a	2.613 ± 0.012	
5D	8e	19a, 23	2.147 ± 0.011	0.82
5	8d	20a	4.615 ± 0.060	
5D	8d	20a, 24	5.612 ± 0.055	1.22
4	8b	16j	463.9 ± 4.04	
4D	8b	25	466.0 ± 22.98	1.00

[a] The initial concentrations of 5 (or 5D) and 8e (or 8d) were respectively 10 and 200 mM in 1:1 $CHCl_3$–EtOH. Dione 4 (or 4D) and 8b were taken in acetonitrile at equal concentrations (100 mM). [b] The rate constants were second-order for 4 (and 4D) and pseudo-first-order for 5 (and 5D).

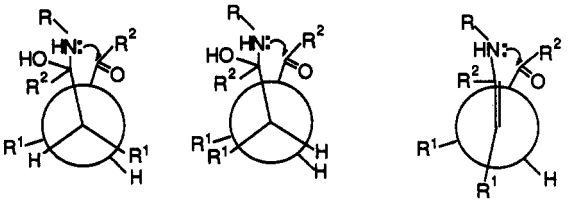
tritzky[10] and others[18] argued that the enamine 15, present in low steady-state concentrations with 11, cyclizes in the rate-limiting step. When the reaction between 4 and a primary amine was followed by NMR, the imine 11 was detected. It slowly increased in concentration and after reaching a maximum, disappeared with the formation of the pyrrole. In the reaction between pentane-2,4-dione and hydroxylamine[19] or hydrazine[20]—compounds that are not primary amines but are bases exhibiting an α effect—the ring closure was found to be faster than the subsequent dehydration of the diol. Based on these observations, a pathway involving 11, 15, and 13 was proposed.[10]

Our first set of results argue against the pathway with 15 in the rate-determining step. If 15 were to cyclize to pyrrole in the rate-determining step, *d,l* and meso isomers of 1 and 2 should react at the same rate, since the enamine is common to both the isomers. However, in nonaqueous solvents and in aqueous solutions near neutrality, *d,l* isomers reacted faster than the corresponding meso isomers. This difference has been observed in the Paal–Knorr reaction with other 3,4-dialkyl derivatives.[4] Although the rate of pyrrole formation was strongly affected by the pH, the solvent, and the nature of substitution on the amine, the higher reactivity of *d,l* compared to meso was always observed. These findings strongly suggest that the rate-limiting step is the same under these conditions and that it preserves the steric difference between the *d,l* and meso diastereomers.

As a separate test for the formation of the enamine prior to the rate limiting step, evidence for isomerization during reaction was sought. Starting with pure diastereomer, if all the equilibrium steps (9 ⇌ 11 ⇌ 15) leading to the enamine are faster than cyclization,[5,10] conversion of unreacted diketone to the other diastereomer should proceed during the reaction. For reactions in water, the unreacted diketone was extracted and its isomeric purity was analyzed by GC. The isomer composition of unreacted diketone was monitored while the pyrrole formation in nonaqueous solvents was followed by GC. Under all the conditions studied, isomerization was not observed.

The meso diastereomer has been shown to have a more stable ground-state conformation (antiperiplanar) than the *d,l* diastereomer (gauche),[4] and this difference was originally proposed to account for the disparity in their reaction rates. However, this difference is small[21a] and cannot account for the enormous variation in the reaction rates of the *d,l* isomers and their meso counterparts.

The slower reactivity of the meso isomer compared to the *d,l* isomer becomes apparent upon inspection of the Newman projections across C-3 and C-4 atoms of the developing pyrrolidine ring. When the meso isomer undergoes ring closure through the nucleophilic attack of the hemiaminal nitrogen on the other carbonyl, the alkyl groups at the 3- and 4-positions are brought into an eclipsed orientation in the transition state (9m). On the contrary, for the cyclization of the hemiaminal with the *d,l* configuration the transition state is less crowded (9r). Although the pyrrolidine ring can assume a puckered half-chair conformation to lessen the overlap,[21b] the strain cannot be eliminated. Furthermore, as the R group becomes more bulky its interaction with substituents at both the 2- and 5-positions of the developing five-membered ring forces a conformation with substantial eclipsing of substituents at 3- and 4-positions. In a similar reaction involving the cyclization of *d,l*- and *meso*-2,3-dimethylsuccinanilic acid to succinic anhydride, the rate for asymmetric isomers was found to be 2.33 times greater than that for the meso.[22]



9r 9m 15

There are two additional consequences of hemiaminal cyclization as opposed to enamine ring closure. First, as the alkyl groups become more bulky the overall reactivity will decrease due to the increasing strain in the eclipsed conformation. Secondly, as the substituent size increases, the steric strain in the transition state is more acutely felt by the meso isomer than the *d,l* isomer. Both of these predictions were borne out in our study. Diketones 1r and 1m reacted with 8b much faster than 2r and 2m could form pyrrole 16g. In addition, the relative rates of reaction, $k_{d,l}/k_{meso}$, increased from 25.3 for dimethyl to 57.0 for diethyl. These differences were amplified by increasing steric crowding around the primary amine. Other studies[4] have shown that the rates are even slower when phenyl or isopropyl groups are present at the 3- and 4-positions and that the decrease in rate is more for the meso isomer than for the racemic mixture. Likewise in aqueous solution (pH 8.2), with 8a the rate of pyrrole formation was slower for 2 than for 1. Therefore, the cyclization of both *d,l* and meso isomers is adversely affected by increases in the size of the substituents and the effect is more severe for the meso diastereomer. Pathways involving cyclization of 15, on the other hand, should be only slightly affected by the size of the substituents on the dione. Furthermore, if both the meso and *d,l* diketones were in equilibrium with the enamine, rapid conversion of the racemic pair to the more stable meso isomer would be expected. This was not observed.

The activation energies for the reaction (Table VI) with 8a at pH 8.2 also substantiate the above results. The activation energy is more for 1m than for 1r. The values increase going from methyl to ethyl substitution and the differences between 2r and 2m is much more than that between 1r and 1m.

An enamine intermediate could also have the structure 14 with the double bond toward the end of the molecule.

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Table VI. Activation Energies for the Paal–Knorr Reaction with 8a at pH 8.2

diketone	ΔE_a, kcal/mol
1r	7.440 ● 0.21
1m	7.810 ● 0.10
2r	8.850 ± 0.24
2m	13.08 ● 0.12

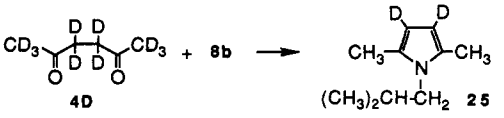
Although 14 is less stable than 15 which possesses a more substituted double bond, the former can be formed more rapidly than the latter.[23] Slow cyclization of enamine 14 could also explain the unequal reactivities of *dl* and meso. However, when the rates of pyrrole formation with 2-aminoethanol in benzene–acetic acid and with ammonium acetate in ethanol were determined for the *d,l* (3r) and meso (3m) isomers of 2,3-dimethyl-1,4-diphenyl-1,4-butanedione (Table III), the *d,l* pair again reacted faster than the meso, indicating that the stereochemical difference was preserved even when the diketone is unable to form enamine away from the middle of the molecule. On this basis, the intermediacy of 14 during ring closure seems unlikely.

Next, we sought to test whether cyclization of the imine 11 was the rate limiting step. The imine was the only intermediate detected in the Paal–Knorr reaction between 4 and a primary amine,[10] and 2-hydroxy-3,4-dihydro-2*H*-pyrroles[24] isolated from 1,4-diketones in liquid ammonia could arise through cyclization of imines. Such a mechanism can also explain the kinetic results discussed so far and in order to differentiate between the ring closures of 9 and 11, 1,4-diphenyl-1,4-butanedione (5) and its dimethoxy (6) and dinitro (7) derivatives were considered (Scheme II). Cyclization of the imine should lead to the iminium intermediate (17) which can be expected to be stabilized by an electron-donating substituent, such as a methoxy group. An electron-withdrawing nitro group, on the other hand, will destabilize 17 and thereby reduce the rate of pyrrole formation. The nature of the substituent would have an opposite effect on the cyclization of 9 to 10. While the para substituent has little effect on the basicity of the hemiaminal nitrogen, an electron-withdrawing group should increase the rate by reducing the electron density of the carbonyl group. Since the latter effect is also present in the cyclization of the imine 11, the rates of pyrrole formation with ammonia as well as methylamine are compared. The reaction involving ammonia gives an uncharged intermediate (18) and hence should be less affected by the nature of substituent on the imine part of the molecule. The substituents were sufficiently removed from the reaction site that their size differences will play a negligible role on the rate. By comparing the relative rates of pyrrole formation with ammonium acetate and methylammonium acetate, it was anticipated that the type of influence the para substitution exerts on the reaction could be deduced. From the data provided in Table IV, the positive effect of an electron-withdrawing substituent on the reaction is apparent and it is still consistent with cyclization of 9. Also, the low basicity of an imine[25] makes its nucleophilic attack on the carbonyl less likely.

Thus it appears that imine 11 is formed from 9 during the reaction, but is not directly involved in forming the pyrrole. When 2-hexanone was mixed with equimolar 8b, ^{13}C NMR showed the formation of signals attributed to the imine until equilibrium was reached. GC–MS data also confirmed the presence of a pair of compounds—presumably syn and anti isomers. When the above mixture was treated with 1r and the reaction followed by GC, the imine peaks decreased and eventually disappeared completely. This suggests that the imine previously observed in mixtures containing 4 and primary amines was in faster equilibrium with the hemiaminal 9, and as the slower cyclization of the latter progressed, the imine was also slowly converted back to the hemiaminal and eventually to the product. In addition, we were unable to detect the imine in a 1:1 mixture of 1r or 1m and 8b or when 4 was treated with 8b in presence of acetic acid.

Recent work of Sammes[24] has suggested the possibility that the reaction might follow different pathways depending on whether the reactant is ammonia or a primary amine. In our studies we were unable to detect any difference in the reactivities of ammonia and amines. The higher reactivity of the *d,l* pair compared to the meso isomer and the decrease in rate as the size of the substituents on the diketone increases were also observed with ammonia. The differences were much smaller than those exhibited by amines but that is quite expected from the smaller size of the reactant. The nature of the steps following the cyclization are not clear from our present studies. In liquid ammonia it is quite possible that dehydration to 12 may be rate limiting,[24] but there is no evidence to show that cyclization involves an intermediate other than the hemiaminal.

Finally, we would like to consider mechanisms with rate-determining steps which do not involve cyclization. The slow formation of the common enamine intermediate 15 from the diastereomeric mixture of 11 at different rates followed by rapid cyclization or the unequal dehydration of cis and trans (with respect to R^1 groups) isomers of the rapidly formed pyrrolidine 10 to 13 could also explain the higher reactivity of the racemic pairs of 1, 2, and 3 compared to the meso isomers. Since both the mechanisms involve cleavage of a C–H bond in the rate-limiting step, they should exhibit a primary deuterium isotope effect. Whether the generation of 15D from 11D is the slowest step or the elimination from the diol 10D is rate limiting (Scheme III), in reactions involving the deuterio analogue 5D, the rate of pyrrole formation should be much slower than the rate of reactions starting with the parent compound 5. Table V presents data which show that 5 and 5D react at a similar rate with ammonium acetate or methylamine and acetic acid. Perdeuteration of 4 also did not alter the rate of pyrrole formation with 8b (Table V). These observations clearly show that the formation of 15 is not a part of the pathway leading to pyrroles and that the dehydration of 10 does not determine the over all rate of the reaction. In addition, these mechanisms fail to explain the influence of the size of amine substituents on the reaction rate. When the unreacted 5D was isolated from the reaction mixture and analyzed by GC–MS and NMR, there was no loss of deuterium. However, the pyrrole was found to undergo considerable deuterium loss. In the same way, when the reaction mixture containing 4D and 8b were analyzed by GC–MS, the unreacted diketone did not lose any deuterium, while the methyl groups attached to the pyrrole ring suffered extensive proton incorporation (25). The scrambling could have occurred



4D 25

either after the irreversible step during the reaction or on the product pyrrole. Furthermore, the lack of deuterium

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loss from the unreacted diketones is again incompatible with the mechanism[10] involving slow cyclization of the enamine **15** which is present in equilibrium with **11**, which in turn is in equilibrium with the dione and amine.

Conclusion

The kinetic experiments described in this paper were designed to differentiate between various pathways proposed for Paal–Knorr synthesis of pyrroles. The bulk of our data gathered in mildly acidic, neutral or mildly basic conditions can be explained only by the mechanism involving the cyclization of **9** in the rate limiting step: (1) Under a variety of reaction conditions with various amines and ammonia, **1r** formed pyrroles faster than **1m**. (2) The reactivity of **2** was always lower than that of **1**, although **2r** was still more reactive than **2m**. These dissimilarities were magnified by increasing the size of the substitution on the amine. (3) This difference in reaction rate was not lost by **3r** and **3m** which can form enamine only toward the middle of the molecule and thereby lose their dissimilarity. (4) The order of reactivity of **5**, **6**, and **7**, whether the other reactant was ammonia or methylamine, was **7** > **5** > **6**. (5) The reactivities of the deuterio analogues **5D** and **4D** were very similar to those of **5** and **4** showing the absence of a primary isotope effect. (6) During the course of the reaction, diastereomers of **1**, **2**, and **3** did not isomerize and **4D** and **5D** did not exchange hydrogen for deuterium. The slow cyclization of the hemiaminal **9** is also not inconsistent with previous observations on the reaction.

Experimental Section

General. Varian Aerograph 1400 fitted with 3% OV-101 column (at 20 mL/min flow rate of nitrogen carrier gas) and flame ionization detector (30 mL/min of hydrogen and 200 mL/min of air) was used for GC analyses. The data from GC were recorded and analyzed by a Hewlett-Packard integrator 3394-A. Spectrophotometric measurements were run on a Beckman DU-8. Proton and ^{13}C Fourier transform NMR spectra were acquired at 300 and 75.5 MHz, respectively, on a General Electric GN 300 WB spectrometer using quadrature detection at room temperature (23–27 °C). All samples were taken in $CDCl_3$ (unless noted otherwise) with tetramethylsilane as internal standard. GC–MS data involving chemical ionization, when specified, were obtained from a Hewlett-Packard 5988-A mass spectrometer (with direct insertion probe) using NH_3 as the reagent gas. The rest of the spectra were run on a Hewlett-Packard GC 5890 II connected to a Hewlett-Packard 5971-A mass spectrometer (operated in EI mode with 70 eV). Melting and boiling points were uncorrected. Purifications by column chromatography were done on silica (200–400 mesh) with positive pressure (argon), and analytical thin-layer chromatography was run on aluminum sheets coated with silica (Merck 60 F); the solvent systems, unless stated otherwise, were mixtures of hexane and ethyl acetate (with ratios given in the parentheses).

Aliphatic Diketones. The diastereomers of 3,4-dimethyl- and 3,4-diethyl-2,5-hexanediones (**1r**, **1m**, **2r**, and **2m**) were synthesized and separated according to published procedures.[4] [$^2H_{10}$]Hexane-2,5-dione (**4D**) was prepared by exchanging **4** (11.4 g, 100 mmol) with D_2O (20 mL) containing 40% NaOD (200 μL) three times.[16] The crude product was distilled at 32–34 °C (1 Torr); 3.2 g (26%); mass spectrum identical to the published data.[16]

Pyrroles. The pyrroles **16** carrying aliphatic substituents were unstable, readily oxidized by atmospheric oxygen, and therefore characterized in the following way. They were formed by stirring 5 mmol of **1**, **2**, or **4D** and 5–10 mmol of the appropriate amine in chloroform (2–5 mL) under Ar at room temperature for 18 h. When the product was detected by GC, it was analyzed by GC–MS. After the completion of reaction, the solvent was removed and the residue was distilled before running the NMR spectrum. For known pyrroles, the spectra were compared with the published data. For others the chemical shifts are provided.

1-(2-Hydroxyethyl)-2,3,4,5-tetramethylpyrrole (16a): yield 370 mg (44%); bp 95–97 °C (0.15 Torr); ^1H NMR δ 1.91 (s, 6 H, C^3-CH_3 and C^4-CH_3), 2.11 (s, 6 H, C^2-CH_3 and C^5-CH_3), 3.62 and 3.80 (t, 2 H each, J = 6 Hz, CH_2CH_2); mass spectrum, m/z 167 (M^+), 136 (M – CH_2OH).

1-(2-Methylpropyl)-2,3,4,5-tetramethylpyrrole (16b): yield 760 mg (85%); bp 58–60 °C (0.55 Torr); ^1H NMR δ 0.87 (d, 6 H, J = 7.5 Hz, $(CH_3)_2C$), 1.92 (s, 6 H, C^3-CH_3 and C^4-CH_3), 1.95 (m, 1 H, CH), 2.09 (s, 6 H, C^2-CH_3 and C^5-CH_3), 3.46 (d, 2 H, CH_2); mass spectrum, m/z 179 (M^+), 136 (M – C_3H_7).

3,4-Diethyl-1-(2-hydroxyethyl)-2,5-dimethylpyrrole (16f): yield 340 mg (35%); bp 105–107 °C (0.3 Torr); ^1H NMR δ 1.06 (t, 6 H, J = 7.5 Hz, CH_2CH_3), 2.12 (s, 6 H, C^2-CH_3 and C^5-CH_3), 2.37 (q, 4 H, CH_2CH_3), 3.60 and 3.80 (t, 2 H each, J = 6 Hz, CH_2CH_2); mass spectrum, m/z 195 (M^+), 180 (M – CH_3).

3,4-Diethyl-2,5-dimethyl-1-(2-methylpropyl)pyrrole (16g): yield 720 mg (70%) from **2r**; bp 63–65 °C (0.35 Torr); ^1H NMR δ 0.87 (d, 6 H, J = 7 Hz, $(CH_3)_2C$), 1.07 (t, 6 H, J = 8 Hz, CH_2CH_3), 1.93 (m, 1 H, CH), 2.11 (s, 6 H, C^2-CH_3 and C^5-CH_3), 2.39 (q, 4 H, CH_2CH_3), 3.48 (d, 2 H, NCH_2); mass spectrum, m/z 207 (M^+), 178 (M – CH_2CH_3).

3,4-Diethyl-1,2,5-trimethylpyrrole (16h): yield 700 mg (85%); ^1H NMR δ 1.08 (t, 6 H, J = 7.5 Hz, 3- and 4-CH_2-CH_3), 2.11 (s, 6 H, C^2-CH_3 and C^5-CH_3), 2.39 (q, 4 H, 3- and 4-CH_2), 3.32 (s, 3 H, 1-CH_3); mass spectrum, m/z 165 (M^+), 150 (M – CH_3).

1-(1-Methylethyl)-2,3,4,5-tetramethylpyrrole (16c)[26] (60% from **1r**), **1,2,3,4,5-pentamethylpyrrole (16d)**[27] (80%), **2,3,4,5-tetramethylpyrrole (16e)**[27] (40%), and **3,4-diethyl-2,5-dimethylpyrrole (16i)**[28] (40%) were identified by their mass spectra.

3,4-Dideuterio-2,5-dimethyl-1-(2-methylpropyl)pyrrole (25):[10] yield 120 mg (80%) starting with 1 mmol of **4D**; ^1H NMR: from the relative areas of the peaks, the signal at 2.19 ppm accounted for 65% deuterium loss from 2- and 5-methyl groups and the singlet at 5.76 indicated the retention of deuteriums at 3- and 4-positions; mass spectrum, m/z 153 (M^+), 110 (M – C_3H_7) with +1, +2, and +3 peaks of considerable intensities.

Kinetics. The kinetics of pyrrole formation in water was followed spectrophotometrically (in the kinetic mode) under controlled temperatures. The actual temperature of the solution in the cuvet was measured with a YSI thermometer 43TA with its thermistor probe inserted into the cuvet. Absorbance at 220 nm was monitored and the extinction coefficient of 7500 M^{-1} cm^{-1} at 220 nm of freshly distilled **16a** was used. Potassium phosphate was selected to cover the pH range 6.2–8.2 and 11. The buffers were purged with nitrogen gas to minimize the loss of pyrrole through oxidation. In a typical run, 200 μL of 10 mM of **1r** was dissolved in 3.6 mL of 0.2 M phosphate buffer, pH 7.2. A 0.2 M solution of **8a** (200 μL) was rapidly added, mixed, and transferred to a cuvet equilibrated in the spectrophotometer, and the kinetic program was immediately started. At the end of the reaction, a wavelength scan was performed on the reaction solution to assure the presence of the products. Pseudo-first-order rate constants (Table II) were obtained from the slopes of ln $([A_o]/[A_o] - [X])$ vs time, where $[A_o]$ was the initial concentration of diketone and [X] was the concentration of pyrrole determined spectrophotometrically at each time point. The values given in all the tables were derived from two measurements. The rate constants for the reactions between **8a** and **1r**, **1m**, **2r**, or **2m** were measured in 4 or 5 °C intervals in the temperature range 16–39.5 °C (±0.25 °C) to determine their activation energies.

To determine whether isomerization between the stereomers can occur during reaction, solutions of **1r** or **1m** in potassium phosphate buffer with isopropylamine were left at room temperature for 1 day and extracted with chloroform. The extract was washed with water, dried over anhydrous Na_2SO_4, concentrated, and analyzed by GC. The purity of the isomers remained unchanged during this operation.

The rate of reaction of **1** and **2** with **8b**, **8c**, **8d**, or **8e** in $CHCl_3$ was followed by GC. For **1r** and **1m** the column was kept at 70 °C for 6 min and heated from 70 to 240 °C at the rate of 20

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°C/min and for **2r** and **2m** the initial isothermal heating was done at 90 °C. The temperature program for **4** and **4D** consisted of 50 °C for 5 min and 20 °C per min there after. In a representative kinetic run 100 μL of 500 mM **1r** in $CHCl_3$ and 100 μL of 500 mM **8b** in $CHCl_3$ were mixed in 300 μL of $CHCl_3$ to get 100 mM ($[A_o]$) each of diketone and amine; 0.4 μL of the reaction mixture was injected for analysis every 15 min for 90 min. The relative areas of the peaks corresponding to **1r** and **16b** were used to arrive at their concentrations ([X]) for using in the second-order rate equation. A plot of $1/([A_o] - [X])$ against time was linear providing the rate constant (entry 5 in Table I). In addition, the isomerization of unreacted **1r** to **1m** was not observed.

Aromatic Diketones. *d,l*- and *meso*-2,3-Dimethyl-1,4-diphenyl-1,4-butanediones (3r and 3m). A solution of propiophenone (0.5 mol, 66.6 mL) in benzene (300 mL) containing lead dioxide (60 g, 250 mmol) was refluxed for 24 h. After removal of unreacted ketone the isomers were separated (20:1) and fractions containing better than 80% of one diastereomer were concentrated and cooled to precipitate the pure isomer. The isomer moving slightly slower was the racemic pair (**3r**): yield 8.0 g (12%); mp 88–89 °C (lit.[29] mp 86–87 °C); ^1H NMR δ 1.31 (d, 6 H, J = 6 Hz, CH_3), 3.99 (q, 2 H, J = 2 Hz, CHCH), 7.4–8.0 (m, 10 H, C_6H_5); ^{13}C NMR δ 15.51 (CH_3), 43.61 (C_2), 128.47, 128.58, 132.92 and 136.12 (phenyl ring), 204.26 (C=O); mass spectrum, m/z 266 (M^+) and 105 (C_6H_5CO). The other isomer was assigned meso: yield 11.5 g (17%); mp 102.5–103.5 °C; m/z 266 (M^+) and 105 (C_6H_5CO); ^1H NMR δ 1.14 (d, 6 H, J = 6 Hz, CH_3), 4.06 (d of q, 2 H, CHCH), 7.4–8.0 (m, 10 H, C_6H_5); ^{13}C δ NMR 17.47 (CH_3), 43.30 (C_2), 128.46, 128.76, 133.32 and 136.84 (phenyl ring), 203.69 (C=O).

2,2,3,3-Tetradeuterio-1,4-diphenyl-1,4-butanedione (5D). Deuterium oxide (6 mL) was added to a solution of **5** in pyridine (20 mL) followed by 40% NaOD in D_2O (50 μL). The resulting solution was stirred for 2 h at room temperature. Pyridine was removed in vacuo, and the residual aqueous solution was extracted with dichloromethane (3 × 25 mL). The combined extracts were concentrated and the residue was subjected to another deuterium exchange. The crude product was purified (5:1): yield 515 mg (70%); ^1H NMR δ 3.45 (m, 0.2 H indicating 95% isotope purity, CD_2CD_2), 7.4–8.1 (m, 10 H, C_6H_5); mp 146–148 °C; mass spectrum, m/z 242 (M^+), 137 ($PhCOCD_2CD_2^+$), 105 (C_6H_5CO).

Pyrroles. 2,5-Diphenylpyrrole (19a) was prepared by stirring the dione **5** (476 mg, 2 mmol) and ammonium acetate (1.54 g, 20 mmol) in ethanol (40 mL) and $CHCl_3$ (60 mL) at room temperature for 70 h. The crude reaction product was purified by flash chromatography (5:1): 310 mg (70%); mp 147–148 °C (lit.[30] mp 143 °C); λ_{max} 329.5 nm (ε 30 900); mass spectrum, m/z 219 (M^+). **2,5-Bis(4-nitrophenyl)pyrrole (19c)** was similarly prepared from the dione **7**: 490 mg (80%) (chromatography 3:1); mp 295–297 °C; ^1H NMR ($CDCl_3$ and $(CD_3)_2SO$) δ 6.88 (s, 2 H, C^2-H and C^3-H), 8.01 and 8.23 (AB q, 8 H, phenyl ring); λ_{max} 440 nm (ε 39 300); mass spectrum (CI), m/z 310 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.59; N, 13.59. Found: C, 62.21; H, 3.62; N, 13.50.

1-Methyl-2,5-diphenylpyrrole (20a). Acetic acid (2.3 mL), methylamine (3.1 mL), and the dione **5** (476 mg, 2 mmol) were stirred in ethanol (40 mL) and $CHCl_3$ (60 mL) at 50 °C for 24 h. The pyrrole **20a** precipitated as white solid on concentration, which was filtered and washed with hexane: 350 mg (75%); mp 206–208 °C (lit.[30] mp 206 °C); λ_{max} 308 nm (ε 22 400); mass spectrum, m/z 233 (M^+). The mixture using **7** in place of **5** was stirred at room temperature for 48 h to give 550 mg (85%) of **1-methyl-2,5-bis(4-nitrophenyl)pyrrole (20c)**: mp 193–195 °C dec (chromatography 5:1); λ_{max} 413 nm (ε 27 250); ^1H NMR δ 3.71 (s, 3 H, NCH_3), 6.53 (s, 2 H, C^2-H and C^3-H), 7.63 and 8.31 (AB q, 8 H, phenyl ring); mass spectrum (CI), m/z 324 $(M + 1)^+$. **Note:** The pyrroles **19c** (bright red) and **20c** (orange) were sensitive to light slowly degrading to dark less soluble materials. Anal. Calcd for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00. Found: C, 63.08; H, 4.07; N, 12.94.

2,5-Bis(4-methoxyphenyl)pyrrole (19b). Ammonium acetate (770 mg, 10 mmol) and the dione **6** (298 mg, 1 mmol) in acetic acid (2 mL) were heated at 100 °C for 2 h and cooled. The precipitated solid was filtered and washed with ethanol: 360 mg (65%); mp 239–240 °C; λ_{max} 324 nm (ε 31 800); ^1H NMR ($CDCl_3$ and CD_3OD) δ 3.83 (s, 6 H, OCH_3), 6.40 (s, 2 H, C^2-H and C^3-H), 6.92 and 7.63 (AB q, 8 H, phenyl ring); mass spectrum (CI), m/z 280 $(M + 1)^+$.[31] Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.38; H, 6.15; N, 5.06.

1-Methyl-2,5-bis(4-methoxyphenyl)pyrrole (20b). A solution of **6** (595 mg, 2 mmol), methylamine (3.75 mL), and acetic acid (2.8 mL) in ethanol (50 mL) and $CHCl_3$ (50 mL) was refluxed for 40 h and cooled to precipitate **20b**. It was crystallized from ethyl acetate: 440 mg (75%); mp 225–227 °C; λ_{max} 300.5 nm (ε 25 100); ^1H NMR δ 3.54 (s, 3 H, NCH_3), 3.85 (s, 6 H, OCH_3), 6.22 (s, 2 H, C^2-H and C^3-H), 6.96 and 7.39 (AB q, 8 H, phenyl ring); mass spectrum (CI), m/z 294 $(M + 1)^+$.[31] Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.71; H, 6.55; N, 4.78.

3,4-Dimethyl-2,5-diphenyl-1-(2-hydroxyethyl)pyrrole (22): A mixture of **3r** and **3m** (1.33 g, 5 mmol) and 2-aminoethanol (1.2 g, 20 mmol) was refluxed in benzene (100 mL) containing 10 mM acetic acid for 24 h. The crude product was purified (9:1): yield 1.1 g (75%); mp 76–77 °C; λ_{max} (ethanol) 305 nm (ε 14 860); mass spectrm, m/z 291 (M^+), 260 ($M - C_2H_5OH$); ^1H NMR δ 2.03 (s, 6 H, CH_3), 3.23 and 4.01 (t, 2 H each, CH_2CH_2), 7.30–7.5 (m, 10 H, aromatic). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.34; H, 7.21; N, 4.78.

3,4-Dimethyl-2,5-diphenylpyrrole (21). Diketone **3** (530 mg, 2 mmol) and ammonium acetate (3.1 g, 40 mmol) in acetonitrile (50 mL) were refluxed for 18 h. The reaction mixture was purified (9:1) to give **21**: 400 mg (80%); mp 144–146 °C (lit.[13] mp 136 °C); λ_{max} (ethanol) 322 nm (ε 25 980), 210 (13 100).

Kinetics. Diketone **3r** or **3m** (20 mM) and **8a** (400 mM) in benzene (12 mL) containing 5 mM acetic acid was refluxed, and samples were removed at various time points up to 8 h. Aliquots (100 μL each) were diluted with ethanol and the absorbance was measured at 305 nm to determine the pyrrole concentration.

A solution of diketone **3r**, **3m**, **5**, **6**, **7**, or **5D** and ammonium acetate (20 times excess) in appropriate solvent was stirred at room temperature. Aliquots were withdrawn from each reaction solution and diluted with 95% ethanol, and the absorbance was measured. The wavelengths for monitoring the concentration of pyrroles were 322 nm for **21**, 330 nm for **19a** and **23**, 324 for **19b**, and 440 nm for **19c**. For studying the reaction with methylamine, absolute ethanol containing methylamine and acetic acid was used in place of ammonium acetate solution. The formation of pyrroles **20a** (or **24**), **20b**, and **20c** was followed at wavelengths 308, 324, and 413 nm, respectively. From the concentrations of pyrrole first-order rate constants were arrived at ás described above. In a typical experiment, dione **7** (26.3 mg, 80 μmol) was dissolved in 6 mL of $CHCl_3$ and an ethanolic solution (4 mL) containing methylamine (400 mM) and acetic acid (400 mM) was added. The resulting solution was stirred at room temperature and an aliquot of 100 μL was withdrawn every 30 min, diluted to 3 mL with ethanol, and the absorbance of the diluted solution was measured at 413 nm to determine the concentration of **20c**. TLC was run at the end of the study to confirm the formation of pyrrole and to make sure that isomerization did not occur in the case of **3r** or **3m**. Reaction mixtures containing **5D** and ammonium acetate or methylammonium acetate were purified (5:1) to isolate unreacted **5D** and pyrrole **23** or **24** and to analyze them by GC–MS and ^1H NMR.

Imine from 2-Hexanone and 8b. A mixture of 2-hexanone and **8b** (500 mM each) in $CDCl_3$ exhibited a ^{13}C signal at 170 ppm characteristic of imine carbon. The same solution in $CHCl_3$ showed two peaks in GC (retention time at 70 °C, 3.43 and 4.54 min in the ratio 1:4); mass spectrum, m/e 155 (M^+), 140 ($M - CH_3$). When it was mixed with **1r** (to give 500 mM) and the reaction followed by GC under conditions described above, the peaks corresponding to the imines decreased and disappeared completely with the formation of **16b**.

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Supplementary Material Available: The ^1H and ^{13}C NMR spectra of pyrroles **16a,b,f-h** which are very rapidly oxidized (10 pages). Ordering information is given on any current masthead page.

Notes

Selenols Catalyze the Interchange Reactions of Dithiols and Disulfides in Water

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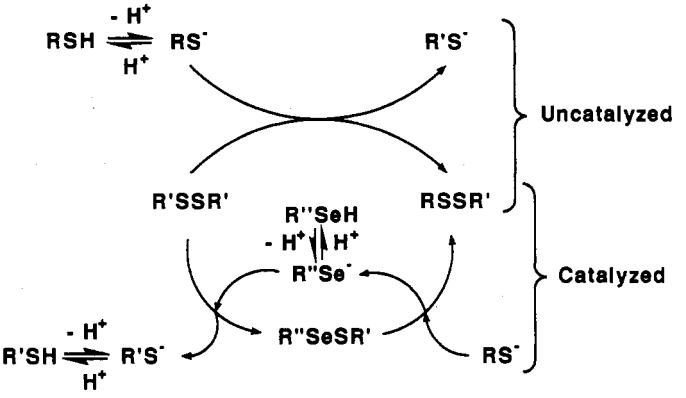
The mechanism of thiol–disulfide interchange reaction involves the nucleophilic attack of thiolate along the S–S bond axis of the disulfide.[1] The reaction is kinetically second order: first order in thiolate and in disulfide.[2-4] At pH 7, only 0.1–1% of typical thiol groups is present as thiolate in water, and the apparent rate constant of the thiol–disulfide interchange reaction is small ($k^{obsd} \approx 0.1$ M^{-1} s^{-1}).[2,5] Protein disulfide isomerase (EC 5.3.4.1) has been suggested to act as a catalyst for thiol-disulfide interchange in vivo, but its lack of specificity and the fact that it induces only moderate rate enhancements make its biological role uncertain.[6-9]

As part of a program examining thiolate–disulfide interchange, we surveyed a number of types of compounds (aromatic thiols, nonthiol nucleophiles, and cations) as potential catalysts for this reaction. The only significant rate enhancement was obtained with phenylselenol.[5] Selenolate is a strong nucleophile toward diselenides and a good leaving group in selenolate–diselenide interchange.[10] The pK_a of selenols is ≈ 7,[11] and at pH 7 the attack of selenol on diselenide is rapid ($k^{obsd} = 1.65 \times 10^7$ M^{-1} s^{-1}).[10] We expected selenolate to be a strong nucleophile toward disulfide and to be a good leaving group in the attack of thiolate on selenosulfide (RS–SeR). Scheme I shows the steps involved in the catalysis of a thiol–disulfide interchange reaction by selenol.

Scheme I. Catalysis of Thiol–Disulfide Interchange by Selenol



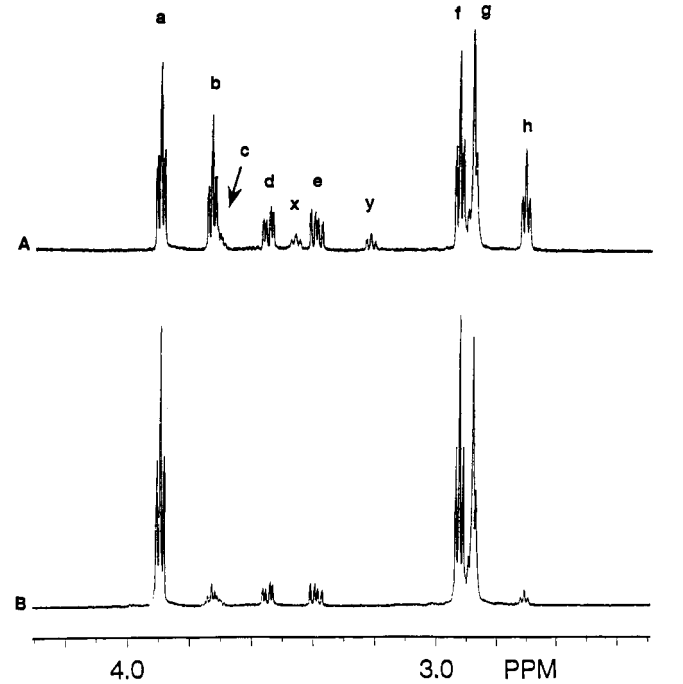


Figure 1. ^1H NMR spectra (500 MHz) of reaction mixtures initially containing dihydroasparagusic acid (DHA, 5 mM) and bis(2-hydroxyethyl) disulfide (ME^{ox}, 5 mM) in phosphate-buffered (50 mM) D_2O at pD 7 under argon: (A) in the presence of 10 mol % 2-aminoethaneselenol (0.5 mM), quenched with DCl after 1.5 min; (B) in the absence of selenol, quenched with DCl after 2.2 min. The peak assignments are a = CH_2OH (ME^{ox}), b = CH_2OH (ME), c = CH (DHA^{ox}), d,e = CH_2 (DHA^{ox}), f = CH_2S (ME^{ox}), g = CH, CH_2 (DHA), h = CH_2S (ME), x = $CH_2NH_3^+$, y = CH_2Se.

In this study we have surveyed in greater detail the ability of several alkaneselenols to catalyze thiol–disulfide interchange reactions. We have examined thiol–disulfide

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(11) Arnold, A. P.; Tan, K. S.; Rabenstein, D. L. *Inorg. Chem.* **1986**, *25*, 2433–2437. Some representative values of pK_a for selenols are as follows: 2-hydroxyethaneselenol, 6.6; selenocysteine, 5.4; selenocysteamine, 5.5; selenoacetic acid, 6.9; selenopropionic acid, 7.3.

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