Acylanthranils. 6. Role of Steric Hindrance in the Reaction of Electrophilic Reagents with Linear Primary Aliphatic Amines[1]

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The product distributions obtained in the reactions of acetylanthranil (**1**) with amines **2** having the generic formula $H_2N(CH_2)_nH$ indicate that reaction via pathway A to give the corresponding acetamidine salt **3**, which requires only minutes for completion, is favored when $n < 4$, but that reaction via pathway B to give the corresponding diamide **4**, which requires hours for completion, is favored when $n \geq 4$. It is postulated that this crossover in selectivity at $n = 4$ is caused by steric hindrance owing to a coiled configuration on the part of the $H_2N(CH_2)_4$ segment held together by intramolecular van der Waals forces. This coiled configuration also appears to account for the small, but measurable, decrease in pK_a for those amines with $n \geq 4$.

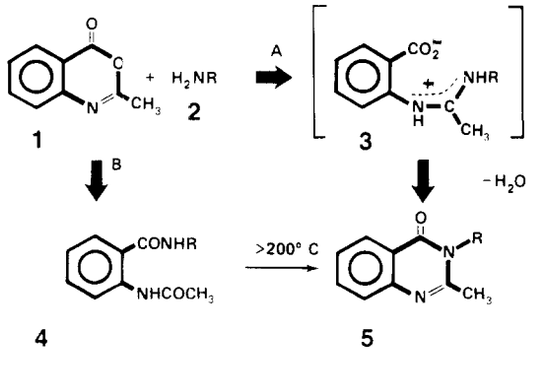
It was reported that the reaction of acetylanthranil (**1**) with amines **2** in nonpolar solvents such as benzene or diethyl ether occurs via alternate pathways[2] to give either the corresponding acetamidine intermediate **3** via pathway A or the corresponding benzamide **4** via pathway B. Primary amines follow pathway A unless some form of steric hindrance precludes addition to the 2 position of **1**, which serves to restrict interaction to the slower alternative pathway B to give **4** as discussed previously.[3,4] Secondary amines, however, follow pathway B exclusively. It was shown that even pseudosecondary amines (i.e., a primary amine such as anthranilic acid or ethanolamine, which can form a five- or six-membered ring by intramolecular hydrogen bonding with the polar group at the β position) follow pathway B in a nonpolar solvent.[5] In a polar solvent, however, these amines behave like normal primary amines and follow pathway A, because the formation of the cyclic configuration is precluded by intermolecular association with the solvent.[5] Tertiary amines do not react with **1** except to serve as an excellent solvent for reaction with other nucleophiles such as water, which gives *o*-acetamidobenzoic acid.[2,4]

It was noted[4] that reaction with primary aromatic amines neat usually requires 2–3 h for completion, whereas the corresponding reaction with methyl-, ethyl-, and *n*-propylamines is complete within 10 min. This difference in reactivity with amines that follow pathway A was ascribed to the relative difference in basicity for the aromatic (pK_a ca. 5) and the aliphatic (pK_a ca. 11) amines.[4] It was decided, therefore, to investigate whether or not the rate of reaction with the amines $H_2N(CH_2)_nH$ via pathway A would increase with n in accordance with the expected electropositive contribution of the polymethylene chain to the nucleophilic center.

Results and Discussion

Acetylanthranil (**1**) was made to react in benzene at room temperature with the set of linear aliphatic amines **2a–h**, wherein n = 0, 1, 2, 3, 4, 6, 10, and 12, respectively. The approximate time required for reaction completion was noted and the product mixtures obtained thereby were separated according to the materials balance procedure described previously.[2] This procedure accounted for more than 95% of the reactants, which were added in equivalent amounts. The percent acetylanthranil isolated as **3, 4,** and **5** was then used to calculate the corresponding selectivity ratio for reaction via pathway A to pathway B, i.e., k_A/k_B = (**3** and/or **5**)/**4**. The materials balance data are collected in Table I and the supporting characterization data are collected in Table II. Unreacted acetylanthranil was either recovered per se (example **2a**) or isolated as *o*-acetamidobenzoic acid (**6**) which was produced by reaction with water as part of the post reaction separation procedure (examples **2g** and **2h**).

Scheme I



Instead of the expected monotonic increase in reactivity without change in selectivity as a function of n, Table I shows that the members of the subset with $n < 4$ follow pathway A, whereas those with $n \geq 4$ follow pathway B. Moreover the former, with the exception of ammonia, required only minutes for reaction completion, whereas the latter required hours. The sharp changes in selectivity and reactivity are especially interesting because both observations infer some form of steric hindrance in this reaction, which is associated with the segment $H_2N(CH_2)_4$–.

The results obtained with ammonia, however, were unique and apparently contradictive. The reaction of **1** in benzene saturated with anhydrous ammonia at room temperature was pseudo-first-order and the half-life of **1** under these conditions was 32 h.[4] About 35% was recovered unchanged after 48 h and the rest was isolated as 2-methylquinazol-4-one (**5a**). The isolation of this product in good yield shows that the reaction follows pathway A exclusively as expected for an amine that does not exhibit steric hindrance, such as methylamine, but the unusually slow rate of reaction is characteristic of amines that exhibit considerable steric hindrance, such as *tert*-butylamine. Because these two observations appear to be inconsistent, more investigation at a later time is required for clarification.

The unexpected observation of a change in selectivity at n = 4 from pathway A, which gives **3** as a precipitate, to pathway B, which gives **4** as a soluble product, offered the additional possibility for following the reactions that go via pathway B spectrophotometrically instead of gravimetrically. Our attempts to do so by IR and/or NMR analysis verified that reaction of **1** with an equivalent amount of an amine **2** having $n \geq 4$ requires 2–6 h for completion and that the reaction is second order (i.e., in a given experiment, the rates of disappearance of the reactants **1** and **2** are both equal to the rate of formation of the product **4**). The reproducibility of the calculated rate constants in a set of repeat experiments with a given amine, however, was not good enough to verify or deny

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Table I. Products Obtained in the Reaction of 1 with $H_2N(CH_2)_nH$ in Benzene at Room Temperature

Amine	Registry no.	n	pK_a[f]	Time allowed for reaction	% 1 isolated as 4	3	5	Selectivity A/B = (3 and/or 5)/4
2a	7664-41-7	0	9.26	2 days[a]	0	0	65	>50/1[b]
2b	74-89-5	1	10.66	1 h[c]	0	100	0	>50/1
2c	75-04-7	2	10.81	1 h[c]	0	100	0	>50/1
2d	107-10-8	3	10.71	4 h[c]	7	93	0	17/1[d]
2e	109-73-9	4	10.61	1 day[e]	100	0	0	<1/25
2f	111-26-2	6	10.56	1 day[e]	96	0	4	1/24
2g	2016-57-1	10	10.64	5 h[e]	96	0	0	<1/25
2h	124-22-1	12	10.63	5 h[e]	97	0	0	<1/25

[a] This rate of reaction ($T_{1/2}$ = 32 h) is unusually slow for an amine that follows pathway A. We have observed that the rate of reaction is fast in polar solvents, but the products depend on the choice of solvent. The reaction of 1 with NH_3, which is unusually complicated, will be discussed fully in a subsequent publication. [b] The remaining 35% was recovered as unreacted **1**. [c] Precipitation of **3** was complete within 10 min indicating reaction completion within this time interval. [d] Reaction was complete within 10 min in n-propylamine neat,[4] and the selectivity was >50/1. [e] Subsequent attempts to follow reaction kinetically by IR and/or NMR analysis indicated that reaction was complete within 2–6 h. [f] pK_a values taken from ref 18 and 19.

Table II. Characterization Data for Products 3, 4, and 5 Noted in Table I

Product	n	Mp, °C	Key IR absorption bands
Acetamidines (**3**) from amine			
2b	1	136–7	3.2–4.4, 6.3
2c	2	109–10	3.0–4.4, 6.3
2d	3	118–20	3.2–4.3, 6.3
2-Methylquinazolones (**5**) from			
2a	0	240–1	6.0, 6.2
2d	3	81–2	6.0, 6.2
o-Acetamidobenzamides (**4**) from			
2d	3	125–7	3.1, 6.1, 6.2, 6.3, 6.5
2e	4	133–4	3.1, 6.1, 6.2, 6.3, 6.5
2f	6	99–100	3.1, 6.0, 6.1, 6.2, 6.3, 6.5
2g	10	85–90	3.1, 6.0, 6.1, 6.2, 6.3, 6.5
2h	12	84–7	3.1, 6.0, 6.1, 6.2, 6.3, 6.5

the expected dependence of rate on n, because the range in calculated rate constants for a given amine was at least as great as the range in average rate constants for the set. It was decided, therefore, to defer publication of these data until the required quantitative reproducibility could be established and the work repeated.

Meanwhile the cause for the qualitative change in selectivity from pathway A to B at n = 4 became more interesting to us than the original objective. Accordingly, the literature was reexamined to see if similar aberrations in the reactions of the linear aliphatic amines $H_2N(CH_2)_nH$ were observed with other electrophiles.

It was noted by Hall et al.[6a,b] that the base strength of these amines does not increase monotonically as a function of n from 1 to 5. Later Brown[6c] noted that the irregularity in chemical behavior when n is 3 or 4 is fairly general and even appears in the gas-phase dissociation of the corresponding addition compounds with trimethylboron. He ascribed[6c] this irregularity primarily to an entropy effect, owing to steric preclusion of certain configurations when $n > 2$.

Although many papers[9,10] and excellent review articles[11–14] have been written about the relative basicity of amines in terms of parameters that reflect Brown's "B-Strain Theory",[15] Trotman-Dickenson's "Solution Theory",[16] and Taft's "σ^* Values",[17a] little further attention was given to the amines $H_2N(CH_2)_nH$, except to note[12] that the pK_a values for this series from n = 1 to 22 fall in the range of 10.7 ± 0.2. Apparently the variance in this set of pK_a values was not considered worthy of further consideration[12,14] since a large change in n causes at most only a small change in pK_a. This attitude is indeed justified, but only if the reported data either deviates randomly about the line pK_a = 10.7 ± 0.2, reflecting experimental error, or increases monotonically from 10.5 to 10.9, reflecting the expected influence of induction within the homologous series. Neither is the case, however, as can be seen from Figure 1, which plots the pK_a data for these amines, taken from ref 18 and 19 as a function of n. In contrast to either alternative condition, it is noticed that the pK_a values rise smoothly from 9.26 at n = 0 to a maximum of 10.81 at n = 2 and then fall to an asymptotic line given by 10.62 ± 0.3, from n = 4 to at least n = 22, the highest member of this series for which a pK_a value is reported. The pK_a values for the members below n = 4 are outside the limits of reproducibility indicated by the data given for the members with $n \geq 4$. This reconsideration of the data suggests that this observed distribution of pK_a as a function of n may be a manifestation of some real factor that suppresses the expected increase in base strength as noted by others.[6]

In contrast to the abnormal behavior of the amines in solution, gas-phase protonation of $H_2N(CH_2)_nH$ appears to be quite normal. It was reported by Aue[20] that the free energy and enthalpy of these reactions with methyl-, ethyl-, n-propyl, and n-butylamine exhibit a simple monotonic increase from n = 1 to 4, indicating that the chemical aberration may be peculiar to the solvated state at relatively lower temperatures.

One would expect the pK_a values in water for the set of amines $H_2N(CH_2)_nH$ to approach rapidly an asymptotic limit as shown by the dotted line in Figure 1 and given by the equation:

$$pK_a^* = 9.26 + 1.40 \sum_{1}^{n} 1/n^3$$

where 9.26 is the pK_a value for n = 0, 1.40 is the difference in pK_a values for n = 0 and 1 (i.e., the first and second members, respectively), and pK_a^* is the idealized value for the $(n + 1)$th

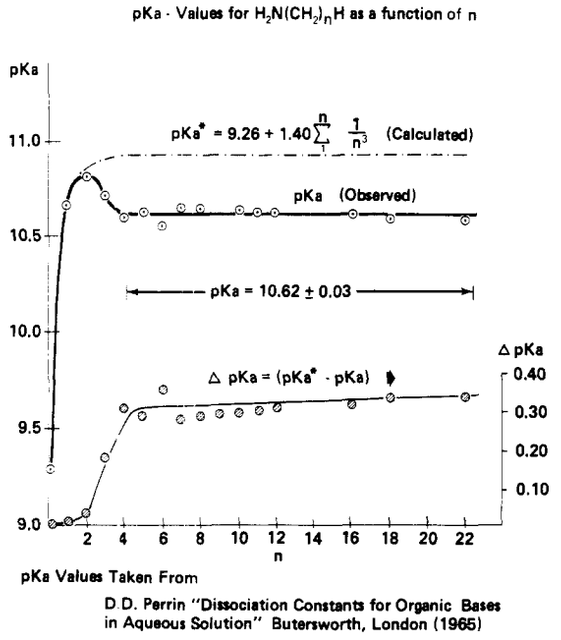


Figure 1.

member of this series. This equation is analogous to that which relates the bond dissociation energies (BDE) for the corresponding bonds in the homologous series $R(CH_2)_nH$ in terms of n,[21] namely:

$$E_n = E_0 + \Delta E_0{}^1 \sum_1^n 1/n^3$$

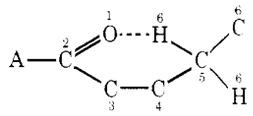
where E_0 is the BDE for the first member, $\Delta E_0{}^1$ is the corresponding difference for the first and second members, and E_n is the value for the $(n + 1)$th member.

The difference between the calculated idealized pK_a^* and the experimentally observed pK_a (i.e., $\Delta pK_a = pK_a^* - pK_a$) approaches rapidly an asymptotic limit of about 0.3 pK_a units, which corresponds to a difference in free energy of less than 0.5 kcal. This difference is constant over the range $n = 4$ to 22 as shown in Figure 1. Since significant increases in ΔpK_a occur only at $n = 3$ and 4, it is concluded that these are the methylene groups primarily responsible for the chemical aberration and that consequently the aberration must be associated with some configuration peculiar to the $H_2N(CH_2)_4$ segment, which might somehow impede the approach of an electrophilic center to the amino group.

If this postulation is correct then one should observe a sharp change in selectivity at about $n = 3$ or 4, when this set of amines with the general formula $H_2N(CH_2)_nH$ is made to react with acetylanthranil in a nonpolar solvent. This is exactly what was observed within the set given by the members $n = 0$, 1, 2, 3, 4, 6, 10, and 12. The data collected in Table I show that reaction in benzene at room temperature follows pathway A exclusively, when n is 0, 1, and 2 (i.e., A/B > 50/1), but that reaction via pathway B is measurable at $n = 3$ (i.e., A/B = 17/1) and is the dominant pathway for all values of $n > 3$ (i.e., A/B < 1/24). This change in selectivity at $n = 4$ corresponds exactly to the first member of this series that manifests maximum ΔpK_a as a function of n as shown in Figure 1. This infers that both effects are manifestations of the same cause, which exhibits its full impact when $n > 3$. Since reaction of a primary amine with acetylanthranil via pathway B is associated with some form of steric hindrance, it implies that here too steric hindrance is somehow responsible for the sharp change in selectivity at $n = 4$. This crossover in selectivity cannot be ascribed to the usual solvent or temperature effects since the same solvent, benzene, and the same temperature, room temperature, were used in each experiment. It is concluded, therefore, that the chemical aberration is due to steric hindrance manifested by the $H_2N(CH_2)_4$ segment, which is precluded (or mitigated, considerably) when $n < 4$.

It is difficult to imagine how the $H_2N(CH_2)_4$ segment might exhibit steric hindrance in this reaction unless it attains a five- or six-membered ring configuration, which is geometrically similar to that of a cyclic secondary amine as described in the first paragraph for ethanolamine and for anthranilic acid. In these two examples, however, the integrity of the pseudocyclic amine structure was maintained by intramolecular hydrogen bonding, which is not available to the $H_2N(CH_2)_4$ segment. If these linear aliphatic primary amines do assume cyclic configurations in solution, then their integrity must be maintained only by intramolecular forces of the van der Waals type, which are very small indeed. Consequently the effect of this weak intramolecular assoication would be felt only in solution at lower temperatures where "balling" would be abetted by gentle collisions with surrounding solvent molecules. In the gas phase, however, the energy state is such that the weak force of intramolecular association is easily overcome by thermal effects and the molecule assumes an open configuration, which is more accessible to a proton. Consequently the chemistry in the gas phase should be quite "normal" as reported by Aue,[20] whereas in solution it manifests the slight aberration first observed by others.[6]

The hypothesis that the $H_2N(CH_2)_n$ segments assume a coiled configuration in solution, which serves to impede reaction with an electrophilic reagent, bears formal resemblance to Newman's "Rule of Six",[17b] which states that in reactions involving addition to a center of unsaturation, the greater the number of atoms in the 6 position, the greater will be the steric hindrance to attack at the center of unsaturation of molecules such as



where A is HO, R_2N, R, or H. Newman[17b] pointed out that the coiled position is effective in hindering attack at the center of unsaturation because (1) the space about the center of unsaturation is partially blocked by the physical presence of the hydrocarbon coil, and (2) when addition occurs from the open direction, the increased spatial requirements involved in going from the ground state to the tetrahedral configuration of the intermediate state are more easily met in an uncoiled, rather than a coiled, configuration.

The idea that intramolecular association to form a six-membered ring can influence the chemistry of organic compounds was first suggested by Dippy,[22] who proposed that intramolecular hydrogen bonding of the carboxyl group with the hydrogen atom of the CH_3 was responsible for the abnormal increase in the ionization constant of butyric acid over propionic acid. Brown[6c] suggested that this might also obtain in the linear aliphatic amine series, but he pointed out correctly that the effect is too small to be attributed to intramolecular hydrogen bonding and suggested therefore that it might be attributable to an entropy effect that favors dissociation of the protonated form.

Although Brown's explanation is valid for reversible reactions that involve dissociation, it is not valid for nonreversible reactions that go in the forward direction, such as the reactions of **1** with $H_2N(CH_2)_nH$ to give either the corresponding **3** or **4** via pathways A or BZrespectively. If steric hindrance is to influence the selectivity in these reactions, it must do so in the forward direction, since the reverse possibility is excluded by definition. It is postulated therefore that this steric hindrance

is caused by the amine in its coiled configuration, which resembles geometrically a cyclic secondary amine.

It was shown that intramolecular hydrogen bonding is indeed strong enough to ensure the integrity of a cyclic configuration in the cases of anthranilic acid and ethanol amine[5] in nonpolar solvents. A key question now is whether or not the weak force of van der Waals attraction is also sufficiently great to hold long chain aliphatic amines in the postulated cyclic configuration.

More experiments are required to test further the hypothesis that these amines indeed manifest a form of "Newman Steric Hindrance" and also to help clarify the unique but mutually inconsistent results on selectivity and reactivity noted with ammonia.

Experimental Section

General Procedure. Reaction of acetylanthranil (**1**) with the amine **2** was made to occur in benzene at room temperature. The products **3, 4,** and **5** were separated and identified according to the chemical procedure described previously.[1,2] The materials balance of products with reactants was usually about 95%. The selectivity for reaction via pathway A relative to pathway B was calculated from the product distribution according to the equation: A/B = (**3** and/or **5**)/**4**. The data for these reactions are collected in Table I. The characterization data for the corresponding products, **3, 4,** and **5,** are collected in Table II. The details for reaction of ammonia (**2a**), methylamine (**2b**), and ethylamine (**2c**) in benzene, at room temperature, and *n*-propylamine (**2d**) neat, at 0 °C, are given in ref 4. The details for reaction of **1** with **2d,** *n*-butylamine (**2e**), *n*-hexylamine (**2f**), *n*-decylamine (**2g**), and *n*-dodecylamine (**2h**) in benzene, at room temperature, are given below:

Reactions of 1 with $H_2N(CH_2)_nH$ in Benzene at Room Temperature. i. With *n*-Propylamine (2d) to Give 3d and Some 4d. A solution of acetylanthranil (5 g) in benzene (50 cm^3) was mixed at room temperature with a solution of *n*-propylamine (**2d**) (2.0 g) in benzene (50 cm^3). Precipitation began to occur within 20 min and appeared to be complete within 4 h. The precipitate (1.9 g; mp 118–120 °C) was separated by filtration and identified as *N*-(2-carboxyphenyl)-*N'*-(*n*-propyl)acetamidine (**3d**) by its IR spectrum, Table II. The mother liquor was evaporated to dryness under vacuum. The residue (5.2 g) was leached sequentially with dilute aqueous base and then with dilute aqueous acid. The base–acid insoluble residue (0.5 g; mp 125–127 °C) was identified as *o*-acetamido-*N*-(*n*-propyl)-benzamide (**4d**) by its IR spectrum. The aqueous extracts were allowed to remain at room temperature overnight, during which time a white crystalline solid (3.0 g; mp 81–82 °C) separated from the alkaline solution. This precipitate was identified as *N*-(*n*-propyl)-2-methylquinazol-4-one (**5d**) by its IR spectrum. It was demonstrated that **5d** is formed from **3d** in aqueous solution by dissolving a 1-g sample of **3d** in dilute aqueous base at room temperature to give a clear solution from which **5d** (0.1 g) precipitated within 4 h.

ii. With *n*-Butylamine (2e) to Give 4e. A solution of **1** (1.6 g) and *n*-butylamine (0.8 g) in benzene (10 cm^3) was allowed to react overnight at room temperature. The reaction mixture was separated as described in i. The only product isolated (2.2 g; mp 132.5–133 °C) was *o*-acetamido-*N*-(*n*-butyl)benzamide (**4e**) which was identified by its IR spectrum and its mp (Table II).

iii. With *n*-Hexylamine (2f) to Give 4f and Some 5f. A solution of **1** (5 g) and *n*-hexylamine (**2f**) (3.0 g) in benzene (50 cm^3) was allowed to react at room temperature overnight. The reaction mixture was separated as described in i. The major component (7.5 g; mp 99–100 °C, after recrystallization from methanol) was isolated as the insoluble fraction after sequential extraction with dilute aqueous base and aqueous acid. It was identified as (*o*-acetamido)-*N*-(*n*-hexyl)-benzamide (**4f**) by its IR spectrum (Table II). Neutralization of the aqueous acid extract with base gave a white precipitate (0.3 g; mp 64–66 °C) which was identified as *N*-(*n*-hexyl)-2-methylquinazol-4-one (**5f**) by its IR spectrum.

iv. With *n*-Decylamine (2g) to Give 4g. A solution of **1** (5 g) and *n*-decylamine (4.8 g) in benzene (30 cm^3) was allowed to react for 5 h at room temperature. The clear solution produced thereby was separated as described under i, and *o*-acetamido-*N*-(*n*-decyl)benzamide, (**4g**) (9.4 g; mp 85–90 °C) was the only product isolated. It was identified by its IR spectrum (Table II). Unreacted **1** was isolated as *o*-acetamidobenzoic acid (0.5 g; mp 185–186 °C).

v. With *n*-Dodecylamine (2h) to Give 4h. A solution of **1** (1.6 g) and *n*-dodecylamine (2.0 g; Armeen-12D) in benzene (40 cm^3) was allowed to react for 5 h at room temperature. The solution was separated as described under i, and *o*-acetamido-*N*-(*n*-dodecyl)benzamide (**4h**) (3.5 g; mp 84–87 °C) was the only product isolated. It was identified by its IR spectrum (Table II). Unreacted **1** was isolated as *o*-acetamidobenzoic acid (0.1 g; mp 186–187 °C).

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Registry No.—**1,** 525-76-8; **3b,** 65452-95-1; **3c,** 61047-28-7; **3d,** 34242-12-1; **4d,** 59525-19-8; **4e,** 59525-20-1; **4f,** 65452-96-2; **4g,** 65452-97-3; **4h,** 65452-98-4; **5a,** 1769-24-0; **5d,** 50677-60-6; **5f,** 65452-99-5.

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