Acylanthranils. 12. Reaction of Acetylanthranil with Alcohols To Give Products of Self-Condensation

L. A Errede,* J. R. Hill, and J. J. McBrady

3M Central Research Laboratories, St. Paul, Minnesota 55144

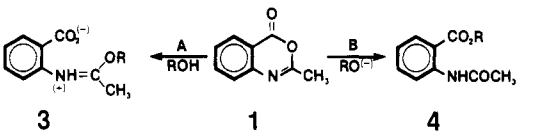
Received April 25, 1980

Material-balance studies on the reaction of acetylanthranil (**I**) in acidified alcohol showed that the end product is neither the expected *N*-(2-carboxyphenyl)acetimidate, **3**, nor the *o*-acetamidobenzoate ester, **4**, but rather mixtures of *N*-(2-carboxyphenyl)-2-methylquinazol-4-one (**5**), *o*-(*o*-acetamidobenzamido)benzoic acid (**6**), CH_3CO_2R, and R_2O, where R is the alkyl group of the alcohol. The stoichiometry in anhydrous media is consistent with the following equation: $21 + (1 + 2x)ROH \rightarrow (1 - x)5 + x6 + CH_3CO_2R + xROR$. Time studies of this self-condensation, monitored by proton NMR, showed that the acetimidate **3** is indeed formed as expected, but it establishes equilibrium with **1** within minutes. The acetimidate, however, reacts slowly with solvent and residual **1** to give products **5** and **6**, respectively, with concomitant formation of CH_3CO_2R and ROR as side products. The instantaneous selectivity ratio $(1 - x)/x$ increases monotonically with percent conversion to acids **5** and **6**. The disappearance of **1** in alcohol solution is pseudo first order. Initially, the rate-controlling step is the slow conversion of **3** to secondary intermediates Y and Z, but ultimately it is the subsequent very slow conversion of Y and Z to end products.

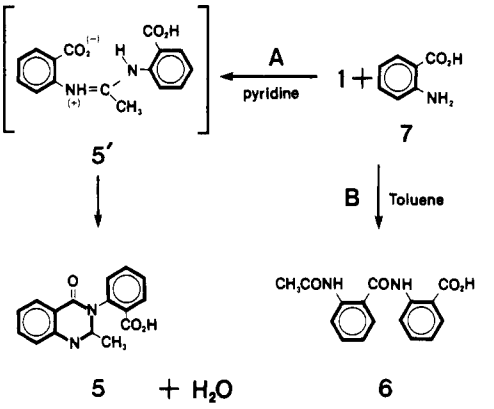
We reported[1] that formation of *o*-acetamidobenzoate esters **4** via reaction of acetylanthranil (**1**) with the anion form of an alcohol (**2**; Scheme I, pathway B) is very facile but that formation of the corresponding *N*-(2-carboxyphenyl)acetimidate **3** via reaction of **1** with the acid form of **2** (pathway A) appears not to occur even in very dilute alcohol solution.

This apparent inertness toward ROH is most unusual in light of the observed ease with which the corresponding reaction occurs with other nucleophiles such as water,[2] ammonia,[3] and amines.[4] We decided, therefore, to investigate this reaction further to see if addition of ROH via pathway A to give **3** can be made to occur under more vigorous conditions.

Scheme I



Scheme II



Results and Discussion

(A) Material-Balance Studies. All of our attempts to effect interaction of **1** with ROH under forcing conditions (i.e., more than 8 h in acidified alcohol solution at room temperature or above) to give either the acetimidate **3** or the ester **4** resulted instead in the complete conversion of **1** to *N*-(2-carboxyphenyl)methylquinazol-4-one (**5**) and/or *o*-(*o*-acetamidobenzamido)benzoic acid (**6**), which are the products formed when **1** is made to react with anthranilic acid (**7**, Scheme II).

Similar results were observed recently by Asakawa et al.,[5] who caused 5-substituted acylanthranils to react in alcohol solution at reflux. They reported that the ratio of **5** to **6** is dependent upon the electronic contribution of the substituent in the 5-position. The material-balance data collected in our studies (Table I) show that this product ratio is also highly dependent upon the experimental conditions. Thus, at room temperature mixtures of **5** and **6** are produced in the presence of organic acids, but **6** is produced exclusively in the presence of strong mineral acid such as H_2SO_4 (expt 6). On the other hand, **5** is the only product of self-condensation (69% yield) when **1** is made to react in 95% ethanol at reflux (expt 4). The other major product is *o*-acetamidobenzoic acid (**8**, 26% yield) which was formed competitively via hydrolysis of **1** in the 5% water–95% ethanol solution.

The material-balance data collected in Table I show that virtually all of the acetyl substituents that were eliminated in the conversion of **1** to products **5–7** were isolated as the acetate ester, E (CH_3CO_2R). The results obtained in expts 1–3 show that when this reaction is made to occur in anhydrous ROH, the corresponding ether, ROR, is produced in a molar amount about equal to that of product **6**. No ether is produced, however, when an equivalent amount of H_2O is added to the methanol solution. The yields of other products are unaffected. Similar results are obtained when this reaction is made to occur in 5% water–95% ethanol (expt 4). These results suggest that the yield of ROR in anhydrous media is decreased in proportion to the amount of water generated via cyclodehydration of the acetimidate intermediate **5′** to give **5** (Scheme II). This implies that the major overall reaction in the absence of added H_2O has the following stoichiometry:

$$21 + (1 + 2x)ROH \rightarrow (1 - x)5 + x6 + E + xROR \quad (1)$$

(1) Part 11: Errede, L. A.; Ashley, P. E.; McBrady, J. J.; Yarian, D. R. *J. Org. Chem.*, preceding paper in this issue.
(2) Part 10: Errede, L. A.; McBrady, J. J.; Tiers, G. V. D. *J. Org. Chem.* **1980**, *45*, 3868–3875.
(3) Part 9: Errede, L. A.; Martinucci, P. D.; McBrady, J. J. *J. Org. Chem.* **1980**, *45*, 3009–3017.
(4) Part 4: Errede, L. A.; McBrady, J. J.; Oien, H. T. *J. Org. Chem.* **1977**, *42*, 656–658.
(5) Asakawa, H.; Matano, M.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1979**, *42* (2), 287–291.

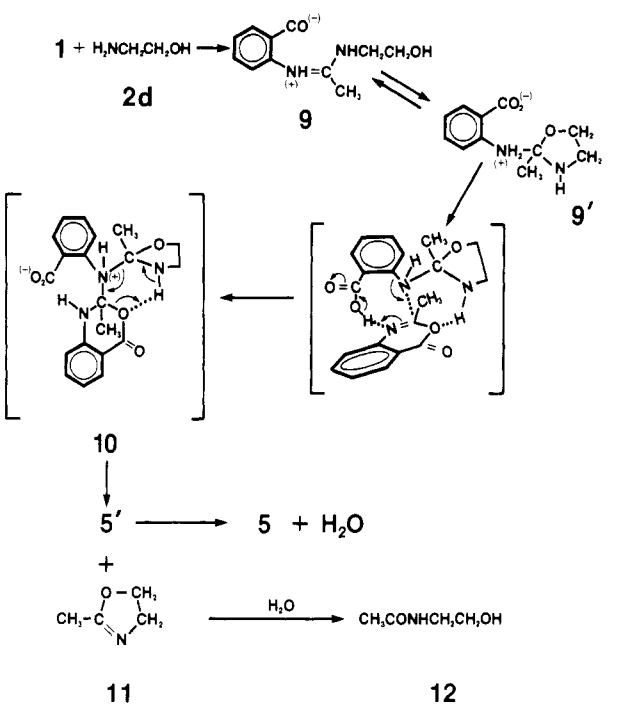
0022-3263/82/1947-3829$01.25/0

Table I. Reaction of 1 with Alcohol To Give Products of Self-Condensation

		reaction conditions				product yields based on 1,[f] %						pseudo-first-order rate const for disappearance of 1, min^{-1}	
expt[d]	alcohol	solvent	added solute[f]	temp[e]	time, days	6	5	7	8	CH_3CO_2R (E)	R_2O	k_i	k_f
1	2a	MeOH	none	rt	14	25	70	1		48	10		
1K	2a	MeOH	0.10 M 8	rt	14	27	73	0	*a*			0.016	0.00036
2	2a	MeOH	0.13 M 8, 0.5 M 7	rt	12	50	50	*b*	*a*	50	20		
2K	2a	MeOH	0.13 M 8, 0.5 M 7	rt	12	58	42	*b*	*a*			0.017	0.0051
3	2a	MeOH	0.11 M 8	rt	12	50	50						
3K	2c	CD_3OD	0.11 M 8	rt	12	53	47	0	0	50	25	0.0014	0.00030
4	2b	95% EtOH	none	rfx	1	0	69	5	26	35	0		
5	2b	95% EtOH	H_2SO_4	rt	1	87	0	0	6	45	0		
6	2d	CH_3CO_2H	$H_2NCH_2CH_2OH$	rt	1	0	95	0	0	45[c]			

[a] Original amount of 8 charged into the reaction mixture was recovered after conversion 1 to products was complete. [b] Original amount of 7 charged into the reaction mixture was recovered after conversion of 1 to products was complete. [c] Product actually isolated was $CH_3CONHCH_2CH_2OH$, presumably via hydrolysis of 2-methyl-4,5-dihydrooxazole (see ref 6). [d] An experiment number with a K indicates kinetic time study, monitored by proton NMR; yield data are based on the final recorded spectrum. [e] rt = room temperature and rfx = reflux. [f] 5 = *N*-(2-carboxyphenyl)-2-methylquinazol-4-one; 6 = *o*-(*o*-acetamidobenzamido)benzoic acid; 7 = anthranilic acid; 8 = *o*-acetamidobenzoic acid.

Scheme III



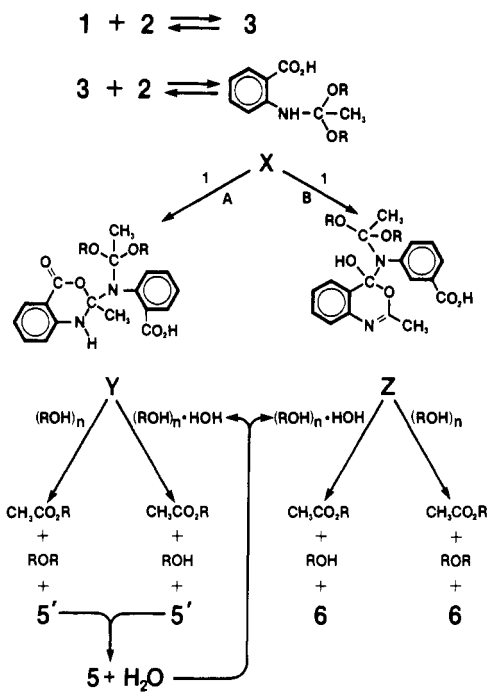
Since anthranilic acid (7) was isolated as a minor product in expts 1 and 4, it was considered possible that the above reaction involved interaction of 1 with ROH to give E, ROR, and 7, which reacts in turn with residual 1 to give 5 and/or 6 as indicated in Scheme II. If this be true, then the molar ratio of end products (5 + 6) to reactant 1 should double when the above reaction is allowed to occur in the presence of an equivalent amount of 7. This is not the case, however, as shown by the material-balance data of expt 2. Virtually all of the added 7 was recovered, and the molar ratio of 5 + 6 to 1 was 1:2, which is essentially the same as that obtained in the absence of added 7. This negative result rules out the possibility that 7 is an intermediate in the stepwise formation of 5 and/or 6. It is concluded, therefore, that the end products are formed via continued reaction of an alcohol adduct, $1\cdot(ROH)_n$, with residual 1.

Additional insight into the possible mechanism for this self-condensation can be gained from results reported earlier[6] for the reaction of 1 with ethanolamine (2d) in various solvents. When 1 is allowed to react with 2d neat, the product is *o*-acetamido-*N*-(2-hydroxyethyl)benzamide; when the reaction is allowed to occur in pyridine, the product is *N*-(2-carboxyphenyl)-*N'*-(2-hydroxyethyl)acetamidine 9 which undergoes cyclodehydration readily to give *N*-(2-hydroxyethyl)-2-methylquinazol-4-one. The products obtained under the above conditions are those expected for direct nucleophilic attack by an amino group at C-4 (pathway B in Scheme I of ref 1) and C-2 (pathway A in Scheme I of ref 1), respectively, as discussed previously.[6] When reaction is allowed to occur in acetic acid, however, the products isolated in about equal amounts are 5 and 2-acetamidoethanol, which is similar to the results reported now for reaction of 1 in acidified alcohol solution.

The formation of 5 and 2-acetamidoethanol in acetic acid solution was rationalized as outlined in Scheme III. Addition of 2d to 1 gives the acetamidine 9, which is in equilibrium with 9′. Reaction of 9′ with 1 gives the intermediate 10, which rearranges in turn to give 2-

(6) Part 5: Errede, L. A.; McBrady, J. J. *J. Org. Chem.* 1977, *42*, 3863–3866.

Scheme IV



methyl-4,5-dihydrooxazole (11) and *N,N'*-bis(2-carboxyphenyl)acetamidine (5′). Cyclodehydration of 5′ to give the corresponding quinazolone 5 occurs readily in acetic acid solution.[6] The water liberated thereby reacts with 11 to give 2-acetamidoethanol (12).

A similar sequence can be written for the reaction of 1 in methanol (2a) or ethanol (2b). It is postulated that reaction in ROH gives the acetimidate 3, as expected (Scheme I, pathway A). This product, however, continues to react with ROH to give the corresponding amino ortho ester X (which is analogous to 9′ of Scheme III). This secondary product can associate strongly with residual 1 to give the complex 1·X by multidentate association that involves alignment of the electron-donating and -accepting sites in both molecules. Complex 1·X eventually undergoes covalent bond formation to give either dimeric adduct Y [which is the equivalent of 10; Scheme III) via pathway A (Scheme I of ref 1)] or Z via pathway B (Scheme I of ref 1). Reaction of the dimeric adducts with $(ROH)_n$ gives CH_3CO_2R, ROR, and 5′ (from Y) or 6 (from Z) as indicated in Scheme IV). The formation of ROR probably occurs via liberation of R^+ or its solvate, which reacts in turn with $(ROH)_n$ to give ROR and H^+. Cyclodehydration of 5′ occurs rapidly in alcohol solution to give 5 and HOH, which apparently is consumed readily by reaction of $(ROH)_n$·HOH with Y and Z as noted above to give H^+ and ROH instead of ROR. Thus, when 6 is produced exclusively, the stoichiometry of eq 1 simplifies to

$$21 + 3ROH \rightarrow 6 + CH_3CO_2R + ROR$$

but when 5 is produced exclusively via cyclodehydration of 5′, it becomes

$$21 + ROR \rightarrow 5 + CH_3CO_2R$$

(B) Kinetic Studies. If one assumes that this self-condensation does indeed involve two types of intermediates (i.e., acetimidate 3 and amino ortho esters X, Y, and Z as suggested in Scheme IV), then it should be possible to obtain evidence for these intermediates by proton NMR spectroscopy. Accordingly, the reaction in methanol was monitored over a period of 12 days, during which time a set of 13 proton NMR spectra were recorded to show the corresponding change in inventory of the CCH_3 protons

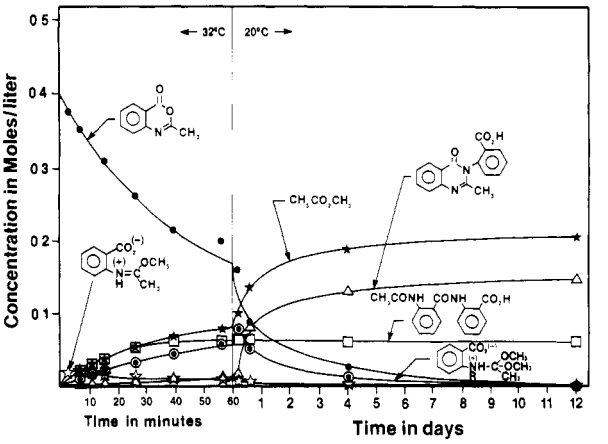


Figure 1. Reaction of 1 (0.4 M) in methanol in the presence of *o*-acetamidobenzoic acid (0.1 M).

as reactant 1 (τ 7.57) is converted to 5 (τ 7.80), 6 (τ 7.98), and E (τ 7.98) as described in the Experimental Section. These data, normalized to exprss concentration, are plotted in Figure 1, in which it is seen that (a) 1 decreases monotonically from 0.40 to 0.0 M, while 5, 6, and E increase accordingly, and that (b) two types of intermediates are formed as expected, attaining maximal concentrations at approximately 5 min and 6 h, respectively.

The proton NMR signal at τ 8.17 for CCH_3 protons of the intermediate that attained maximal concentration at 5 min corresponds well with that expected for the methyl protons of a $CH_3CR{=}NR$ structure. Consequently, this signal was attributed to the expected acetimidate 3. The proton NMR signal at τ 8.60 for the methyl protons of the intermediate that attained maximal concentration at t = 6 h corresponds well with that expected for a $CH_3C(OR)_2NR_2$ structure. Consequently, this signal was attributed to the combined contributions of postulated intermediates X, Y and Z (i.e., X + Y + Z = U). The decrease in 3, after attaining a maximum concentration of 0.025 M, was such that the ratio of 1/3 was equal uniformly to (20 ± 1)/1. This implies that 1 and 3 are related by the equilibrium

$$1 + HOCH_3 \rightleftarrows 3$$

and that the corresponding equilibrium constant is about 2×10^{-2}. After U attained its maximal concentration of 0.08 M at t = 6 h, the concentration ratio for 1/U remained essentailly constant at ca. 2:1, which implies that the rate of disappearance of 1, after 1 half-life, is controlled by the combined rates at which Y and Z are coverted irreversibly to end products 5′ and 6.

That 1 is in sequential equilibrium with 3 and X is supported by the negative results obtained in an attempt to isolate the intermediates 3 and X accumulated after 6 h in methanol at room temperature. At that point in time, the composition of this solution was 1 (0.16 M), 3 (0.02 M), U (0.08 M), 5 (0.02 M), 6 (0.05 M), and 8 (0.10 M) as indicated by the proton NMR spectrum of an aliquot sample. Directly thereafter the solution was evaporated to dryness at 1 torr and 50 °C. The NMR spectrum of the residue in pyridine, however, indicated the presence of only four components, namely, 1, 8, 5, and 6 in relative ratios 12:5:1:2, respectively. Apparently, removal of ROH by evaporation drives the sequential equilbria toward regeneration of the original reactants, 1 and 2, leaving a mixture of reactants 1 and 8 and stable end products 5 and 6 as a nonvolatile residue.

Similarly, the apparent failure to undergo reaction with solvent, when 1 was purified by recrystallization from hot

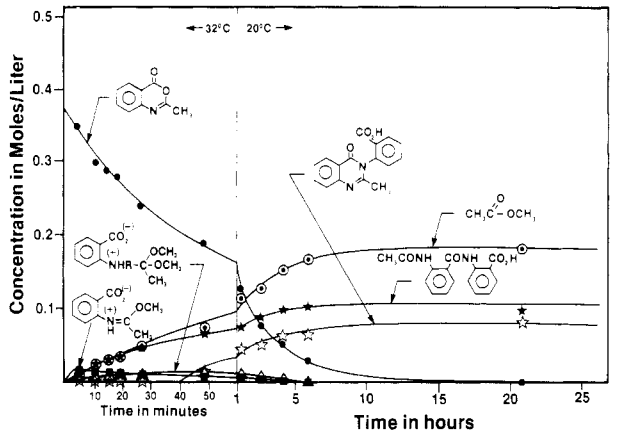


Figure 2. Reaction of 1 (0.37 M) in methanol in the presence of anthranilic acid (0.5 M) and *o*-acetamidobenzoic acid (0.13 M).

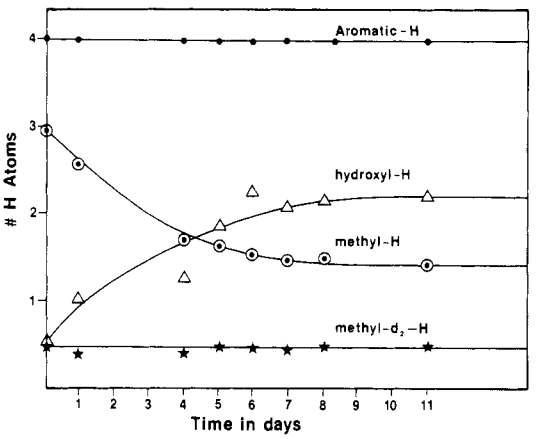


Figure 3. Inventory of methyl H and hydroxyl H as a function of reaction time.

methanol or ethanol, as reported at the beginning of this paper, can also be rationalized on the basis of reversibility. When the hot solution of reactants (**1**, **2**, and **8**), intermediates (**3** an X), and end products (**5**, **6**, and E) is cooled to 0 °C, reactant 1 crystallizes from solution, shifting the equilibria to regenerate the reactants. Thus, ca. 90% of the orginal acetylanthranil was recovered in pure form, leaving in solution the original impurity, **8**, and a small amount of **1** which was converted to **5**, **6**, and E via reaction with solvent.

The disappearance of **1** in methanol solution is pseudo first order. The initial rate constant, k_i, from 0 to 60 min (i.e., about 1 half-life, during which time the reaction tube was kept in the proton NMR cavity at 32 °C) was observed to be 0.016 min^{-1}, and the final rate constant, k_f, from 3 h to 12 days (during which time the reaction tube was stored at 20 ± 0.5 °C until needed for recording the next NMR spectrum) was observed to be 0.000 36 min^{-1}. The approximate activation energy, calculted from these two data, is 56 kcal/mol. It was observed, however, that the product selectivity ratio (i.e., **5**/**6**) increased from about 1:6 at t = 0.5 h to about 3:1 at t = 4 days (Figure 1). It was suspected, therefore, that the change in temperature from 32 to 20 °C may not be the only factor that affects the observed decrease in rate; i.e., a change in mechanism and/or a change in the rate-controlling step for consumption of **1** might be superimposed on the temperature effect.

When **1** was made to undergo self-condensation in the presence of an excess amount of anthranilic acid, (**7**; expt 2K, Table I), the initial rate constant was essentially unchanged (i.e., k_i = 0.017 min^{-1} vs. 0.016 min^{-1}), but the final rate constant increased by more than a power of ten (i.e., k_f = 0.0051 min^{-1} vs. 0.000 36 min^{-1}). The approximate activation energy calculated from these two data is 18 kcal/mol, which is about one-third of that noted for expt 1K. Comparison of this time study (Figure 2) with the above study (Figure 1) shows that the concentration intermediate X + Y + Z = U reached a maximal concentration of only 0.02 M (instead of 0.08 M), which was attained at t = 40 min (instead of t = 6 h), and that the ratio of **3** to U remained constant thereafter at about 1:1. The ratio of **1** to **3** in both studies, however, remained constant (after the first few minutes required to establish equilibrium) at about 20:1. Again the product selectivity ratio (**5**/**6**) increased with percent conversion of **1** to end products **5** and **6**, but the magnitude of change was less (i.e., from 1:8 at t = 0.5 h to 3:4 at the end of reaction, in this case only 5 h instead of 5 days). These results support the point of view that the accumulation of acid products **5** and **6** affect autocatalytically the rate and selectivity for conversion of intermediate X to intermediates Y and Z, which determines the selectivity ratio for end products **5** and **6**.

When self-condensation of **1** was carried out in methanol-d_4, k_i and k_f were found to be 0.0014 and 0.000 30 min^{-1}, respectively (expt 3K, Table I). Although the final rate constant is essentially the same as that for reaction in methanol (expt 1K), the initial rate constant is a power of ten smaller, reflecting the relatively lower reactivity of **1** toward CD_3OD (vs. CH_3OH) to give the corresponding **3** and X intermediates. The approximate activation energy calculated from these two data is 23 kcal/mol, which is closer to that found in expt 2K than that found in expt 1K.

It was noted that conversion of **1** in methanol-d_4 is accompanied by hydrogen–deuterium exchange as shown in Figure 3. The total integration area for aromatic hydrogen atoms in the solutes and the total integration area for HCD_2OD hydrogen atoms in the solvent always remained constant at 4.0 and 0.49, respectively, showing that these hydrogen atoms were not participating in the exchange. The total integration for the CH_3C protons of the solutes, however, decreased monotonically from 2.9 at t = 0 to 1.41 at t = 11 days, while the corresponding integration for OH hydrogens in the solvent and solutes increased from 0.51 to 2.21 over the same time interval. Most of this change (75%) occurred within the first 4 days, when the concentrations of **1**, **3**, and U were relatively high and those of **5**, **6**, and E were correspondingly lower, implying that the set of three end products were not participating in the interchange. The validity of this implication was confirmed in separate experiments in which 0.5 M solutions of **5**, **6**, and E in methanol-d_4 were monitored by proton NMR; no evidence for conversion of these solutes to the corresponding deuterated product was obtained over a period of 7 days at room temperature. It was concluded, therefore, that the hydrogen–deuterium interchange occurred only during the formation and/or subsequent conversion of the intermediates to stable end products. Nevertheless, it was necessary to apply a point-by-point correction factor (based on Figure 3) to each set of proton NMR integration data in order to account for changes in solute concentrations that reflect progressive losses in the CH_3C inventory owing to formation of the corresponding partially deuterated compounds. The resultant time pattern (Figure 4) shows qualitative similarity to the corresponding time study with ordinary methanol (Figure 1).

After equilibrium between **1** and **3** was established within the first few minutes, the ratio of these solutes

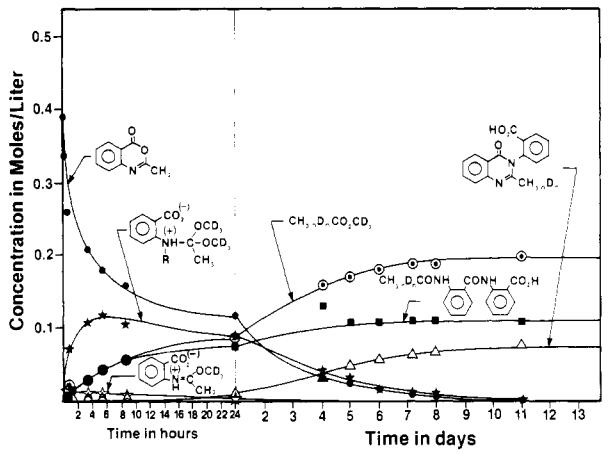


Figure 4. Reaction of 1 (0.39 M) in methanol-d_4 in the presence of *o*-acetamidobenzoic acid (0.11 M).

remained constant at about 21:1. Again, U reached a maximal concentration of 0.1 M at t = 6 h, after which time the ratio of 1/U remained constant at about 1:1.

These results are consistent with the point of view that the solvent ($HOCH_3$ or $DOCD_3$) participates as a reactant in the sequential conversion of 1 to Y and/or Z but not in the final step that gives stable end products. The results also suggest that the former may be the rate-determining step for consumption of 1 during the first half-life and that the latter may be the rate-determining step after U attains its maximal concentration.

Summary and Conclusions

The above material-balance and time studies have shown that acetylanthranil (1) reacts with alcohols **2** to give the corresponding *N*-(2-carboxyphenyl)acetimidate, **3**, as noted in Scheme I (pathway A). The reaction, however, is reversible, and equilibrium is established within minutes. When the solution is allowed to remain in room temperature, the primary product **3** reacts slowly with the solvent and residual 1 to give dimeric intermediates Y and Z via reaction of X with 1 as suggested in Scheme IV. The dimer intermediates, Y and Z, undergo rearrangement very slowly and irreversibly to give mixtures of *N*-(2-carboxyphenyl)-2-methylquinazol-4-one (**5**, from Y), *o*-(*o*-acetamidobenzamido)benzoic acid (**6**, from Z), CH_3CO_2R, and ROR′, where R is the alkyl group of the alcohol and R′ is either R or H. Although anthranilic acid (**7**) was sometimes isolated as a very minor component of the product mixture, it is not an intermediate in the formation of **5** and **6** via reaction with 1, despite the fact that this is known to occur in nonreactive solvents such as toluene and pyridine.[6]

Disappearance of 1 in alcohol solution is pseudo first order. The initial rate constant, k_i, that obtains during the first half-life, however, is about two powers of ten greater than the final rate constant, k_f, that obtains during subsequent half-lives. The rate-determining step during the first half-life appears to be the slow conversion of intermediate X to intermediates Y and Z; whereas the very slow irreversible conversion of Y and Z to end products **5** and **6**, respectively, and side products CH_3CO_2R and ROR′ appears to be the rate-determining step during subsequent half-lives. When self-condensation is made to occur in the presence of excess anthranilic acid (**7**), k_f is increased by a power of ten, but k_i is unaffected. On the other hand, when self-condensation is made to occur in methanol-d_4 instead of methanol, k_i is decreased by a power of ten, but k_f is unaffected. These results are consistent with the point of view that the solvent is a reactant in the sequential reversible conversions of 1 to Y and Z but not in the subsequent irreversible conversions to end products **5** and **6**. The latter reactions, however, are affected markedly by the presence of acidic solutes, as indicated by the monotonic change in product selectivity as a function of accumulated acid products **5** and **6** and by the marked increase in k_f in the presence of added anthranilic acid (**7**).

Experimental Section

General Methods. The melting points, elementary analyses, and IR and NMR data were obtained as described in the General Methods reported in our preceding publication.[1] Gas chromatographic separations and subsequent determinations by mass spectrometry were made by using a Varian 2740 gas chromatometer and a Du Pont 21-491B mass spectrometer.[7]

(1) Reaction of Acetylanthranil (1) with Methanol (2a). (a) Material-Balance Study (Expt 1). A solution of 1 (1.62 g, 0.01 mol) in **2a** (20 mL) was allowed to react at room temperature for 2 weeks. The solution was separated by evaporation to dryness at 35 °C in a closed system at 1 torr. The molecular composition of the condensate collected at −78 °C was determined by gas–solid chromatography and mass spectrometric analyses on an aliquot sample.[7] In addition to methanol, this distillate contained 0.005 mol of methyl acetate and 0.0009 mol of dimethyl ether. The IR spectrum of the nonvolatile residue (1.4 g) indicated that it was a mixture of *N*-(2-carboxyphenyl)-2-methylquinazol-4-one (**5**) and *o*-(*o*-acetamidobenzamido)benzoic acid (**6**). This observation was confirmed by its NMR spectrum, which also showed that the ratio of **5** to **6** was 2.8/1. The mixture was separated essentially as described previously[6] to give **5** (mp 253–254 °C), **6** (mp 214–215 °C), and a small amount (0.03 g) of impure anthranilic acid (**7**). Thus, the material balance showed that 70% of 1 was recovered as **5**, 25% as **6**, and about 1% as **7** and that 1 mol of methyl acetate and 0.2 mol of dimethyl ether were produced as side products for every 2 mol of 1 consumed.

(b) Kinetic Time Study (Expt 1K). A sample (0.040 g) of powdered acetylanthranil (1; 20% of which was hydrolyzed by water vapor to *o*-acetamidobenzoic acid (**8**) as described previously[2]) was weighed into an NMR tube. Methanol (0.50 mL) and tetramethylsilane (0.02 mL) were added to form a clear solution. The first proton NMR spectrum was recorded 2 min after addition of the solvent. This spectrum showed signals at τ 6.65 for OCH_3 of methanol, at τ 7.57 for CCH_3 of 1, at τ 7.80 for CCH_3 for **8**, and a mountain of signals from τ 1.75 to 2.25 for the aromatic hydrogens of 1 and **8**. The proton integration areas (I_i) for these signals established that the ratio of 1/**8** was 4:1 (i.e., $I_{7.57}/I_{7.80}$ = 4:1) and confirmed that the ratio of total aromatic hydrogens to total CCH_3 hydrogens was 4:3; i.e., $I_{1.75\text{–}2.25}/(I_{7.57} + I_{7.80})$ = 4:3.

The next five spectra were recorded within the first hour after preparation of the reaction solution, during which time the NMR tube was allowed to remain in the NMR cavity (32 °C). Thereafter the NMR tube was stored at 20 ± 0.5 °C until needed for recording the next spectrum. The next four spectra were recorded at about 1-h intervals, and the last three were recorded at 18 h, 4 days, and 12 days. In addition to the signals exhibited in the first spectrum, subsequent spectra exhibited new signals at τ 7.98, 8.17, and 8.60. The proton integration areas for the signal at τ 7.57 (i.e., $I_{7.57}$) decreased monotonically with time, while $I_{7.80}$ and $I_{7.98}$ increased montonically. The integration areas $I_{8.17}$ and $I_{8.60}$ exhibited maxima at times of 5 min and 6 h, respectively, and decreased monotonically thereafter to essentially zero in the final spectrum.

In all 13 spectra, the ratio for aromatic hydrogens to total CH_3 hydrogens remained essentially constant at 4:3 [i.e., 4:3 = $I_{1.75\text{–}2.25}/(I_{7.57} + I_{7.80} + I_{7.98} + I_{8.17} + I_{8.60})$], showing that the inventory of CCH_3 protons accounted from beginning to end for virtually all the acetyl substituents of 1 as it underwent conversion to end products **5**, **6**, and methyl acetate (E). The individual

(7) We are indebted to Dr. W. L. Stebbings of 3M for the gas chromatographic separations and subsequent determination of molecular composition by mass spectrometry.

reference spectra of 5, 6, 8, and E in methanol showed that both 5 and 8 contribute to the signal at τ 7.80 (i.e., $I_{7.80} = I_{5+8}$) and that both E and 6 contribute to the signal at τ 7.98 [i.e., $I_{7.98} = I_{E+6}$]. Only one component, however, contributes to the signal at τ 7.57, namely, 1, and consequently $I_{7.57} = I_1$. At time zero the contribution $I_{7.80}$ came only from 8 (i.e., $I_{7.80} = I_8$), and since the material-balance study had shown that 8 is not formed at room temperature, any increase in this signal is caused by accumulation of 5. Consequently, I_5 at time t can be calculated by subtracting $I_{7.80}$ at time zero from $I_{7.80}$ at time t, (i.e., $I_5 = I_{7.80} - I_8$). The materials-balance study had shown also that the stoichiometry of this self-condensation is such that E = 5 + 6. Consequently, $2I_E = I_5 + I_6 + I_E$, and since $(I_6 + I_E) = I_{6+E} = I_{7.98}$, I_E is given by $1/2(I_{7.98} + I_5)$.

The signal at τ 8.17 is consistent with that expected for the CCH_3 protons of the acetimidate 3, and assignment was made accordingly (i.e., $I_{8.17} = I_3$). The signal at τ 8.60 is consistent with that expected for amino ortho esters of the type exemplified by intermediates X–Z (Scheme IV). Accordingly, this signal was attributed to the sum total contribution of all such intermediates, i.e., $I_{7.80} = I_{X+Y+Z}$.

Since 0.5 M is the sum total concentration of all the components containing aromatic groups, the concentration of each aromatic component, C_i, is given by $0.5(I_i/\sum I_i)$. The normalized concentration data are plotted as a function of time in Figure 1.

The logarithm of the concentration of 1 was also plotted as a function of time to give a curved line that appeared to be a composite of two straight lines with different negative slopes. The initial slope, which included the data recorded during the first hour (Fig 1), corresponded to an initial pseudo-first-order rate constant (k_i) equal to 0.016 min^{-1}, whereas the slope of the second line, which included the data recorded during the last 11 days (Figure 1) corresponded to a final pseudo-first-order rate constant (k_f) equal to 0.000 36 min^{-1}.

(c) Reaction in the Presence of Excess Anthranilic Acid (7; Expts 2 and 2K). A solution of acetylanthranil (1; 0.030 g, 1.86×10^{-4} mol), *o*-acetamidobenzoic acid (8; 0.010 g, 5.6×10^{-5} mol), anthranilic acid (7; 0.030 g, 2.1×10^{-4} mol), methanol (0.50 mL) and tetramethylsilane (0.02 mL) was allowed to react at room temperature. The conversion to products was monitored by proton NMR as described above under procedure 1b. The corresponding time-study data are plotted in Figure 2. The initial pseudo-first-order rate constant for disappearance of 1 (k_i) was calculated to be 0.017 min^{-1}, which is essentially the same as that noted in the absence of added anthranilic acid. The subsequent pseudo-first-order rate constant (k_f) was calculated to be 0.0051 min^{-1}, which is 14-fold faster than the corresponding rate in the absence of anthranilic acid. In accordance with this greater rate of k_f, the concentration of intermediates U = X + Y + Z) was uniformly below 0.02 m. After the kinetic study was complete, the solution was separated by evaporation to dryness at 35 °C in a closed system at 1 torr. The distillate was analyzed by gas–solid chromatography and mass spectrometry as before. Again methyl acetate (1×10^{-4} mol) and dimethyl ether (4×10^{-5} mol) were detected as minor components of the distillate.[7] The residue (0.07 g) was leached with hot water (3 mL). The water-soluble fraction was evaporated to dryness. The NMR spectrum of the residue (0.04 g) in pyridine indicated that this was a mixture of anthranilic acid (7) and *o*-acetamidobenzoic acid (8) in the ratio of about 3:1, showing that virtually all of these components were recovered unchanged. The NMR spectrum of the water-insoluble products (0.03 g) indicated tht this residue was a mixture of 5 and 6 in about equal amounts.

(d) In Methanol-d_4 (Expts 3 and 3K). A solution of acetylanthranil (1; 0.03 g, 1.9×10^{-4} mol), *o*-acetamidobenzoic acid (8; 0.009 g, 5×10^{-5} mol), methanol-d_4 (0.50 mL), and tetramethylsilane (0.02 mL) was allowed to react at room temperature for 11 days. The conversion of products was monitored by proton NMR as described in 1b. The integration areas (I_i) for aromatic hydrogen atoms remained statistically constant for the 12 spectra recorded during this interval. The same was true for the HCD_2OD proton present as an impurity in the methanol-d_4 solvent. The ratio of aromatic hydrogen to methan-d_3-ol hydrogen was constant at 4.00/0.49, showing that either or both could serve as an internal reference to permit calculation of changes in the molar concentration of reactant 1 and products 5, 6, and E. It was observed that the total number of *C*-methyl hydrogen atoms 5, 6, 8, and E per four aromatic hydrogen atoms decreased monotonically with time from 2.90 at $t = 0$ to 1.41 at $t = 11$ days, whereas the ratio of OH hydrogen atoms to four aromatic hydrogen atoms increased from 0.51 to 2.21 during the same interval as shown in Figure 3. This indicated that the concentration of products 5, 6, and E based on integrated NMR signals for the corresponding *C*-methyl substituent would be low, owing to a proton–deuterium interchange. Consequently, the appropriate point by point correction factor, based on Figure 3, was applied to the original NMR data as a function of time to preserve the inventory of *C*-methyl substituents. These corrected data are plotted in Figure 4. It was noted that the initial pseudo-first-order rate constant for disappearance of 1 during the first 8 h in methanol-d_4 ($k_1 = 0.0014$ min^{-1}) was 11-fold slower than the corresponding rate in methanol but that the rate of disappearance during the last 6 days in methanol-d_4 ($k_f = 0.000\,36$ min^{-1}) was about the same as that in methanol (see Table I).

After the kinetic study was complete, the solution was separated into volatile and nonvolatile fractions as described previously. Methyl-d_3 acetate (1×10^{-4} mol) and dimethyl-d_3 ether (5×10^{-5} mol) were identified as minor components of the distillate.[7] The residue was leached with hot water (2 mL) to remove 8 (0.01 g). The NMR spectrum of the water-insoluble residue (0.03 g) in pyridine indicated that this was a mixture of 5 and 6 in about equal amounts. Attempts to effect quantitative separation were unsuccessful, but enough of each component was isolated for identification by comparison of their respective IR spectra and melting points with those of authentic samples.[6]

(2) Reaction of Acetylanthranil (1) with Ethanol (2b). (a) At Reflux To Give *N*-(2-Carboxyphenyl)-2-methylquinazol-4-one (5, Expt 4). A solution of 1 (5 g, 0.031 mol) in 95% ethanol (100 mL) was allowed to react at reflux for 24 h. The solvent was removed by evaporation to dryness at 35 °C in a closed system at 1 torr. A sample of the condensate (100 mL), collected in a cold trap at −78 °C, was analyzed by gas–solid chromatography and mass spectrometric analyses. Ethyl acetate was identified as a minor component (0.013 mol), but diethyl ether was not detected.

The nonvolatile residue was extracted with boiling water. A white crystalline material (1.8 g, mp 165–166 °C) separated on cooling of the mixture to room temperature. Its IR spectrum was very similar to that of *o*-acetamidobenzoic acid (8) except that it had small absorption bands at 2.8 and 2.9 μm, indicating that anthranilic acid (7) might be present as an impurity. The NMR spectrum indicated that it was a mixture of 8 and 7 in the ratio of about 5:1. The melting point and IR spectrum of this material did not change despite recrystallization from hot water and again from water–ethanol, suggesting that this might be a true molecular complex, whose proportions are 5:1, thus indicating that the amount of anthranilic acid that coprecipitated with *o*-acetamidobenzoic acid in the 1.8 g of material that melted at 165–166 °C is about 0.2 g, which corresponds to about 5% of the original acetylanthranil.

The IR spectrum of the insoluble solid residue (2.9 g; mp 248–250 °C), from which 8 and/or unreacted 1 was removed by extraction with hot water, indicated that it was mostly *N*-(2-carboxyphenyl)-2-methylquinazol-4-one (5). This residue was recrystallized from ethyl acetate to give 5 in the form of colorless needles (mp 252–253 °C; no depression with an authentic sample). The IR spectrum was also identical with that of an authentic sample.[6] Thus, of the 0.03 mol of 1 reacted in ethanol at reflux, 69% was recovered as 5, 26% as *o*-acetamidobenzoic acid (8), and 5% as anthranilic acid (7). The number of moles of ethyl acetate isolated in the distillate (0.013 mol) corresponds approximately to the sum of the number of moles of product 5 (0.010 mol) and 7 (0.001 mol).

(b) In the Presence of H_2SO_4 at Room Temperature To Give *o*-(*o*-Acetamidobenzamido)benzoic Acid (6, Expt 5). A solution of 1 (3.2 g, 0.02 mol) in ethanol (100 mL) containing 1 drop of concentrated H_2SO_4 was allowed to react at room temperature overnight, during which time a white crystalline product (2.3 g; mp 216–217 °C) separated from solution. The product was identified as *o*-(*o*-acetamidobenzamido)benzoic acid (6) by its melting point and IR spectrum which were identical with those of an authentic sample.[6] The mother liquor was then

separated into volatile and nonvolatile fractions as described above. Again, ethyl acetate was identified by gas chromatographic analysis as a minor component (0.0071 mol) of the distillate, but no diethyl ether was detected.

The nonvolatile residue (0.5 g) was recrystallized from hot water to give an additional 0.3 g of **6** (mp 216–217 °C). The mother liquor was evaporated to dryness, and the IR spectrum of the residue indicated that this was a mixture of **6** and *o*-acetamidobenzoic acid (**8**).

Registry No. **1**, 525-76-8; **2a**, 67-56-1; **2b**, 64-17-5; **2d**, 141-43-5; **3** (R = Me), 82666-35-1; **5**, 4005-06-5; **6**, 58426-37-2; **7**, 118-92-3; **8**, 89-52-1; **9**, 82666-36-2; 2-acetamidoethanol, 142-26-7; *N*-(2-hydroxyethyl)-2-methylquinazol-4-one, 10376-59-7; *o*-acetamido-*N*-(2-hydroxyethyl)benzamide, 63703-31-1; 2-[[(1,1-dimethoxy)ethyl]-amino]benzoic acid, 82666-37-3.

Radical Reorganization and Bond Energies in Organic Molecules

R. T. Sanderson†

Arizona State University, Tempe, Arizona 85281

Received August 11, 1981

The results of a study of contributing bond energies and bond dissociation energies of organic molecules are given. A set of theoretical and empirical contributing bond energies is presented that are accurately additive to give atomization energies and heats of formation of organic compounds of most common functional types. With the help of these values and literature values for radicals, the reorganizational energies of 27 common radicals have been determined and are reported herein. Breaking a bond requires both supplying the contributing bond energy and reorganizing the radicals formed. The bond dissociation energy is the sum of the contributing bond energy and the reorganizational energies of the radicals. These radical energies include the following hydrocarbon series (kcal/mol): benzyl, −13.9; allyl, −10.5; *tert*-butyl, −1.7; isopropyl, 0.7; *n*-propyl, 1.3; ethyl, 1.5; methyl, 3.6; vinyl, 10.0; and phenyl, 12.3. Also reported are the following (kcal/mol): phenoxy, −24.0; nitro, −10.5; acetyl, −7.1; benzoyl, −7.1; aldehyde, −5.8; methyl sulfone, −5.1; methoxy, −4.0; phenylthio, −3.9; ethoxy, −3.8; carboxylic acid, −3.5; acetate, −2.9; hydroxymethyl, −1.7; thiol, 2.9; methylthio, 5.1; hydroxyl, 9.7; methylamino, 12.1; amino, 19.5; cyano, 24.8.

The strength of a chemical bond, as evaluated by the bond dissociation energy (BDE), has two components. One is the contributing bond energy (CBE), which is that part of the total atomization energy of the molecule that a particular bond contributes. Contributing bond energies, impossible to evaluate experimentally except for diatomic molecules wherein they are identical with BDE, or as average bond energies in molecules where all bonds are alike, can be calculated accurately by the theory of polar covalence.[1] They are assumed to be accurate when the sum for all the bonds in the molecule equals the experimental atomization energy. The experimental atomization energy is the difference between the sum of the energies required to atomize each of the elements involved, and the standard heat of formation of the compound, in the gaseous state. The second component of the BDE is the reorganizational energies of the radicals formed by the breaking of the bond. If the radicals are single atoms, no further change occurs, the reorganizational energies being zero. If the radical consists of more than one atom, however, the liberated bonding electron will influence the remaining bonds in the radical. If possible, it will strengthen the bonding, releasing energy that reduces that needed for bond dissocn. If it cannot strengthen the bonding, it will weaken it, absorbing energy and thus increasing the energy required for dissociation. The purpose of this paper is to show how both components may be evaluated and, to a useful degree, understood.

Special emphasis is placed on the evaluation of the reorganizational energies of free radicals, for these can be more informative than either the standard heat of formation of the radical or the bond dissociation energy, from the viewpoint of understanding the origins of bond strength and the mechanisms of chemical reactions involving free radicals. Textbooks of organic chemistry commonly include a table of dissociation energies of specific bonds in familiar compounds, which could advanta-

Table I. Reorganizational Energies of Some Free Radicals

radical	H_f°	ref	E_R, kcal/mol
C_6H_5O	11.4	6	−24.0 (−24.0)
$C_6H_5CH_2$	45.1	6	−13.9 (−13.9)
$CH_2{=}CHCH_2$	41.4	6	−10.5 (−10.1)
NO_2	6.0	6	−10.5 (−10.5)
CH_3CO	−5.8	6	−7.1 (−7.1)
C_6H_5CO	26.1	6	−7.1 (−6.5)
CHO	7.7	6	−5.8 (−5.8)
CH_3SO_2	−57.2	6	−5.1 (−5.9)
CH_3O	3.8	6	−4.0 (−4.0)
C_6H_5S	56.8	6	−3.9 (−3.7)
C_2H_5O	−4.1	6	−3.8 (−3.7)
COOH	−53.3	6	−3.5 (−3.3)
CH_3COO	−49.6	6	−2.9 (−2.2)
t-C_4H_9	10.5	7, 8	−1.7 (−2.0)
CH_2OH	−6.2	6	−1.7 (−1.9)
i-C_3H_7	20.6	7	0.7 (0.7)
n-C_3H_7	22.6	6, 9	1.3 (1.2)
C_2H_5	28.2[a]	7[a]	1.5 (1.9)
SH	33.1	6	2.9 (3.3)
CH_3	35.1	10, 11	3.9 (3.6)
CH_3S	34.2	6	5.1 (5.8)
OH	9.2	6	9.7 (9.7)
$CH_2{=}CH$	68	6	10.0 (10.0)
CH_3NH	45.4	6	12.1 (11.7)
C_6H_5	77.7	6	12.3 (12.2)
NH_2	47.2	6	19.5 (18.0)
CN	101	6	24.8 (24.8)

[a] References 6 and 9 give 25.9 corresponding to E_R = −0.7.

† Address correspondence to 4725 Player Drive, Fort Collins, CO 80525.

(1) R. T. Sanderson, "Chemical Bonds and Bond Energy", 2nd ed., Academic Press, New York, 1976.

0022-3263/82/1947-3835$01.25/0