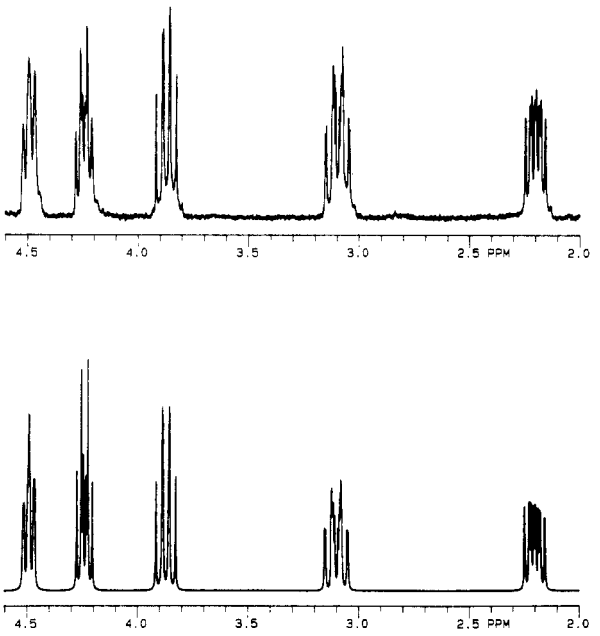

Figure 2. The 300-MHz NMR spectrum of (*Z*)-7-cyano-6b,7,8,8a-tetrahydrocyclobut[*a*]acenaphthylene ((*Z*)-**8**, top) and its simulated spectrum (bottom) from use of the data in Table I (supplementary material).

min of reflux, the warm mixture was gravity filtered, and the filtrate poured into 100 mL of ice water. The aqueous solution was extracted with 2 × 50 mL of CH_2Cl_2, and the combined organic phase was washed with 50 mL of saturated $NaHCO_3$ and 50 mL of water and then dried over $MgSO_4$. Treatment of the organic phase with charcoal followed by rotary evaporation produced a pale yellow oil that slowly solidified. NMR analysis of the mixture indicated that by comparison with authentic samples[3] 27% of **7** and 73% of **8** were present in the mixture.

Synthesis of (*Z*)-7-Carboxamido-6b,7,8,8a-tetrahydrocyclobut[*a*]acenaphthylene (10). A mixture of mercury(II) acetate (0.027 g, 0.085 mmol), 5.0 mL acetic acid, and **8** (0.035 g, 0.17 mmol) was refluxed for 25 h. The cooled reaction mixture was poured into ice water and extracted with 3 × 25 mL CH_2Cl_2, and the combined organic phases were washed with 3 × 25 mL of saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, and rotary evaporated to a crude solid, 0.027 g, 71%. Recrystallization of the solid from $CHCl_3$:heptane produced **10**: mp 222.5–223.5 °C; IR (KBr) 3380, 3190, 1648, 1620, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (d, 2 H), 7.50 (m, 2 H), 7.3 (dd, 2 H), 5.40 (br s, 2 H, NH_2), 4.43 (m, 1 H), 4.22 (m, 1 H), 3.05 (m, 1 H), 2.85 (m, 1 H), 2.3 (m, 1 H). Anal. Calcd: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.41; H, 5.90; N, 6.08. See Figures 1 and 2 for actual and simulated ^1H NMR spectra of (*E*)-**7** and (*Z*)-**8**.

Synthesis of (*E*)-7-Carboxamido-6b,7,8,8a-tetrahydrocyclobut[*a*]acenaphthylene (9). This compound was prepared from **7**[3,18] as described for **10** in 65% yield, mp 179–180 °C; IR (KBr) 3380, 3190, 1650, 1620, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (d, 1 H), 7.63 (d, 1 H), 7.48 (dd, 2 H), 7.37 (d, 1 H), 7.25 (d, 1 H), 5.17 (br s, 2 H, NH_2), 4.51 (m, 1 H), 4.18 (m, 1 H), 3.80 (q, 1 H), 2.85 (m, 1 H), 2.1 (m, 1 H). Anal. Calcd: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.60; H, 5.53; N, 6.16.

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Supplementary Material Available: ^1H NMR data for **1–10** (1 page). Ordering information is given on any current masthead page.

Kinetics of the Reaction between Carbon Dioxide and Tertiary Amines

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The reaction between carbon dioxide and amines is of great technical importance and has been the subject of many investigations.[1] We have shown that the reaction for secondary amines in anhydrous ethanol[2] and in aqueous solution[3] is exclusively second-order in amine and that the zwitterion intermediate postulated by Danckwerts[4] is probably of negligible significance in the mechanism. The reaction with tertiary amines has also been studied, but the data are less controversial. The product of the reaction is an alkylammonium hydrogen carbonate rather than the alkylammonium carbamate formed with a primary or secondary amine. Hydrogen carbonate ions are also formed by the direct reaction of carbon dioxide with water and with hydroxide ion, so that the following reactions occur in aqueous alkaline media. When an aqueous solution of carbon dioxide at its natural pH, around 4, is mixed with excess of an aqueous solution of a tertiary amine at its natural pH, around 9, hydrogen carbonate ions are formed at a rate given by:

$$CO_2 + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H^+ + HCO_3^-$$

$$CO_2 + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} HCO_3^-$$

$$R_3N + CO_2 + H_2O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} R_3NH^+ + HCO_3^-$$

$$d[HCO_3^-]/dt = k_1[H_2O][CO_2] + k_2[OH^-][CO_2] + k_3[R_3N][H_2O][CO_2] \quad (1)$$

Terms involving k_{-1}, k_{-2}, and k_{-3} are insignificant due to the magnitude of the various equilibrium and rate constants. Under these conditions, carbon dioxide is almost completely converted to hydrogen carbonate ion. Since $[R_3N] \gg [CO_2]$, we can rewrite eq 1 as:

$$d[HCO_3^-]/dt = k_o[CO_2] \quad (2)$$

where

$$k_o = k'_1 + k_2[OH^-] + k'_3[R_3N] \quad (3)$$

where the concentration of water has been included in the rate constants k'_1 and k'_3.

In order to complete our studies of the reactions of carbon dioxide with amines, using our conductimetric stopped-flow apparatus, we have studied this reaction for MDEA (methyldiethanolamine, IUPAC name *N*-methyl-2,2′-iminodiethanol) and TEA (triethanolamine, IUPAC name 2,2′,2″-nitrilotris(ethanol)). Our attempts to study this reaction with triethylamine and for quinuclidine failed. These amines are such strong bases (pK_a 10.75 and 10.95, respectively) that $[OH^-]$ is so large that $k_2[OH^-]$ dominates eq 2, and the contribution from the k_3 term is not seen.

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Table I. Kinetic Data[a] at 25 °C

pH	k_{AM}, dm^3 mol^{-1} s^{-1}	k_W, s^{-1}	k_W(calc), s^{-1}
	TEA		
8.00	1.58	0.04	0.034
9.00	1.58	0.17	0.109
9.30	1.66	0.25	0.192
	MDEA		
8.00	3.4	0.04	0.034
9.00	3.6	0.11	0.109
9.30	3.5	0.22	0.192

[a] Estimated error in k_{AM}, ±5%; in k_W, ±15%. k_W(calc) is calculated from k_W(calc) = $k'_1 + k_2$[OH$^-$], using k'_1 = 0.0258 s^{-1} and k_2 = 8320 dm^3 mol^{-1} s^{-1} (values from ref 5).

Table II. Activation Parameters[a]

	ΔH^*, kJ mol^{-1}	$-\Delta S^*$, J K^{-1} mol^{-1}
MDEA	9.6	200
TEA	11.6	200

[a] Data at pH 9.00. Errors in ΔH^* ±10%; in ΔS^*, ±15%.

Table III. Comparative Values of k'_3 (dm^3 mol^{-1} s^{-1}) at 25 °C

ref	method[a]	TEA	MDEA
6	1	17	-
7	2	50	-
8	3	2.7	-
5	4	2.85	-
1, 9	5	2.9	4.8
10	4	-	3.2
this work	6	1.6	3.5

[a] Methods: (1) CO_2 absorption in wetted-wall reactor. (2) Stopped-flow with thermal detection. (3) Facilitated transport of $^{14}CO_2$ in membrane. (4) Stopped-flow with optical detection. (5) CO_2 absorption in stirred cell. (6) Stopped flow with conductimetric detection.

Results and Discussion

All reactions were studied with large excess of amine (0.1–0.6 mol dm^{-3}) over CO_2 (0.01 mol dm^{-3}). The pH of each solution was adjusted to a preset value by addition of hydrochloric acid. Sets of runs were performed at pH 8.00, 9.00, and 9.30 to see if there was a kinetic term in [R_3N][OH$^-$]. No such term was discovered. The variation of observed first order rate constant, k_o, fitted the equation:

$$k_o = k_W + k_{AM}[R_3N] \quad (4)$$

where [R_3N] is the concentration of free, unprotonated amine. Comparison of eq 3 and 4 shows that k_W can be identified with ($k'_1 + k_2$[OH$^-$]) and k_{AM} with k'_3. Values of k'_1 and k_2 have been determined by previous workers.[5]

Some typical data at 25 °C are shown in Figure 1 and summarized in Table I. Runs for pH 9.00 were performed over a range of temperatures from 15 °C to 35 ° at 5 K intervals to enable the calculation of ΔH^* and ΔS^* for the reactions between amines and carbon dioxide. The results are given in Table II. Values of k'_3 obtained by previous workers are listed in Table III. Apart from obviously erroneous data,[6,7] perhaps due to the use of impure amines, agreement is fairly good. It is disappointing that our value for TEA differs from that obtained by three independent workers using three widely-different techniques.[1,5,8] In these other studies, k'_3 was evaluated by long calculations from the raw data, and it might be expected that our simple, direct method would give the best value. As can be seen from the figure, the discrepancy is outside the range of experimental error.

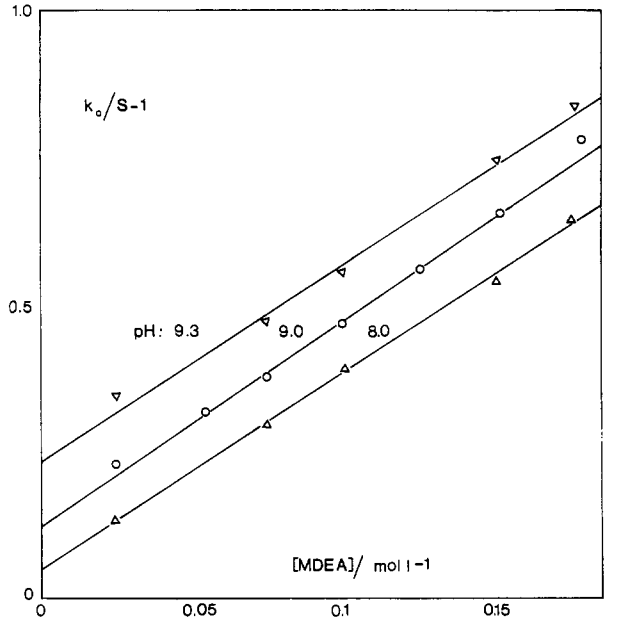
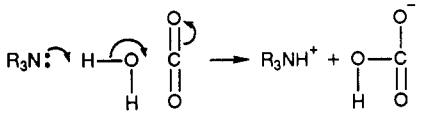


Figure 1. Observed first-order rate constants for MDEA at 25 °C. Runs at pH 9.3 (▽), runs at pH 9.0 (○), runs at pH 8.0 (△).

The order of the reaction and the large negative activation entropy strongly suggests that the mechanism is:



This is in accordance with the proposed mechanism for the reverse reaction, the acid-catalyzed cleavage of carbamate anions, which involves protonation in a fast preequilibrium followed by a rate-determining expulsion of amine.[11]

There remains the problem of why tertiary amines react differently to secondary and primary amines. Tertiary amines cannot form carbamates, but other amines could form alkylammonium hydrogen carbonates rather than carbamates. A good comparison can be made between MDEA and DEA (diethanolamine, IUPAC name 2,2′-iminodiethanol), which differ only in that MDEA has a methyl group on the nitrogen. These have similar pK_a values:[11] 8.52 for MDEA, 8.88 for DEA. The third-order rate constant for hydrogen carbonate formation is k'_3/[H_2O], i.e. k_{AM}/[H_2O], which has the value 0.029 dm^6 mol^{-2} s^{-1} for MDEA at 25 °C. This is much less than k_W, the third-order rate constant for carbamate formation, which is[3] 1.4 dm^6 mol^{-2} s^{-1} for DEA. The significant difference between the two reactions is seen to lie in the less negative entropy of activation for carbamate formation (ΔS^* = −66 J K^{-1} mol^{-1} for DEA[3]); the activation enthalpy being larger (ΔH^* = 53 kJ mol^{-1} for DEA[3]). The fraction of DEA in the equilibrium mixture which exists as carbamate rather than alkylammonium hydrogen carbonate is given by R, where

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$$R = [R_2NCO_2^-]/[R_2NH_2^+]$$

If we define

$$K_R = [R_2NCO_2^-][H^+]/[R_2NH][CO_2]$$

then $R = [H^+][HCO_3^-]K_R(DEA)/(K_a(CO_2)K_a(DEA))$. Taking the value of $K_a(CO_2)$ to be[13] 4.3×10^{-7} mol dm^{-3}, of K_a(DEA) to be[12] 3.0×10^{-9} mol dm^{-3}, and of K_R to be[14] 3.7×10^{-6}, and taking typical values of $[H^+]$ and $[HCO_3^-]$ to be 10^{-9} and 0.01 mol dm^{-3}, respectively, gives a value of R of 0.022. In our study[3] of DEA, most of the DEA would eventually form the alkylammonium hydrogen carbonate, even though the carbamate is the initial product. The further reaction from carbamate is very slow, as it proceeds via the free amine and carbon dioxide present at low concentrations in the reaction mixture.

Experimental Section

Materials. TEA and MEA were Analar grade, supplied by the Aldrich Chemical Co. Carbon dioxide was from cylinder (Distillers).

Kinetic Measurements. Aqueous solutions of amine and of carbon dioxide were mixed in a stopped-flow apparatus with conductimetric detection (Hi-Tech Scientific Ltd.) and product formation monitored as previously described.[2]

Registry No. MDEA, 105-59-9; TEA, 102-71-6; $MDEAH^+ \cdot HOCO_2^-$, 2604-14-0; $TEAH^+ \cdot HOCO_2^-$, 2471-07-0; CO_2, 124-38-9.

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General Procedure for the Synthesis of *o*-Aminophenylacetates by a Modification of the Gassman Reaction

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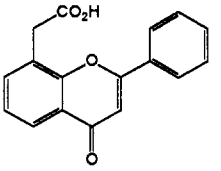
During the course of study directed toward the synthesis of a series of heteroaromatic analogues related to the novel NCI investigational antitumor agent FAA (**1**, flavone acetic acid),[1] we required *o*-aminophenylacetic acids of general formula **2**. These aniline derivatives seemed most easily obtained by using the synthesis of oxindoles as developed by Gassman[2] and adapted by Walsh.[3] This reaction is characterized by the ease of carrying out the procedures, the high yields considering that 5–6 steps are actually accomplished in a one-pot reaction, and the availability of starting materials.

The reaction as outlined in Scheme I for the synthesis of oxindoles can be used to prepare *o*-aminophenylacetic



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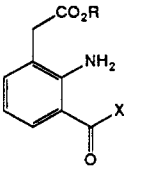

2a X=NH_2
2b X=OCH_2Ph

acid derivatives if the intramolecular addition of the amine to the carbonyl can be prohibited or at least discouraged from occurring. Gassman was able to isolate the relatively unstable amino ester **4a** in some cases,[2] but treatment with dilute acid, prolonged standing at room temperature, or heating gave the cyclized product, **5**. He was able to isolate the *o*-aminoacetic acid derivatives if the sulfide used in the reaction was (methylthio)acetamide (e.g., to give **4b**) or if the amine was acetylated by treating the reaction mixture with trimethylamine and acetyl chloride before purification or acid treatment. Walsh obtained *o*-aminophenylacetic acids by allowing the cyclization to the oxindole to take place and subsequently reopening the oxindole with boiling 3 N sodium hydroxide.[3] Ideally, we wanted to stop or at least hinder the cyclization to the oxindole **5**, thus avoiding the harsh conditions employed by Walsh to reopen the oxindole to the aniline acetic acid.

In our synthesis we were unable to use the acetamide sulfide or acetylation of the amine as a means of stopping the formation of the oxindole. In the case of the acetamide sulfide, conversion of the acetamide to an acid at some later stage of the synthesis was anticipated to be problematic because of the prolonged heating in acid or base that would be necessary to effect the hydrolysis. Similarly, trapping of the amine by acetylation would at some point require deprotection in the presence of the ester so that subsequent condensations on the amine could be carried out. Instead, we proposed to stop the intramolecular cyclization of the amine with the ester by changing the protecting group of the starting acetic acid sulfide to render the ester less susceptible to attack by the amine. The *tert*-butyl ester comes immediately to mind since it is easily removed under mild acidic conditions and bulky enough to provide steric hinderance to nucleophilic attack by the amine.

Compound **7**, the required *tert*-butyl ester of (methylthio)acetic acid, was synthesized by reacting the lithium salt of *tert*-butyl alcohol[4] with (methylthio)acetyl chloride[5] (**6**) in 51% yield. An alternative route[6] using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC) to couple (methylthio)acetic acid and *tert*-butyl alcohol at room temperature in methylene chloride gave only small amounts of the desired product.

The synthesis of the (*o*-aminophenyl)(methylthio)acetic acid esters **9** is illustrated in Scheme II. In a typical procedure, *tert*-butyl (methylthio)acetate (**7**) is treated with sulfuryl chloride[7] at −70 °C in methylene chloride followed by the addition of the appropriate aniline **8** and Proton Sponge (Aldrich) (as an HCl trap) to give the azasulfonium salt.[2b,7] This was treated directly with triethylamine and allowed to warm to room temperature to produce the desired Sommelett–Hauser rearrangement product in overall 85–90% yields. The *tert*-butyl esters **9** are quite stable to dilute acid and silica gel chromatog-

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