Structural Factors Influencing Rotational Isomerism and Alkylation Properties in Some α-Haloacetanilides[1a]

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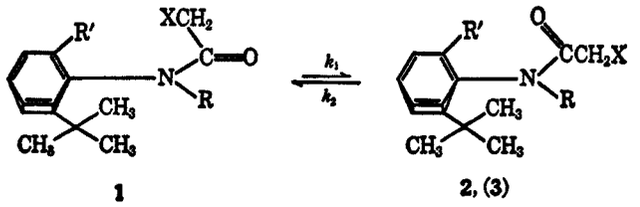
Received September 27, 1968

Widely divergent rotational and alkylation properties recently reported for *ortho*-substituted α-halo-N-methylacetanilides and their N-hydrogen homologs prompted further investigation of higher N-substituted 2-halo-6′-*t*-butyl-*o*-acetotoluidides. The relationship between alkylation and rotational isomerism has been verified; alkylation conditions are defined that coincide with conversion of the major isomer **1** to the reactive minor isomer **2**. From direct nmr measurements and the more precise and convenient alkylation technique developed, kinetic and thermodynamic values for isomer interconversion were determined for a series of homologous N-alkyl and other N-substituted anilides. Results and rationales for the measured equilibrium constants, rates, and thermodynamics found for the different series are discussed, and compared to current knowledge on the subject.

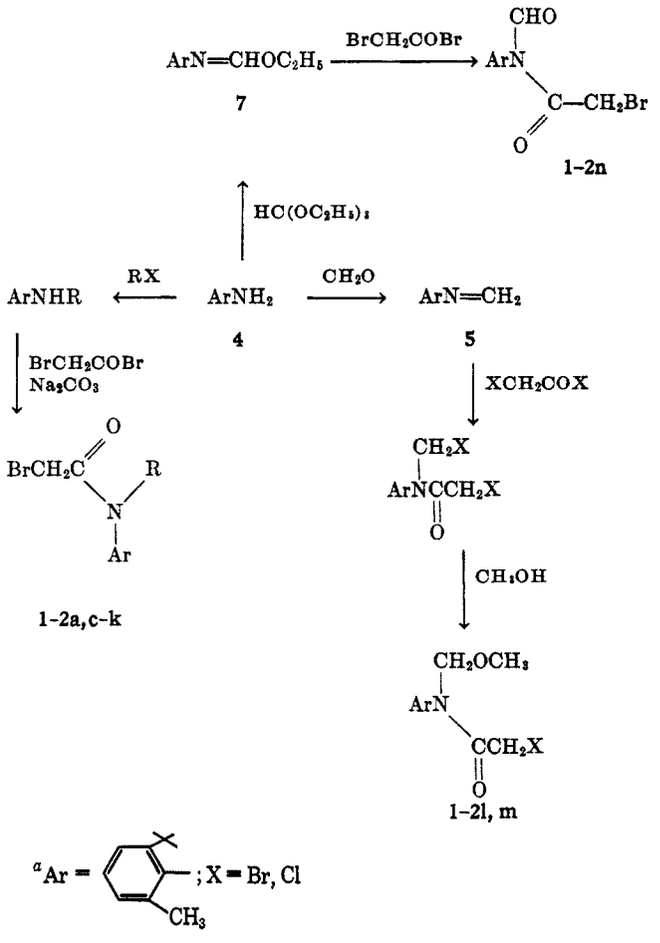
A recent study[1b] of α-halo-N-methyl-2′-*t*-butyl-6′-alkylacetanilides derived from 2-*t*-butyl-6-methyl- or -6-ethylaniline revealed that they exist in two separable rotomeric forms, **1** and **2**, with major isomer **1** having the halomethylene group *cis* and orthogonal to the anilide ring. In this spatial arrangement the halogen was shown to be unreactive toward usual nucleophilic displacement. Alkylation by anilide **1** proceeded by prior isomerization to **2**, the latter possessing a much more labile halogen. It was further found that the corresponding secondary anilides displayed quite different properties from the N-methyl compounds, the former apparently exhibiting no isomerism and having a spatial arrangement and alkylating ability akin to **2**.

In view of the significant contrast found between N-methyl and N-hydrogen α-haloacetanilides, it became of interest to study the interconversion properties of other N-substituted α-haloacetanilides within the same *ortho*-substituted series so that structural factors influencing the kind and degree of rotational isomerism could be more fully delineated. This is all the more important when it is appreciated that rotational isomerism in these biologically active materials can greatly influence alkylation rates; indeed, under favorable circumstances, the latter can be made to coincide with isomer equilibration kinetics. As pointed out earlier[1b] from studies of N-methylanilides, a fair approximation of k_1 (defined in Table I) may be measured where first-order kinetics control alkylation in suitably hindered tertiary anilides. From k_1 and the equilibrium constant K, interconversion kinetics could thereby be obtained solely from **1** or even an equilibrium mixture containing predominately this isomer. It was therefore of added interest to confirm and utilize this rule in the study of higher N-substituted α-haloacetanilides.



1 **2, (3)** (A)

SCHEME I[a]



Results

Synthesis and Spectral Characteristics.—Synthesis of the requisite anilides (Scheme I and Table I) features 6-*t*-butyl-*o*-toluidine (**4**) as the starting amine. Materials **1-2a,b,d-k** were prepared by alkylating **4** with the corresponding alkyl halide, followed by reaction of the secondary amine with bromoacetyl bromide. Of interest is the synthesis of **1-2l,m** from azomethine **5**. The latter material is monomeric and appears to possess a stable shelf life; refractive index and spectra of the purified monomer remain unchanged over a prolonged period, thus surpassing the stability of the azomethine from *t*-butylamine, which slowly poly-

(1) (a) Presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Abstract ORGN-144. (b) J. P. Chupp and J. F. Olin, *J. Org. Chem.*, **32**, 2297 (1967).

TABLE I
α-HALOACETANILIDES[a]

Material	R'	X	R	Mp, °C	Nmr (CCl4), ppm XCH2	Nmr (CCl4), ppm ArCH3	Formula	Calcd, % N	Calcd, % X	Found, % N	Found, % X
1a	CH3	Br	CH3	59–61	3.54	2.28	$C_{14}H_{20}BrNO$	4.70	26.80	4.79	27.07
2a	CH3	Br	CH3	90.5–91.5	3.85	2.13	$C_{14}H_{20}BrNO$	4.70	26.80	4.63	26.71
1b	CH3	Br	(CH3)2CH	85–86	3.50	2.35	$C_{16}H_{24}BrNO$	4.29	24.49	4.22	24.74
1c	H	Br	(CH3)3C	97–98			$C_{16}H_{24}BrNO$	4.29	24.49	4.35	24.35
1d	CH3	Br	C2H5	58–60	3.58	2.30	$C_{15}H_{22}BrNO$	4.49	25.59	4.56	26.13
1e	CH3	Br	n-C3H7	70–71	3.54	2.29	$C_{16}H_{24}BrNO$	4.29	24.49	4.40	24.59
1f	CH3	Br	n-C4H9	76–78.5	3.52	2.28	$C_{17}H_{26}BrNO$	4.12	23.48	4.12	23.18
1g	CH3	Br	CH2=CHCH2	92–93	3.52	2.23	$C_{16}H_{22}BrNO$	4.32	24.65	4.42	25.14
1h	CH3	Br	HC≡CCH2	75–78	3.52	2.30	$C_{16}H_{20}BrNO$	4.35	24.80	4.24	24.05
1i	CH3	Br	NCCH2	116–118	3.61	2.36	$C_{15}H_{19}BrN_2O$	8.67	24.72	8.43	25.06
1j	CH3	Br	CH3O(CH2)2	74–75	3.51	2.28	$C_{17}H_{26}BrNO_2$	3.93	22.43	3.98	22.43
1k	CH3	Br	CH3O(CH2)2	69–70	3.58	2.29	$C_{16}H_{24}BrNO_2$	4.09	23.35	4.23	23.48
1l	CH3	Br	CH3OCH2	51.5–52	3.58	2.32	$C_{15}H_{22}BrNO_2$	4.27	24.35	4.32	24.02
2l	CH3	Br	CH3OCH2		4.04	2.19					
1m	CH3	Cl	CH3OCH2		3.64	2.28					
2m	CH3	Cl	CH3OCH2	78–79	4.18	2.16	$C_{15}H_{22}ClNO_2$	4.94	12.49	5.00	12.43
3	CH3	Br	H	120.5–121.5	4.07[b]	2.21[b]	$C_{13}H_{18}BrNO$	4.93	28.12	4.82	28.04
1–2n	CH3	Br	CHO	116–117	3.90[b]	2.12[b]	$C_{14}H_{18}BrNO_2$	4.49	25.60	4.26	25.69

[a] See eq A in text for position of R, R', and X. [b] Nmr measured in $CDCl_3$.

merized on standing.[2] **1–2n** was prepared by reaction of imidate **7** with bromoacetyl bromide. Unhindered N-formylated acetanilides made in this fashion are notoriously unstable, giving secondary anilides upon thermal treatment.[3] **1–2n** will convert into **3** only upon prolonged heating.

With some exceptions it is not immediately obvious that the tertiary anilides listed in Table I are capable of existing in both rotational forms **1** and **2**. When purified by simple recrystallization, the materials give pure isomer **1**. Thus the nmr spectra for materials **1b–l** display the XCH_2 group as a singlet at *ca.* 3.5 ppm, upfield from the usual position for this group in **2** or **3**. Similarly the aryl methyl in **1** shows the characteristic singlet at *ca.* 2.23–2.36 ppm, while spectra of authentic samples of **3**, **2a**, and **2m** in chlorinated or aqueous acetone solvents display this group at slightly higher field. Further structure proof for isomer **1** rests on the observed alkylation properties discussed below.

With the exception of **1–2a,k,l,m**, casual examination of the nmr spectra from aged solutions of **1** fails to reveal immediately the presence of **2**. This is due to the complex spectra displayed by anilides containing an N substituent higher than methyl. Thus **1d–m** possess an $N\text{-}CH_2$ group with the methylene hydrogens nonequivalent to each other, displaying an AB-type resonance. This arises from assymmetry in these anilides caused by restricted rotation about the Ar–N bond, and is identical with well-known methylene proton nonequivalence first observed in assymmetric ethers,[4] and later in anilides.[5,6] Moreover, most of the methylene protons are further spin coupled with protons on neighboring carbon atoms, making the absorption complex in the 3–5-ppm region. Thus, if the equilibrium amount of **2** is small, the N substituent and halomethylene group of this isomer can be quite obscured. A further complication is the capability of the XCH_2 from **2** to exist also in certain solvents as an AB pair.

To determine whether in fact **2** existed in equilibrium with **1**, it was necessary to examine the resonance of the aryl methyl and aryl *t*-butyl. The latter proved to be more insensitive, usually displaying a single singlet even for equilibrium amounts of **1–2a** in chlorinated solvents. More reliable is the aryl methyl resonance at 2–3 ppm. By examination with 100-cps scans, the emergence with time of a singlet for the aryl methyl group from **2** was readily apparent.

Of interest is **1–2n.** Temperature studies reveal $BrCH_2$ and CHO to have single, broadened resonances at room temperature, becoming sharp and narrow at higher temperature (60°). At −40° two distinct nonequivalent resonances emerge for both groups at *ca.* 3.8, 4.2 and 9.7, 9.5 ppm, respectively. It is apparent then that **1–2n** represents a rapidly interconverting system at room temperature.

Some attempts were made actually to isolate pure **2**, to further characterize this isomer. However, only **2a** and **2m** were isolated in pure crystalline form. Although it is tempting to blame unfavorable stabilities

(2) Brochure on *t*-Alkyl Primary Amines (Rohm and Haas), CP-558/61, p 35.
(3) H. L. Wheeler and P. T. Walden, *Amer. Chem. J.*, **19**, 129 (1897).
(4) F. Kaplan and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 4666 (1961).
(5) B. J. Price, J. A. Eggleston, and I. O. Sutherland, *J. Chem. Soc.*, *B* 922 (1967).
(6) T. H. Siddall, III, *J. Org. Chem.*, **28**, 1296 (1963).

TABLE II

EQUILIBRIUM AND EQUILIBRATION RATE CONSTANTS AS DETERMINED BY NMR IN AQUEOUS ACETONE

Material	K	$k_1 \times 10^7$, sec^{-1}	$k_2 \times 10^7$, sec^{-1}	Correlation coeff r[a]
2a	0.16	4.5	28	0.9978
1d	0.12	18	150	0.9490
1e	0.12	19	160	0.9861
1f	0.12	49	400	0.9853
1g	0.10	60	590	0.9326
1h	0.09	82	890	0.9770
1j	0.10	46	480	0.9950
1k	0.21	190	910	0.9957
1l	0.35	680	1900	0.9912
2m	0.31	750	2400	0.9980

[a] As determined from average seven points; see Experimental Section.

and/or equilibrium constants for failure, it is possible that success in separating isomers is largely determined by a fortuitous combination of favorable melting point and solubility. Thus equilibrium constant and isomer stability are approximately the same for **1-2l,m**; yet it was not possible to isolate **2l** in the purification of **11**, although attempts were made to do so. On the other hand, the oily equilibrium mixture of **1-2m** deposits an enriched mixture of **2m** from which by simple recrystallization this isomer is obtained pure, while **1m** (never obtained pure) probably is an oil or low-melting solid. Hence large amounts of the otherwise minor isomer **2m** can easily be obtained by utilizing the shift in equilibrium as this isomer crystallizes from an oily mixture originally rich in **1m**.

Rate Determinations.—In order to validate the alkylation method as feasible for measuring equilibration kinetics, it was first necessary to obtain direct nmr rate data, however approximate, for comparison. Equilibration kinetics were followed by measuring the increasing intensity ratio (**2**:**1**) of the aryl methyl resonance as a function of time. Equilibrium constant K was then the value of this ratio after at least ten half-lives. From these data k_1 and k_2 could be calculated as before.[1b] It is apparent from linear correlation constants, r given in Table II, that straight-line plots necessary to determine kinetics are less reliable as the amount of **2** in equilibrium with **1** decreases. As noted earlier,[1b] the best determinations by nmr are from measurements initiated with **2**.

In order to take advantage of alkylation rates as an aid in determining equilibration characteristics it is necessary that the system follow fairly "pure" kinetics. Without recourse to steady-state approximations and other manipulations, eq 1, 2, and 3 serve to illustrate the relationships between the observed pseudo-first-order rate constant, $k_{\psi obsd}$, obtained by measuring bromide ion formation, and the previously defined equilibration rate constants, k_1 and k_2.

nucleophile dependent alkylation for **2** (or **3**)

$$\text{alkylation rate} = k_{\psi obsd}([2^0] - [Br^-]) \cong k_{\psi obsd}[2] = k_\psi[2] \quad (1)$$

($[2^0]$ = initial concentration of **2**; k_ψ[7a] $\gg k_1$ and k_2)

nucleophile independent alkylation for **1**

$$\text{alkylation rate} = k_{\psi obsd}([1^0] - [Br^-]) \cong k_{\psi obsd}[1] \cong k_1[1] \quad (2)$$

($[1^0]$ = initial concentration of **1**; $k_\psi \gg k_1$ and k_2)

nucleophile dependent alkylation for **1**[8]

$$\text{alkylation rate} = k_{\psi obsd}([1^0] - [Br^-]) \cong k_\psi[2eq] < k_1[1] \quad (3a)$$

$$K = [2eq]/[1eq]$$

$$k_\psi[2eq] = k_{\psi obsd}([1eq] + [2eq]) \quad (3b)$$

$$K = k_{\psi obsd}/(k_\psi - k_{\psi obsd})$$

([1eq] and [2eq] are equilibrium concentration)

Equation 1 represents alkylation kinetics initiated with reactive isomer **2**. For the pseudo-first-order rate constant k_ψ[7a] to be equivalent to $k_{\psi obsd}$ it is necessary that **2** react more quickly with piperidine than its transformation to **1**, (*i.e.*, $k_\psi \gg k_1$ or k_2). That **2** (or **3**) does in fact react very fast with excess piperidine *via* a classical SN2 process has been verified previously[1b] and is also shown in several examples contained in Table III (**3**, **2a**, **2l**, **1-2n**). The fast interconversion between **1n** and **2n** observed at room temperature by nmr serves to explain the fast second-order kinetics although undoubtedly additional electronic factors[7b] operate to make this anilide the most potent alkylator listed in Table III.

For the alkylation rate initiated with **1** to be truly nucleophile independent and equal to its equilibration rate as given in eq 2 ($k_{\psi obsd} = k_1$), it is necessary for **2** to react with piperidine nearly as fast as it is formed (in the slow step) from **1**. Then the rate of bromide ion formation will be equivalent to disappearance of **1**. If **2** does not react in this fashion, either because k_ψ or [**2**] is too small, the alkylation of piperidine starts to

TABLE III

OBSERVED PSEUDO-FIRST-ORDER RATE CONSTANTS FROM ALKYLATION IN THE PRESENCE OF EXCESS PIPERIDINE

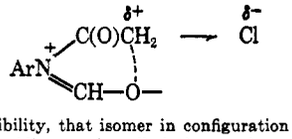
Material	$k^1\psi_{obsd} \times 10^7$ sec^{-1} (amine/amide 50:1)	$k^2\psi_{obsd} \times 10^7$ sec^{-1} (amine/amide 20:1)	Approx % SN2[a]
1a	7.6	6.4	10
1b	13	5.0	100
1c	18	6.5	80
1d	29	26	10
1e	29	26	10
1f	31	28	10
1g	50	43	10
1h	73	64	10
1i	130	63	70
1j	28	25	10
1k	140	120	10
1l	470	420	10
3	16,500	6,300	100
2l	18,400	9,200	70
2a	32,200	12,100	100
1-2n	36,000	14,000	100

[a] See Experimental Section for calculation.

(7) (a) The constant k_ψ is defined as follows.

$$\mathbf{2} + \text{excess piperidine} \xrightarrow{k_\psi} \text{alkylation product}$$

(b) Anchimeric assistance by the formyl oxygen in promoting lability of the halogen is a possibility.



(8) The other possibility, that isomer in configuration **1** reacts directly *via* SN2 kinetics with piperidine to give alkylation product, is minimized by the fact that **1a**, the least hindered and most stable tertiary anilide under study, gives little or no evidence of such reaction. The other bulkier and shorter lived tertiary anilides in this configuration would be expected to be even less susceptible to this form of alkylation.

TABLE IV
ACTIVATION PARAMETERS FOR CONVERSION 1 → 2 FROM TEMPERATURE-DEPENDENT STUDY OF $k^2_{\psi obsd}$

Material	E_a, kcal	Log A, sec^{-1}	$\Delta S^{\ddagger}$ (25°), eu	Correlation coeff r^a
1a	25.1	12.2	−4.5	0.9996
1d	23.7	11.8	−6.5	0.9998
1e	23.1	11.3	−8.5	0.9995
1f	23.1	11.4	−8.5	0.9990
1g	21.9	10.7	−11.5	0.9984
1k	21.4	10.8	−11.0	0.9991
1l	21.5	11.4	−8.5	0.9988

[a] As determined from four points on plots of log $k^2_{\psi obsd}$ *vs.* $1/T$ between 25 and 40° (±0.02°).

become the slow rate-determining step, and the reaction becomes nucleophile dependent.

It is for this reason that k_ψ has been kept as large as possible by choosing for alkylation studies high concentrations of reactive piperidine with the α-bromo- rather than α-chloroacetanilides. Nevertheless if the equilibrium concentration of **2** as derived from **1** is small enough, the low effective concentration of **2** will slow its reaction with piperidine sufficiently to allow the equilibration to exceed the alkylation rate. Equation 3 is useful to explain apparent anomalies (**1b,c,i**) in Table III. With fast equilibration, compared with alkylation, the observed rates approach dependence on the equilibrium concentrations, [1eq] and [2eq]. Equation 3 gives the relationship between $k_{\psi obsd}$, k_ψ, and K. Thus if k^1_ψ for **2b** is assumed to have an appreciable value, approaching that for **2a** (*i.e.*, *ca.* 10^{-3} sec^{-1}) and inserting the value for $k^1_{\psi obsd}$ from **1b** of 1.3×10^{-6} sec^{-1}, K is calculated at 1.3×10^{-3}. This small value of K gives an equilibrium concentration of only *ca.* 0.1% **2b**, and explains the failure to observe this isomer by nmr. Similarly, **1c** and **1i** give "mixed" kinetics between eq 1 and eq 3 because of a low equilibrium constant. Spectrally, an aged solution of **1c** shows no **2c**, while **1i** gives only 2% **2i**.

Since **2l** could not be isolated in pure form, the alkylation kinetics for it are derived from data plotted in Figure 1; the plot further serves to confirm the

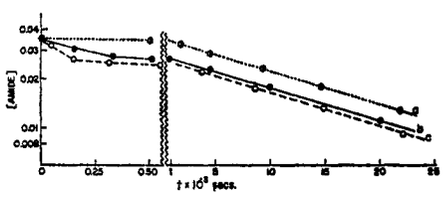


Figure 1.—Log [amide] *vs.* *t*, with initial concentration of amide at 0.0358 *M*. Dotted lines (a) represent plot from piperidine/**1l** of 50:1 without prior equilibration. Solid lines (b) and dashed lines (c) represent, respectively, initial piperidine/**1-2l** at 20:1 and 50:1, both with prior equilibration. The two time scales used as the abcissa are designed to show the early differences and later equality in slopes between a, b, and c. Estimated $k_{\psi obsd}$ in Table III for **2l** are from the slopes of b and c given by the first three points.

dependence of alkylation on rotational isomerism. Thus alkylation by **1l** without prior equilibration gives the usual slow amine independent reaction reflecting the rate-determining conversion of **1l** to isomer **2l**. Prior equilibration to give an approximately 25–30% equilibrion concentration of reactive isomer **2l** causes the subsequent alkylation reaction to be initially fast and piperidine dependent, followed by slow amine independent kinetics equal to that shown by pure **1l**. The small divergence of the kinetics from SN2 for **2l** is due not only to error in obtaining true values of $k^1_{\psi obsd}$ and $k^2_{\psi obsd}$ from the slopes of the lines b and c in Figure 1, but also comes from the significant contribution of k_2 [**2l**] in this rather rapidly equilibrating system, such that eq 1 does not strictly apply.

The relationship between equilibration and alkylation discussed earlier is confirmed. Thus k_1, extending in value over two orders of magnitude, when approximately measured from direct equilibration experiments by nmr (Table II) is in substantial agreement with values of $k_{\psi obsd}$ calculated from alkylations *governed primarily by first-order kinetics* (Table III).[9] Advantage was taken of this more convenient and precise alkylation method for measuring equilibration to calculate the thermodynamics for conversion of **1** → **2** by temperature-dependent studies of $k^2_{\psi obsd}$ (Table IV).

Discussion

Previous studies[10] regarding tertiary amides indicate that the more abundant rotational isomer be sterically favored, minimizing nonbonded interactions by having the larger groups attached *trans* to each other. If the same steric explanation applied to the tertiary anilides in Table I, then apparently the halomethylene and N-alkyl substituent, structured *trans* in the predominate isomer **1**, are the two larger groups. The trigonal nature of the aromatic carbon, coupled with orthogonal positioning to the amide moiety of the otherwise bulky aryl group, presumably minimizes this group's steric requirements in the ground state. The steric explanation is at least consistent with the observation that secondary acetanilides also have the two smallest groups *trans* (O and H)[1,11] while, with higher N-alkyl substitution than N-methyl, the amount of the more abundant isomer increases, becoming nearly 100% with N-isopropyl and *t*-butyl. It is obvious however that the steric explanation is only partially successful in predicting isomer distribution. The amount of **2** found in rotomeric systems possessing N-methoxyalkyl substituents increases with increasing proximity of the ether to the carbonyl oxygen (compare K in **1-2j,k,l**). This indicates perhaps an unfavorable dipole–dipole interaction operable between the *cis*-oriented oxygen atoms. On the other hand the electronic rationale for the small amount of **2i** observed in not clearly understood.

Rotational isomerism as observed in amides has traditionally been explained as arising from the interaction of the unshared pair of electrons on nitrogen with the carbonyl oxygen, giving rise to a rigid polar resonance form, –OC=N$^+$—consequently the greater the resonance interaction, the more the energy barrier to isomerization. The resonance contribution is also important in anilides studied here, even though bulky

(9) The discrepancies noted between k_1 and $k_{\psi obsd}$ are not only due to experimental error, but to the necessarily somewhat different concentrations and solvent systems employed in the two different types of measurement.

(10) L. A. LaPlanche and M. J. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).

(11) H. Kessler and A. Rieker, *Z. Naturforsch*, **22b**, 446 (1967).

ortho substituents reinforce the energy barrier to rotation. Thus electron-withdrawing groups attached to nitrogen cause an increase in interconversion rate. The formyl group as expected is quite effective in this regard, while the methoxy group exerts its inductance most effectively in anilide **1-2l**, with a fall-off with increasing chain length (**1-2j,k**). Similarly, mild deactivators such as allyl and propargyl increase the interconversion rate moderately. Measurement of the destabilizing effect of an electron-withdrawing N substituent has been observed before, although not necessarily with such consistancy, especially with moieties several carbons distant. Thus lowered energy barriers were observed for some N-vinylformamides, but not for similarly substituted N-(2-chloroethyl)formamides.[12]

It becomes incumbent to reconcile the mild interconversion rate enhancement with ascending N-*n*-alkyl substitution (steric acceleration of rotational rates). In most systems the inductive electron-donating ability of ethyl and *n*-propyl groups is higher than methyl;[13] indeed studies of ^{14}N chemical shifts in simple ureas and amides have recently shown increasing electron delocalization of the nitrogen lone pair (*via* the stabilizing dipolar form) with increasing size of the N-alkyl substituent.[14] It might be expected then that ascending N-*n*-alkyl substitution would cause *decreases* in interconversion rates. The apparent anomaly observed here may be overcome by assuming an increasingly unfavorable steric interaction between the carbonyl oxygen and higher N-alkyl groups in the planar polar form, $^{-}OC{=}N^{+}$, accompanied perhaps by less solvation in the more bulky amides. These effects would tend to increase the relative energy in the ground state thus leading to lower energies of activation.

High collision frequencies (A) and small positive activation entropies are usually observed from accurately determined energy barriers in unhindered amides.[15] This is due to the change from a rigid, stabilizing dipolar amide form (solvated) in the ground state, to a less rigid, less polar form in the activated complex. However, it is not inconsistent to expect, as observed here, small negative activation entropies for conversion $1 \rightarrow 2$, increasing somewhat with higher N substitution. An appreciable portion of the energy barrier to rotation in the amides studied here is due to steric hindrance, and thus strains, with resultant loss of rotational freedom encountered in the transition state, are not surprising. Similar observations have been made in rotational studies of other sterically hindered systems including anilines.[16]

Experimental Section

N-2-Di-*t*-butylaniline.—To 8 mol of *o*-*t*-butylaniline was added 950 g (17 mol) of isobutene with 240 g of acid-treated clay. The mixture was heated in a 3-l. rocking autoclave for 212 hr at 100–120°. After filtration of the autoclave contents the material was distilled, and that collected at 117–137° (13 mm) was refractionated through a 4 ft × 16 mm packed column to give the pure aniline: bp 129–130° (14 mm); $n^{25}D$ 1.5145.

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.78; H, 11.29; N, 6.92.

6-*t*-Butyl-*o*-tolylglycinonitrile.—The procedure is similar to that used by Elliott.[17] To 200 ml of 50% (v/v) alcohol was added 163 g (1 mol) of 6-*t*-butyl-*o*-toluidine[1] (**4**) and the resulting mixture heated to reflux with stirring. Glycolonitrile (1 mol, 81 g of 70% solution in water) was added over 45 min with the mixture stirred at 90° for an additional 18 hr. Upon solvent removal under vacuum, the viscous oily residue was recrystallized from cold toluene to give, after a further wash with water and heptane, crystals, mp 84–86°.

Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97. Found: C, 77.17; H, 8.98.

6-*t*-Butyl-N-(3-methoxypropyl)-*o*-toluidine.—A mixture of 188 g of 3-chloropropyl methyl ether (3.2 mol), 522 g of **4** (3.2 mol), and 265 g of potassium iodide (1.6 mol) in 1 l. of methanol was heated with stirring in an autoclave at 110° for 16 hr. After cooling, the suspended salt was filtered, and the filtrate heated with 1 l. of 10% caustic. After drying, the organic portion was fractionated, bp 152–158° (8 mm), to give 153.5 g of product, $n^{25}D$ 1.5130.

Anal. Calcd for $C_{15}H_{25}NO$: N, 5.95. Found: N, 6.38.

6-*t*-Butyl-N-ethyl-*o*-toluidine.—To **4** (163 g, 1 mol) was added 200 g of acetonitrile and 175 g (1.12 mol) of ethyl iodide and the resulting mixture refluxed for 48 hr. The reaction mass was cooled, 100 ml of water added, and the excess ethyl iodide and solvent were removed under vacuum. After the residue was treated with 20% NaOH, the oily layer was separated, washed with water, then 170 g collected by fractional distillation, bp 110–119° (9.5 mm). This material was redistilled to give 143 g of product: bp 115–117° (9.5 mm); $n^{25}D$ 1.5186.

Anal. Calcd for $C_{13}H_{21}N$: N, 7.32. Found: N, 7.32.

6-*t*-Butyl-N-methylene-*o*-toluidine (5).—A mixture of 1 kg of **4** (6.12 mol), 240 g of paraformaldehyde, 10 g of 25% trimethylamine in methanol, and 500 ml of *n*-heptane was heated to reflux at 95°. By separation of the azeotrope, water was collected, and then the solvent removed by distillation to a pot temperature of 140°. After cooling, the reaction mass was filtered and the filtrate fractionated through a 16-in. packed column. Azomethine (1047 g, 97.5% yield) was collected: bp 114–116° (14 mm); $n^{25}D$ 1.5284. The refractive index remained unchanged on storage under nitrogen for over 6 months.

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.79; N, 7.99. Found: C, 81.86; H, 9.85; N, 7.77.

6-*t*-Butyl-N-methyl-*o*-toluidine has been reported previously, prepared by methylation of **4**.[1b] An alternative procedure which gives a nearly quantitative yield of pure product involves the lithium aluminum hydride reduction of **5**. A 1-l. ethereal solution containing 430 g of **5** (2.46 mol) was added dropwise to 72 g of $LiAlH_4$ slurried in ether. The temperature was kept at reflux by suitable adjustment of the addition rate. Wet ether was then introduced, and the hydrolyzed reaction mixture filtered. After drying the ethereal solution over magnesium sulfate, solvent was removed to give 415.2 g of essentially pure 6-*t*-butyl-N-methyl-*o*-toluidine.

Ethyl N-(6-*t*-Butyl-*o*-tolyl)formimidate (7).—Ethyl orthoformate (233 g, 1.57 mol) and 245 g of **4** (1.5 mol) were heated together in a flask provided with a short vigreux column and distillation head. At a pot temperature of 130°, alcohol began to distil slowly. The reaction mixture was heated over 20 hr at 145–180°, with heating terminated after a further 0.5 hr at 198°. A total of 124 g of ethanol was removed. The residue was distilled to give 287 g, bp 125–125.5 (6.5 mm), $n^{25}D$ 1.5116. On standing, **7** solidified, mp 34–35°.

Anal. Calcd for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.32.

Preparation of N-Isopropyl, -propyl, -butyl, -allyl, -propargyl-6-*t*-butyl-*o*-toluidines.—These materials were made, respectively, from reaction of an equimolar or excess amount of alkyl bromide or iodide with **4**. The reactions were all carried out at reflux in acetonitrile at ordinary pressure for 24–48 hr. The cooled mixture was then vacuum treated to remove solvent and the residue treated with 10% NaOH, then extracted with ether. After drying over magnesium sulfate and ether evaporation, the

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residues were distilled through a 4 ft × 16 mm packed glass helice column. A cut, rich in the desired secondary aniline, was taken between 50 and 80° (*ca.* 0.3 mm). Assay of the desired aniline by glpc and nmr revealed contamination by **4** and the N,N-disubstituted 6-*t*-butyl-*o*-toluidine. Rather than attempt further purification of the secondary aniline, the distillate was converted directly into the α-haloacetanilide.

Preparation of α-Haloacetanilides (1a–k, 3).—These materials were prepared in essentially the same manner using Schotten–Bauman conditions. The preparation of **1j** is typical. 6-*t*-Butyl-N-(3-methoxypropyl)-*o*-toluidine (50 g, 0.212 mol), 20 g of sodium carbonate, 250 ml of water and 200 ml of benzene were mixed together. With agitation and external cooling a 10–20% molar excess of bromoacetyl bromide was added dropwise at 5–10°. After addition the external ice bath was removed and the stirred mixture allowed to reach room temperature. The organic phase was separated, washed with water and dried over magnesium sulfate. After solvent removal the material was purified by recrystallization from heptane to give 50 g of **1j**. Other solvents found acceptable for anilide purification were aqueous methanol, methylcyclohexane, and hexane. Although no attempt was made to optimize conditions, yields of recrystallized product were usually 50–80%. Physical constants and analyses are provided in Table I.

2-Bromo-6′-*t*-butyl-N-methoxymethyl-*o*-acetotoluidide (1–2l).—Azomethine **5** (130 g, 0.74 mol) was dissolved in 300 ml of toluene. With agitation 160 g (0.79 mol) of bromoacetyl bromide was added over 45 min with stirring, the temperature of the reaction mixture reaching 85°. The resulting turbid solution was transferred to a separatory funnel and added over 1 hr to 240 g (1 mol) of 25% trimethylamine in methanol, maintaining the temperature between 10 and 15° with external cooling. After addition the reaction mixture was stirred an additional 0.5 hr, then washed twice with water. After filtration and evaporation of toluene the product (155 g) was induced to crystallize. A final purification was performed by recrystallization from heptane to give pure **11**.

6′-*t*-Butyl-2-chloro-N-methoxymethyl-*o*-acetotoluidide (1–2m).—To chloroacetyl chloride (113 g, 1 mol) mixed with 250 ml of heptane was added 175 g (1 mol) of **5** over 20 min. During addition the temperature of the mixture reached 80°. The turbid solution was refluxed for 10 min whereupon it became clear. The mixture was cooled to 5° and a total of 221 g of solid was collected, most of it melting between 86 and 89°. A portion (20 g, 0.07 mol) of the crude 6′-*t*-butyl-2-chloro-N-chloromethyl-*o*-acetotoluidide was mixed with 100 ml of a 25% solution of trimethylamine in methanol. The methanol and excess trimethylamine were then evaporated, water added to the residue and the resulting oily layer extracted with hexane. When cooled the hexane solution deposited solid containing both **1** and **2m**. A further recrystallization from cold hexane gave pure **2m**. The oil (upon melting **2m**, *ca.* 70% **1m** formed), only slowly, over a period of days, deposited crystals rich in **2m**.

2-Bromo-6′-*t*-butyl-N-formyl-*o*-acetotoluidide (1–2n).—Bromoacetyl bromide (110 g, 0.55 mol) was mixed with 175 ml of heptane and to this solution was added dropwise 109.2 g of **7** (0.5 mol). The mixture was allowed to warm to 80–85°, with apparent reflux of ethyl bromide. After 0.5 hr at this temperature the reaction mixture was cooled to −15°, whereupon crystals formed. The solid was collected, washed twice with 100 ml of cold hexane to give 150.5 g of product. Small amounts of contaminating **3** could be removed by elution with chloroform through silicic acid to give **1–2n**.

Determination of Interconversion Rate (1 and 2).—The interconversion rate between **1–2a** and **1–2n** was determined by measuring the relative areas corresponding to the nuclear magnetic resonances of both XCH_2 and NCH_3, starting with pure isomer **2**. This method has been described previously.[1b] The other interconversion rates listed in Table II were determined by measuring the relative areas of the $ArCH_3$ group corresponding to **1** and **2**. At time zero, 0.13 g of pure crystalline **1** was dissolved in 1.0 g of a solution containing 85% acetone-d_6, 15% D_2O. The solution was then placed in a sealed nmr tube at 25 ± 1° and at intervals, momentarily inserted in the nmr probe. The Varian A-60 was adjusted to a 100-Hz scan. The Ar–CH_3 resonance from **1** was always downfield from that for **2**, as well as being downfield from the multiplet for acetone-d_5.[18] In certain instances the resonances furthest downfield in this nearly symmetrical five-peak multiplet coincided with the absorption singlet for $ArCH_3$ from **2**. In this event, to determine the relative amounts of **1** and **2** for time t, the area corresponding to $ArCH_3$ from **2** was calculated by subtracting from the total area of this singlet at time t a constant amount, equivalent to the area of the resonance peak for acetone-d_5 at highest field. Equilibrium constants K were determined after permitting the solution to stand for at least ten times the observed half-life of the reaction. From the above data, rate constants k_1 and k_2 could be calculated as before.[1] The data in Table II are derived from linear plots averaging seven points per line, with the correlation coefficients r calculated therefrom.

Determination of Nucleophilic Substitution Rate (1, 2, and 3).—The determination of observed pseudo-first-order rate constants, $k_{\psi obsd}$, by plotting log (initial[amide] − [Br^-]) *vs.* t, derived from potentiometric titrations for halide ion has been described before.[1] The rate constants $k^1_{\psi obsd}$ and $k^2_{\psi obsd}$ were obtained by employing an initial ratio of piperidine/amide concentration of 50:1 and 20:1, respectively. The approximate percentage of SN2 character was then estimated from the expression, $100[(k^1_{\psi obsd}/k^2_{\psi obsd}) - 1]/1.5$. Points making up the linear plots (average of seven per line) were obtained from determinations extending over at least two-thirds of the alkylation reaction. Correlation coefficients, r, calculated from all linear plots to determine $k_{\psi obsd}$ in Table III averaged 0.998 ± 0.002. Average deviation of $k_{\psi obsd}$ as determined from multiple determinations was ±2%. To obtain the data from **1–2** listed in Table III and necessary for preparing Figure 1, the following procedure was carried out. Pure **11** (0.2935 g, 0.000895 mol) was mixed with a solution containing 85 parts acetone and 15 parts water to a total volume of 10 ml. The amide was allowed to equilibrate by permitting the solution to stand 1 week. At time zero the solution was mixed with 85% aqueous acetone containing piperidine (3.80 and 1.52 g, respectively, at initial amine/amide ratios of 50:1 and 20:1), so that the total mixture including washings totaled 25 ml. At intervals of *ca.* 2.5 min thereafter, 0.5-ml aliquots of the solution were withdrawn at time t and pipeted into 50 ml of an acid solution (pH 2–3 with H_2SO_4) containing *ca.* 45 ml of acetone and 5 ml of water. After 7–15 min, longer time intervals were permitted between determinations of [Br^-]. The rate data derived for pure **11** was collected in identical fashion except no prior equilibration was permitted.

The determination of Arrhenius energies of activation, E_a, listed in Table III were calculated from the slopes of linear plots of log $k^2_{\psi obsd}$ *vs.* $1/T$. Four points at 5° intervals (±0.02°) between 25 and 40° make up each line. The essentially first-order character of the alkylations was assured by comparing $k^1_{\psi obsd}$ and $k^2_{\psi obsd}$ throughout this temperature range. In no case in the temperature-dependent studies was the percentage SN2 > 10%.

Registry No.—**1a**, 19298-40-9; **1b**, 19298-41-0; **1c**, 19298-42-1; **1d**, 19298-43-2; **1e**, 19298-44-3; **1f**, 19298-45-4; **1g**, 19298-46-5; **1h**, 19298-47-6; **1i**, 19298-48-7; **1j**, 19298-49-8; **1k**, 19298-50-1; **1l**, 2163-81-7; **1m**, 4212-91-3; **1n**, 4649-37-0; **3**, 6873-41-2; **5**, 2760-41-0; **7**, 4655-11-2; N,2-di-*t*-butylaniline, 19298-56-7; 6-*t*-butyl-*o*-tolylglycinonitrile, 19298-57-8; 6-*t*-butyl-N-(3-methoxypropyl)-*o*-toluidine, 19298-58-9; 6-*t*-butyl-N-ethyl-*o*-toluidine, 19298-59-0.

(18) NMR Spectra Catalog II (Varian Associates), 1963 p 388.