(Aldrich), and hexafluoroacetone trihydrate (Hynes) were used without further purification. The latter was stored under refrigeration. Standard buffer solutions, pH 2.00 ± 0.02, 25° (potassium chloride–hydrochloric acid buffer), 0.05 M, and pH 9.00 ± 0.2, 25° (boric acid–potassium chloride–sodium hydroxide buffer), 0.1 M, were purchased from Fisher Scientific Co.

(S)-(+)-Lactic acid and (R)-(−)-lactic acid, 100%, were purchased from Mann Research Laboratory.

(R)-(−)-**Mandelic acid**, mp 132–134°, [α]D −155 ±5° (c 5, water), was purchased from Fluka AG.

(S,S)-3,6-**Dimethyl-1,4-dioxane-2,5-dione** [(S,S)-**Lactide**] (I). —The (S,S)-lactide was prepared according to the method of Carothers, et al.:[39] mp 98.7°; [α]^{25}D +298° {lit.[40] mp 98.7°; [α]D −298° (for the [R,R]-lactide)}.

(R,R)-3,6-**Diphenyl-1,4-dioxane-2,5-dione** [(R,R)-**Diphenylglycolide**] (II).—A modified procedure of Schoberl and Wiehler[41] using naturally occurring (R)-(−)-mandelic acid[42] was used.

The crude glycolide was recrystallized from dioxane repeatedly to give 4 g (9.07%) of white crystals: mp 285–286°; [α]^{26}D +91.2° (c 1, dimethylformamide).

1,8,8-**Trimethyl-3-oxabicyclo[3.2.1]octan-2-one** (α-**Campholide**) (III).—α-Campholide was prepared according to the method of Salmon–Legagneur:[43] mp 208–218°; [α]^{25}D −21.0° (c

(39) W. H. Carothers, G. L. Dorough, and F. J. Van Natta, *J. Amer. Chem. Soc.*, **54**, 761 (1932).

(40) J. Kleine and H. H. Kleine, *Macromol. Chem.*, **30**, 23 (1959).

(41) A. Schoberl and G. Wiehler, *Ann.*, **595**, 101 (1955).

(42) Fluka Chemische Fabrik, [α]^{20}D −155 ± 5° (c 5, water), mp 132–134°.

(43) F. Salmon-Legagneur and J. Vène, *Bull. Soc. Chim. Fr.*, **4**, 448 (1937).

0.5317, gram/milliliter in ethanol) {lit. mp 209.5–211.5°,[44] 210–211°;[45] [α]D −20° [46] (ethanol)}.

Methyl (R)-Mandelate.—(R)-Mandelic acid (10 g, 0.066 mol) and methanol (5.3 ml, 0.132 mol) were dissolved in 50 ml of dry benzene containing 0.1 ml of concentrated sulfuric acid. The reaction mixture was refluxed for 3 hr, during which water was removed azeotropically using a Dean–Stark trap. The reaction mixture was allowed to cool and was then extracted three times with 50-ml portions of a saturated sodium bicarbonate solution. The aqueous layer was then washed three times with 50-ml portions of ether. The combined ether and benzene solutions were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resultant yellow oil was vacuum distilled (85° at 1.5 mm) to give a colorless liquid which solidified on cooling. The white solid was recrystallized from petroleum ether to give 9.3 g (85%) of a white crystalline material: mp 57–58°; [α]^{25}D −128.6° (c 1, ethanol).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.32; H, 5.95.

(44) R. B. Saurs, *J. Amer. Chem. Soc.*, **81**, 925 (1959).

(45) J. Tabel and H. Bublitz, *Ber.*, **38**, 3806 (1905).

(46) J. Vène, *Bull. Soc. Chim. Fr.*, **9**, 776 (1942).

Homogeneous Metalation of Alkylbenzenes

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Metalations of benzene, toluene, ethylbenzene, cumene, t-butylbenzene, and anisole, using n-butyllithium in conjunction with N,N,N',N'-tetramethylethylenediamine, were compared. Rearrangement of the kinetically favored products was *not* significant within the time periods used in this study. The extent of ring metalation, compared with benzylic metalation, follows the order toluene < ethylbenzene < cumene. Metalation at *ortho* positions is less extensive than at either *meta* or *para* positions in all cases. The ratio of *meta*/*para* derivatives was statistical (2:1) from metalation of ethylbenzene, cumene, and t-butylbenzene. Competitive metalation of benzene–alkylbenzene mixtures showed an order of benzylic reactivity of 6:1:0.1 for toluene/ethylbenzene/cumene, relative to benzene. The *ortho* positions of all alkylbenzenes underwent reaction less readily than that of benzene. Little difference was observed between the reactivities of either *meta* or *para* positions of alkylbenzenes and those of benzene. Competitive metalation of a benzene–anisole mixture shows that the *ortho* position of anisole undergoes metalation ca. 10² times faster than that of benzene. These observations are compared with those of metalations with alkylsodium and -potassium reagents and of base-catalyzed isotopic exchange studies involving the same substrates.

Metalation of alkylbenzenes, using organosodium and -potassium compounds, has received considerable attention in the chemical literature, resulting in a variety of mechanistic interpretations.[1] In recent years it has become rather commonly accepted that these reactions involve proton-abstraction processes.[1b,c,2] This conclusion is based primarily on the observation of rather large primary isotope effects[3] and comparison of metalation reactions with base-catalyzed isotopic exchange.[4] Recently, very extensive advances have been made in the area of base-catalyzed exchange of hydrocarbons by such workers as Shatenshtein,[4] Streitwieser,[5] and the Esso research group.[6] A very important contribution to the task of understanding metalation systems was the observation that homogeneous reaction could be effected using n-butyllithium in conjunction with N,N,N',N'-tetramethylethylenediamine (TMEDA).[7,8]

(1) (a) A. A. Morton, C. E. Claff, Jr., and F. W. Collins, *J. Org. Chem.*, **20**, 428 (1955); (b) D. Bryce-Smith, *J. Chem. Soc.*, 1079 (1954); (c) R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *J. Amer. Chem. Soc.*, **85**, 3984 (1963); (d) R. A. Benkeser, A. E. Trevillyan, and J. Hooz, *ibid.*, **84**, 4971 (1962).

(2) M. Schlosser, *Angew. Chem.*, **76**, 124 (1964).

(3) D. Bryce-Smith, V. Gold, and D. P. N. Satchell, *J. Chem. Soc.*, 2743 (1954).
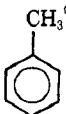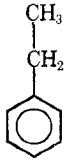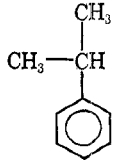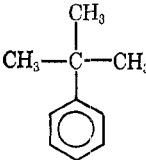
(4) Summarized in A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 155 (1963).

(5) See A. Streitwieser, Jr., R. A. Caldwell, R. G. Lawler, and G. R. Ziegler, *J. Amer. Chem. Soc.*, **87**, 5399 (1965), and references cited therein.

(6) See J. E. Hofmann, A. Schriesheim, and R. E. Nickols, *Tetrahedron Lett.*, 1745 (1965), and leading references.

(7) (a) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964). (b) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965). (c) It has been reported that alkyllithium–amine complexes metalate t-butylbenzene on the ring [C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965)]. (d) M. D. Rausch and D. J. Ciappenelli [*J. Organometal. Chem.*, **10**, 127 (1967)] report metalation of benzene with this reagent. (e) R. West and P. Jones [*J. Amer. Chem. Soc.*, **90**, 2656 (1968)] have studied polylithiation of toluene using n-butyllithium–TMEDA complexes.

(8) The term homogeneous describes the fact that solid materials are not present. The state of aggregation of the various organometallic species is not known.

Since this discovery provides a means of circumventing the mechanistically troublesome heterogeneity of alkyl-sodium and alkylpotassium systems, it was decided that a comparison of this new metalation system[9] with the previous ones and with base-catalyzed exchange was in order. This paper reports the results of such a study and considers such items as the operation of kinetic vs. thermodynamic control, the trend in reactivity of alkylbenzenes with increasing methyl substitution at the benzylic positions, and the reactivity of benzene vs. alkylbenzene substrates.

Results

The present observations on metalation of alkyl-benzenes, competitive metalation of benzene–alkylbenzene mixtures, and trans-metalation reactions are summarized in Tables I, II, and III. Results from the competitive metalation of an anisole–benzene mixture are given in the Experimental Section. All metalation reactions were conducted at ca. 30° using a 4:1 molar ratio of aromatic substrate to n-butyllithium. Analyses were performed on methyl esters resulting from carbonation and esterification of metalation reactions. Products were identified by a combination of gas–liquid phase chromatographic (glpc) comparison with authentic samples and collection of pure samples by glpc followed by examination of proton magnetic resonance spectra (pmr).

TABLE I

METALATION OF AROMATIC HYDROCARBONS WITH
n-BUTYLLITHIUM–TMEDA

	Substrate	Time, hr	Benzyl, %	ortho, %	meta, %	para, %
1.	CH₃[a,b]	0.25	89	3	9	
		0.5	90	2	8	
		1.0	88	3	9	
		2.0	92	2	6	
2.	CH₃ / CH₂	0.5	38	9	36	17
		1.0	37	9	36	17
		6.5	38	9	36	17
3.	CH₃ / CH₃—CH	2.0	3	10	57	30
		24	3	8	59	30
4.	CH₃ / CH₃—C—CH₃	4.0			68	32

[a] Phenylmalonic acid (15% relative yield) was also detected. This is accounted for under benzyl, since it most probably arises from metalation of lithium phenyl acetate [see ref 7e; see also A. J. Chalk and T. J. Hoogeboom, *J. Organometal. Chem.*, 11, 615 (1968)]. [b] In the case of toluene, the *meta* and *para* isomers were only partially resolved under the glpc conditions used (see Experimental Section). These areas were therefore combined to determine the relative percentages.

(9) Metalation of heteroatom substrates by n-butyllithium is of course well known [cf. H. Gilman and J. W. Morton, Jr., Org. Reactions, 8, 283 (1954)].

Discussion

One of the primary concerns in a mechanistic study of metalation systems must be a consideration of the possibility that kinetic vs. thermodynamic processes are operative. Thus, Benkeser[1c,10] has shown that metalation of aromatic substrates can be followed by reaction of the first-formed products with excess substrate (*trans* metalation) to give more stable organometallic species. However, it has been shown recently that these subsequent *trans*-metalation reactions occur slowly relative to the initial metalation process during metalation of both toluene[11] and olefinic substrates.[12,13] The data presented in Tables I, II, and III demonstrate that kinetic vs. thermodynamic processes are of little consequence in the present homogeneous metalation system.

Entries 1 and 2 of Table I show that variation of reaction time has no measurable effect on the product distribution obtained from metalation of either toluene or ethylbenzene. Chalk and Hoogeboom[14] have recently reported essentially identical results from metalation of toluene with n-butyllithium–TMEDA. Since n-butyllithium is present in these reaction mixtures, as evidenced by the formation of valeric acid upon carbonation, the operation of rapid *trans*-metalation processes would require more rapid reaction by the less basic aromatic organometallic species. While this order of reactivities might be possible,[12,15] it would be surprising.

Better evidence that rapid *trans* metalation is *not* important is found in Tables II and III. Entries 1 and 2 of Table II show that the product distributions obtained from competitive metalations of benzene–toluene and from benzene–ethylbenzene mixtures do not vary significantly with these reaction times. To demonstrate that rapid *trans*-metalation processes are *not* operative during these reactions, the experiments outlined in Table III were conducted. Thus, phenyllithium was prepared by the metalation of benzene, toluene was added to the reaction mixture, and aliquots were carbonated at the time intervals reported. It is apparent that little metalation of toluene by phenyllithium took place during the 2-hr reaction period which was used for the competitive metalation experiment (entry 1, Table III). Similar metalation of toluene and addition of benzene shows no metalation of benzene after 2 hr and only ca. 2% after 16 hr (entry 2, Table III). Therefore, the products analyzed during the time intervals involved in this study are the result of the initial metalation process, since further reaction of the first-formed products occurs slowly. Now that this point is established, several aspects of the present data merit discussion.

First, it is apparent that increasing the number of methyl groups at the benzylic position results in increased ring metalation (Table I). This trend is quite reasonably explained on the basis that metalation

(10) It was also shown that alternately synthesized ring-substituted organosodium compounds underwent conversion into the benzyl isomer in the presence of ethylbenzene.

(11) C. D. Broaddus, J. Amer. Chem. Soc., 88, 4174 (1966).

(12) C. D. Broaddus, J. Org. Chem., 29, 2689 (1964).

(13) C. D. Broaddus and D. L. Muck, J. Amer. Chem. Soc., 89, 6533 (1967).

(14) A. J. Chalk and T. J. Hoogeboom, J. Organometal. Chem., 11, 615 (1968).

(15) R. Waack and P. West, J. Amer. Chem. Soc., 86, 4494 (1964).

TABLE II

COMPETITIVE METALATION OF BENZENE–ALKYLBENZENE[a] MIXTURES

Substrates	Time, hr	Methyl benzoate, %	Benzyl, %	ortho, %	meta, %	para, %
1. Benzene	0.5	21	68	~2	9	
and	1.0	21	68	~2	9	
toluene	2.0	23	67	~2	8	
(average)		22	68	~2	9	
2. Benzene	0.5	46	17	7	20	9
and	1.0	51	16	6	18	8
ethylbenzene	2.0	52	14	5	19	9
(average)		49	16	6	19	9
3. Benzene						
and	2.0	61	~1	4.9	22	11
cumene						
4. Benzene						
and		67			22	11
t-butylbenzene						

[a] Equimolar amounts of benzene and alkylbenzenes were used in these experiments with the mole ratio of aromatic hydrocarbon to *n*-butyllithium being 4:1.

TABLE III

trans METALATION OF BENZENE AND TOLUENE

Reactants	Time,[a] hr	Methyl benzoate, %	Methyl phenyl acetate, %	Methyl toluates, %
1. Phenyllithium	0	100		
and	0.25	99		
toluene	0.5	99	<1	
	1.0	98	<1	
	2.0	98	~1	
2. Metalated	0		88	11
toluene and	2		87	13
benzene	16	~2	87	12

[a] As described in the Experimental Section, zero time was taken as that time immediately before the addition of the aromatic substrate to the metalation mixture of *n*-butyllithium–TMEDA and either benzene or toluene.

SCHEME I

R and R' = H or CH₃

proceeds by competitive proton-abstraction mechanisms,[16] and that the transition states leading to benzyl carbanionic species are destabilized by an increased number of methyl groups relative to those involved in metalation at ring sites. These results can be depicted as in Scheme I.
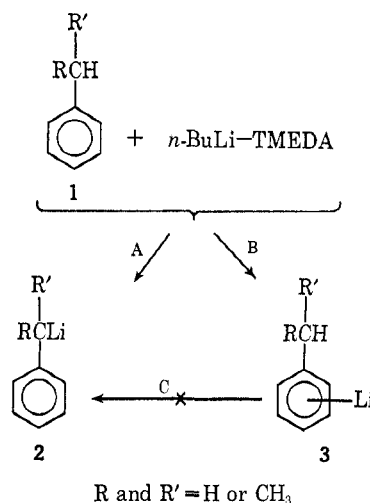
With toluene, reaction path A to produce 2 predominates. Increased alkyl substitution at the benzylic position of ethylbenzene destabilizes the transition state for formation of anionic intermediate 2, relative to 3, thereby increasing the importance of path B. In the case of cumene, further alkyl substitution results in the predominance of path B. Path C does not operate under the reaction conditions.

Depression of the relative rates of benzylic metalation in the series toluene, ethylbenzene, and cumene by steric effects of the methyl groups cannot be eliminated by the present data. However, the decreases[17] in reactivity are very similar to those observed in base-catalyzed exchange systems. Since there is evidence that steric effects are not important in exchange systems,[18] it appears more reasonable to ascribe this retardation to inductive effects of the methyl groups.

The relative amounts of *ortho-*, *meta-*, and *para*-substituted derivatives obtained from these alkylbenzenes are also significant. Ratios of 2:1 for *meta* to *para* derivatives of ethylbenzene, cumene, and *t*-butylbenzene were obtained. This indicates identical reactivity at these sites, since the *meta* position is favored statistically by a factor of two. The data of Table I also show that reaction at *ortho* positions is depressed in all cases relative to reaction at *meta* and *para* sites. It appears clear that *ortho* metalation of *t*-butylbenzene is inhibited by the steric effect of the *t*-butyl group. Thus, *ortho* metalation is depressed with all these alkylbenzenes; however, only *t*-butylbenzene shows an absence of *ortho* product. Since no precipitous change in electronic effects would be expected in this series, it appears that the steric effect of the *t*-butyl group inhibits *ortho* metalation. The present data do not allow separation of steric and electronic effects in the depression of *ortho* metalation of toluene, ethylbenzene, and cumene.

Further insight into the factors controlling metalation of alkylbenzenes with this homogeneous metalation

(16) Shirley [D. A. Shirley and J. P. Hendrix, *J. Organometal. Chem.*, 11, 217 (1968)] has recently suggested a four-step mechanism for metalation of phenyl ethers involving (1) radical-anion formation, (2) capture of a lithium cation by the radical anion, (3) combination of alkyl and aromatic radicals, and (4) loss of an alkane to yield the *ortho*-lithiated product. This mechanism was proposed to account for apparently low steric requirements in the metalation of ethers.

(17) From the data of Table II, reactivities of toluene, ethylbenzene, and cumene, relative to toluene, are ca. 1.0, ca. 0.02, and ca. 0.02. See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 28, for the rather close agreement with exchange systems.

(18) A. Streitwieser, Jr., and D. E. Van Sickle, *J. Amer. Chem. Soc.*, 84, 249 (1962).

system is provided by the competitive metalations outlined in Table II. These studies provide rates of reaction at benzylic and ring positions relative to the rate of metalation of benzene. This assumes that inclusion of benzene into the metalation mixture simply adds another competitive metalation route without complicating the reaction scheme. The data presented in Table III, which was discussed earlier, support such an assumption, as does the agreement between isomer ratios in the metalation (Table I) and competitive metalation (Table II) experiments.

The order of reactivity at the various benzylic sites, relative to benzene, is toluene > ethylbenzene > cumene. After statistical differences are accounted for, reactivities at the benzylic positions of toluene, ethylbenzene, and cumene are *ca.* 6.0, *ca.* 1.0, and *ca.* 0.1, respectively, relative to benzene. This trend is, of course, consistent with the earlier discussion of benzylic *vs.* ring metalation.

A similar comparison of the rates of ring metalation of alkylbenzenes relative to benzene is possible from the data of Table II. As discussed earlier, the rates of *ortho* metalation are depressed relative to the rates of reaction at *meta* and *para* sites. These competitive experiments show further that *ortho* metalation is depressed in all cases relative to benzene metalation. It is also apparent that the relative rates of metalation at *meta* and *para* positions of these alkylbenzenes are very similar to the rate of benzene metalation, once statistical differences are taken into account. This observation shows that the alkyl substituent has little or no effect on reactivity at these positions. Thus, the 2:1 ratios of *meta/para* products shown in Table I could be accounted for by balancing inductive and electrometric effects. However, this observation that *meta* and *para* reactivities are essentially equal to that of benzene shows that neither effect is significant in this system. This could be taken as support for steric retardation of *ortho* metalation of toluene, ethylbenzene, and cumene. However, the extent to which the inductive effect of alkyl groups is attenuated at *meta* and *para* positions is difficult to estimate.[19]

The observations on these metalation reactions may be summarized as follows. All the results are explicable on the basis of competitive proton abstractions by the saturated metalating agent. Rearrangement of the first-formed organometallic species occurs slowly if at all. Increasing the degree of alkyl substitution at the benzylic site retards the rate of metalation at this position appreciably, while having no observable effect on the reactivity at *meta* and *para* positions. Furthermore, *ortho* metalation is depressed relative to *meta* and *para* metalations and to metalation of benzene in all cases.

Similarities in general trends between this homogeneous metalation system and the earlier studies on metalation of alkylbenzenes with alkylsodium and -potassium reagents are apparent.[1c,1d,11,20] This suggests that heterogeneity does *not* play a *dominant* role in organosodium and -potassium metalations even though the reagents exhibit little or no solubility.

This agrees with the conclusions of Benkeser[1d] and Bryce-Smith.[21]

Since the present metalations are homogeneous and appear to be controlled by proton-abstraction processes, a brief comparison with the more extensively investigated base-catalyzed isotopic exchange of substituted benzenes is warranted. Similarities between the two types of reaction are immediately obvious. In both metalation and base-catalyzed exchange systems, relative reactivities at benzylic positions decrease in the order toluene > ethylbenzene > cumene. Moreover, if the reactivities are calculated relative to toluene, the decrease in all systems is very similar[17] to the order observed in these metalation experiments, *i.e.*, *ca.* 1.0, *ca.* 0.2, and *ca.* 0.02. Also, the reactivities at ring positions of substituted benzenes show similarities. For example, Streitwieser[5] finds the rates of *ortho*, *meta*, and *para* exchange of toluene to be 0.12, 0.54, and 0.45, respectively, relative to benzene. Table II indicates *ortho*, *meta*, and *para* reactivities of ethylbenzene to be 0.2, 1.0, and 1.0, respectively, relative to benzene. Shatenshtein[22] reports exchange of anisole to be 4–5 $\times$ 10^2 times faster than benzene, using either potassium amide in liquid ammonia or potassium *t*-butoxide in dimethyl sulfoxide. We find that the *ortho* position of anisole undergoes metalation on the order of 10^2 times faster than does benzene (see Experimental Section). It should be emphasized that these similarities in relative reactivities are obtained by comparing similar sites of reaction. That is, all the benzylic positions are compared with the benzylic position of toluene and ring positions are compared with the reactivity of benzene. Nevertheless, these similarities certainly suggest the operation of similar mechanisms in the various systems.[4]

A more complicated picture arises if benzylic reactivities are compared to the reactivity of benzene using these various base systems. Table IV summarizes some pertinent data. Inspection of Table IV shows that the reactivities of benzylic positions, relative to benzene, decrease markedly in the order potassium *t*-butoxide–DMSO >> potassium amide–ammonia > *n*-butyllithium–TMEDA.

TABLE IV

VARIATIONS IN REACTIVITIES AT BENZYLIC POSITIONS OF
TOLUENE, ETHYLBENZENE, AND CUMENE RELATIVE TO BENZENE
WITH CHANGE IN BASE SYSTEM

Base	Toluene	Ethylbenzene	Cumene
n-BuLi–TMEDA	~6	~1	~0.1[a]
KNH₂–NH₃[b]	70	9.8	2.1
KO-*t*-Bu–DMSO[b]	~10^6	2.2 $\times$ 10^5	2.3 $\times$ 10^4

[a] This relative reactivity was obtained from the data in Table I by comparing benzylic with *para* reactivity. Table II shows that reactivity of the *para* position is very similar to the reactivity of benzene. [b] From ref 22.

This distinction between amide and potassium *t*-butoxide–DMSO systems has been noted previously and explanations based on "internal-return" phenomena have been offered.[23] That is, if the carbanionic

(19) M. J. S. Dewar and A. P. Marchand, *J. Amer. Chem. Soc.*, **88**, 354 (1966), and references cited therein.
(20) A. A. Morton, "Solid Organoalkali Metal Reagents," Gordon and Breach Science Publishers, Inc., New York, N. Y., 1964, p 41.

(21) D. Bryce-Smith, *J. Chem. Soc.*, 5983 (1963).
(22) A. I. Shatenshtein, I. O. Shapiro, and I. A. Romanskii, *Dokl. Akad. Nauk SSSR*, **174**, 1138 (1967).
(23) A. Streitwieser, Jr., and H. F. Koch, *J. Amer. Chem. Soc.*, **86**, 404 (1964).

species derived from benzene underwent extensive "internal return" in DMSO, an inordinately slow exchange rate would be observed. Moreover, if this factor were less important with benzyl intermediates, a larger spread in rates of exchange at the two types of position would be observed in DMSO than in solvents wherein "internal return" was not operative. While this factor may account for at least part of the large difference between nitrogen base systems and potassium *t*-butoxide in DMSO, it does not appear to offer a reasonable rationale for the decreased benzylic reactivity with *n*-butyllithium–TMEDA, as compared with the amide systems. It appears unlikely that this factor operates during metalation. Thus, significant primary isotope effects have been observed[3,15] during metalation, which indicates that "internal return" is not operative. Also, the return mechanism would require proton removal from butane, which seems highly improbable. Since Streitwieser[24] has shown that "internal return" is not important during base-catalyzed exchange in amine solvents, it appears that arguments based on this mechanism cannot be used to account for the differences in metalation and amide-catalyzed exchange.

It does appear, however, that a reasonable rationalization of the existing data is possible from the differences in basicities of the reagents used. It appears clear that the order of basicities in these systems is *n*-butyllithium > potassium amide > potassium *t*-butoxide. The data of Table IV then shows increasing reactivity at benzylic positions relative to benzene with decreasing base strength. If one accepts the principle that the C–H bond will be broken to the largest extent in the transition state involving the weakest base,[25] it may be reasonably proposed that electron-delocalization factors will also be largest with the weakest base. That is, more charge is developed on carbon; therefore delocalization is a more important factor; and thus reaction is favored at benzylic positions relative to sp^2 C–H positions.[26]

Another way to state this proposal is that an increase in base strength has *less* effect on the rate of reaction at benzylic positions owing to decreased effectiveness of resonance stabilization. If it is assumed that both types of positions undergo reaction more rapidly with stronger bases, the data require that ring positions increase in reactivity to a greater extent than benzylic positions with the same increase in base strength. This then suggests that the relationship between reactivity and basicity is different for resonance-stabilized and ring positions or that the two types of positions would *not* fit on the same Brønsted plot. It will be recognized that the above discussion closely resembles that of Bell[27] on the molecular interpretation or deviations from the Brønsted relation and can perhaps be seen most clearly by construction of energy diagrams similar to those presented by Hine.[28]

In conclusion then, it appears that metalation and base-catalyzed exchange of hydrocarbons involve very similar processes, but that fairly subtle differences[29] cause drastic changes in relative reactivities. It can also be seen that, while metalation can be effected conveniently with *n*-butyllithium–TMEDA, rather complex mixtures are often obtained. This lack of selectivity obviously limits the synthetic utility of the reaction system.

Experimental Section

Materials.—*n*-Butyllithium was purchased from Foote Mineral Co. as a *ca* 1.6-*M* solution in hexane. Benzene, toluene, ethylbenzene, cumene, and *t*-butylbenzene were purchased from Matheson Coleman and Bell and used as received. N,N,N',N'-Tetramethylethylenediamine came from Matheson Coleman and Bell and was distilled from dry potassium hydroxide before use.

Metalation Reactions.—All metalation reactions were conducted under an argon atmosphere at *ca*. 30° using a 4:1 molar ratio of aromatic substrate to *n*-butyllithium. A complete description of the metalation of toluene is given as a typical example.

Metalation of Toluene.—Tetramethylethylenediamine (7.6 g, 0.065 mol) was added to 40 ml of 1.6 *M* *n*-butyllithium in hexane contained in a three-necked flask under an argon atmosphere. The temperature of the solution rose from *ca*. 30 to *ca*. 45°. The solution was stirred with a magnetic stirrer until a temperature of 30° was regained, whereupon toluene (23.5 g, 0.256 mol) was added rapidly through a rubber septum by means of a syringe. The resulting reaction mixture was allowed to stir and aliquots were removed at the time intervals reported in entry 1 of Table I. Each aliquot was carbonated by discharging over excess Dry Ice through a syringe. After the Dry Ice had sublimed, water was added and the usual work-up procedure to isolate carboxylic acids was employed. The total weight of the acidic products was 4.2 g, approximately equally divided among the four aliquots. In a separate run, in which the entire mixture was carbonated after 2 hr, 5.5 g of the crude acidic product was obtained. The acidic product was esterified by refluxing in methanol using a catalytic amount of concentrated sulfuric acid. The resulting esters were analyzed by gas chromatographic (glpc) comparison with authentic samples of methyl *o*-toluate, methyl *m*-toluate, methyl *p*-toluate, and methyl phenyl acetate to give the product distribution shown in Table I. An additional peak at long retention time was shown to be due to dimethyl phenyl malonate by collection and proton magnetic resonance spectroscopy. A multiplet centered at τ 2.7, a singlet at τ 5.45, and a singlet at τ 6.3 in relative area ratios of 5:1:6 confirm this structure. The peak accounted for 15% of the total area, which was added to the area due to methyl phenyl acetate, since the malonic acid derivative most probably arises from metalation of lithium phenyl acetate. Peak areas were obtained using a planimeter. Weighed mixtures of the authentic samples of the toluates mentioned above agreed with the glpc analysis within ±2%. It was not possible to resolve completely the *meta* and *para* isomers under the conditions used (20% diethylene glycol succinate suspended on Chromosorb W at column temperatures of 100–150° with a helium flow rate of *ca*. 60 ml/min); so the combined areas of these two peaks were used to calculate the compositions reported in Table I.

Metalation of Ethylbenzene.—Metalation of ethylbenzene was performed in a manner identical with that described above. From 27 g (0.256 mol) of this material, a total weight of 4.9 g of crude acidic product was obtained by carbonating three aliquots taken at the time intervals reported in Table I. The composi-

(24) A. Streitwieser, Jr., and F. Mares, *J. Amer. Chem. Soc.*, **90**, 644 (1968), and references cited therein.

(25) See J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, p 158.

(26) This assumes that resonance factors are of little importance in determining reactivity at ring positions. See ref 4, p 188.

(27) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 171.

(28) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 117.

(29) It should be emphasized that correlation of metalation reactions with base-catalyzed exchange on the basis that metalations are simply less selective owing to their greater basicity does not agree with some of the present data. Examination of the varying results obtained with cumene is instructive. With potassium *t*-butoxide, reaction is very selective at the benzylic position; with potassium amide, reaction at the benzylic position and reaction with benzene become more competitive; and, finally, metalation favors reaction of benzene relative to the benzylic position of cumene. Decreasing selectivity due to increasing basicity should result in more random reaction in the metalation system, *not* a change in position of selectivity.

tions reported were determined by glpc analysis in which the relative peak areas were assumed to represent the relative amounts of isomers present. To identify the isomers, pure compounds were separated by glpc of the two larger components and were analyzed by proton magnetic resonance (pmr) spectroscopy.[30] Identification of the minor components of the mixture of esters was accomplished by glpc comparison with authentic samples prepared by carbonation of Grignard reagents. Also, weighed mixtures of the standards agreed with glpc analysis within ±2%.

Metalation of Cumene.—Cumene (30 g, 0.25 mol) was subjected to metalation for the time intervals reported. A total yield of 6.0 g of crude acids was obtained. Identification of the isomers was accomplished by collecting pure samples from glpc and recording the pmr spectra.[30] To identify one of the minor peaks, a mixture of o- and p-bromocumene was converted into the corresponding mixture of Grignard reagents, carbonated, and esterified. Samples of each component of this mixture were then collected by glpc and the pmr spectra were recorded. One component gave a pmr spectrum identical with that of methyl p-isopropylbenzoate and had the same retention time on glpc as did the 30% component, confirming that identification. The other component of the ester product obtained through the Grignard reaction gave a pmr spectrum which showed it to be methyl o-isopropylbenzoate.[30] By comparing this mixture of methyl o-isopropylbenzoate and methyl p-isopropylbenzoate with the product obtained from metalation of cumene by glpc, it was seen that one of the minor components of the metalation mixture (ca. 10%) was the *ortho* derivative.

The other minor component (ca. 3%) was identified as methyl α,α-dimethylphenyl acetate by glpc comparison with an authentic sample purchased from K & K Laboratories. The pmr spectrum of the purchased material was consistent with the designated structure.

Metalation of t-Butylbenzene.—Similar metalation of t-butylbenzene (34.3 g, 0.256 mol) provided 5.7 g of acidic product. Esterification and glpc analysis gave the results recorded in Table I. It was assumed that the relative peak areas indicated the composition of the isomeric mixture. Product identification came from glpc collection of pure samples and pmr analysis.[30]

Competitive Metalation Reactions.—The competitive metalations outlined in Table II were conducted in a manner identical with the metalations described above, with the exception that a mixture of aromatic hydrocarbons was added to the previously prepared n-butyllithium–TMEDA complex. In all cases a molar ratio of 2:2:1 of benzene to alkylbenzene to n-butyllithium was employed. Product identification in these experiments was accomplished by glpc comparison with methyl benzoate and the previously identified products described in the foregoing experiments. In all cases the glpc analysis was verified by pre-

paring weighed mixtures of authentic methyl benzoate admixed with the ester products obtained from metalation in the absence of benzene. The agreement was good (±2%) in all cases except for analysis of the toluene experiments, for which a mixture weighed as 70% toluene derivatives and 30% methyl benzoate, on a mole basis, was indicated to be 62% toluene derivatives and 38% methyl benzoate by glpc analysis. Part of this discrepancy is most probably due to the formation of some methyl phenyl malonate which was not accounted for in this experiment.

Attempted Metalation of Toluene Using Phenyllithium.—Benzene (20 g, 0.256 mol) was added to 40 ml of ca. 1.6-M n-butyllithium in hexane to which 10 ml of TMEDA had been previously added. The resulting solution was allowed to stir overnight, whereupon a 20-ml aliquot was removed and carbonated. Work-up and esterification provided the product, which was analyzed by glpc to provide the data listed as zero time in entry 1 of Table III. Immediately after removal of this aliquot, toluene (23 g, 0.256 mol) was added to the reaction mixture and stirring was continued. Additional 20-ml aliquots were removed at the time intervals reported in Table III and carbonated by syringing over excess Dry Ice. The usual work-up and esterification provided esters which were analyzed by glpc to provide the additional results recorded in entry 1 of Table III.

Attempted Metalation of Benzene Using Metalated Toluene.—Toluene (23.5 g, 0.256 mol) was added to 40 ml of n-butyllithium which had been complexed with TMEDA. The reaction mixture was stirred for 6 hr, whereupon a 10-ml aliquot was removed and syringed over Dry Ice. The usual work-up and analysis provided the data listed as zero time in entry 2 of Table III. Immediately after this aliquot was removed, benzene (20 g, 0.256 mol) was added with continued stirring. Aliquots were removed after 2 and 16 hr to provide the additional results recorded in entry 2 of Table III.

Metalation of Anisole.—In a manner similar to the previous examples, anisole (14.4 g, 0.133 mol) was added to n-butyllithium (0.064 mol) containing TMEDA. A slightly exothermic reaction resulted. The reaction mixture was stirred for 2 hr before being syringed over Dry Ice. Work-up provided 5.2 g of acidic product. Esterification with methanol and sulfuric acid provided a product which was indicated to be one component by glpc analysis. Comparison with authentic samples[31] by glpc shows the material to be methyl o-methoxybenzoate. A competitive metalation using anisole (0.13 mol), benzene (0.13 mol), and n-butyllithium–TMEDA (0.064 mol) gave 5.5 g of acidic product. Analysis of the resulting esters by glpc shows ca. 0.5% methyl benzoate and ca. 99% methyl o-methoxybenzoate.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; ethylbenzene, 100-41-4; cumene, 98-82-8; t-butylbenzene, 98-06-6; anisole, 100-66-3; n-butyllithium, 109-72-8; N,N,N',N'-tetramethylethylenediamine, 110-18-9.

(30) All spectra were entirely consistent with the proposed structures and were compared with published spectra in readily available sources as well as with the authentic samples described in the text. Detailed descriptions of these spectra are omitted to conserve space.

(31) The three methoxybenzoic acids were purchased from Eastman Organic Chemicals and esterified by standard procedures.