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2,4-Diazapentadienes. II. A Carbanion Cyclization

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The mechanism of the cyclization and 1,3-proton shift of 1,3,5-triaryl-2,4-diaza-1,3-pentadienes (1) catalyzed by phenyllithium and by potassium methoxide-methanol has been studied. On the basis of substituent effects, hydrogen-deuterium exchange, isotope effects, and solvent effects, it was deduced that both the cyclization and prototropy involve a common W-shaped carbanion which rapidly cyclizes. A kinetic deuterium isotope effect of 2 was calculated for protonation of this intermediate carbanion in methanol.

On étudie le mécanisme de cyclisation et de migration-1,3 de proton dans les triaryl-1,3,5 diaza-2,4 pentadiènes-1,3 (1) catalysées par le phényllithium et par le méthylate de potassium-méthanol. En se fondant sur les effets des substituants, de l'échange hydrogène-deutérium, des effets isotopiques et des effets de solvant, il en a été conclu que la cyclisation ainsi que la prototropie impliquent un carbanion commun en forme de W qui se cyclise rapidement. Un effet isotopique cinétique du deutérium d'une valeur de 2 a été calculé pour la protonation dans le méthanol de ce carbanion intermédiaire.

Canadian Journal of Chemistry, 50, 678 (1972)

Introduction

The reaction of benzaldehvde with ammonia to form hydrobenzamide 1 and the 'thermal' isomerization of 1 to amarine 2 must stand among the first organic reactions studied (1). Yet surprisingly little attention has been paid to these and related molecules especially from a mechanistic point of view (2). Particularly intriguing to us was the highly stereoselective cyclization of 1 to form 2, the cyclic isomer with the phenyl rings *cis* to each other. Since the preliminary report (3) which noted that this reaction was base-catalyzed and in which orbital symmetry was invoked, the study of this reaction using phenyllithium in THF has been further elaborated. Also the study has been extended using methanol-methoxide and examples of 1 substituted p, p', p'' in an attempt to obtain a more complete understanding of this reaction. The preparations, reactions, and structural assignments for 1 and related compounds have been described in the preceding article (4). As an example of the nomenclature to be used in the following sections, $p-CH_3-1$

will refer to the tris-*p*-methyl substituted hydrobenzamide (1).

Results and Discussion

As indicated in Scheme 1, the cyclization of 1 to 2 is catalyzed by a variety of bases (4) (e.g. KOtBu-HOtBu at room temperature) and produces 2 highly selectively (<1% of 4). The *cistrans* interconversion of 2 to 4 requires more vigorous conditions (*e.g.* KOtBu-HOtBu at reflux) thereby allowing a study of the basecatalyzed reactions of 1 under conditions where 2 is not reactive. The equilibrium mixture of 2 and 4 in *t*-butyl-alcohol at 100° contains 96% of 4 and 4% of 2 as might be expected.

Reactions with Phenyllithium

The results of treating 1 and its derivatives with phenyllithium in tetrahydrofuran are gathered in Table 1. As run 3 indicates, when 1 is reacted with an equivalent of phenyllithium at -78° and then warmed to room temperature, only 2 is observed by t.l.c. and n.m.r. in the reaction mixture and an 80°_{6} yield of 2 can be



		Substrate		T.	0 1	Product	s (%)	
Run	p-X	Concentration (M)	<i>T</i> (°C)†	(min)‡	Quencher nature§	1	2	4
1	н	0.05	- 78	360	Н	44	56	0.8
2	Н	0.075	- 78	850	н	66	34	0.7
3	Н	0.13	- 78 to 25	270	н	<0.2	100¶	<0.5
4	CH ₃	0.13	- 78 to 25	1000	н	<0.2	100	<0.5
5	Cl	0.024	- 78	30	\mathbf{H}^{\prime}	26	74	<0.5
6	CN	0.026	- 78	~1	D	<0.2	100	<0.5
7	Н	0.016	- 78	90	D	88 (<0.15 atoms D)	12	
8	C1	0.024	-78	15	D	34(<0.15 atoms D)	66	
9	CN	0.026	-130	~1	D	49 (<0.10 atoms D)	51	
10	Н	0.07	-65	360	н	84	13	3
11	Н	0.08	- 78	1050	н	71	26	2.5
12	Н	0.05	-40	375	н	<0.2	93	7
13	н	0.07	-20	360	Н	<0.2	99	0.8
14	CI	0.11	-130 to -90	5	H	26	73	**
15	2	0.08	78	1080	H		97	3
16	4	0.08	- 78	695	H	_	<0.7	99

TABLE 1. Reactions of p-substituted hydrobenzamides 1 with phenyllithium* in THF

*One equivalent of 0.5 or 0.72 *M* phenyllithium in THF was used except for run 3 (a two-fold excess of base). †Dry lce-acetone temperature is reported as -78; -78 to 25 refers to reaction begun at -78° and allowed to warm to room temperature. ‡Times reported in italics are for runs involving irradiation (see Experimental). §H refers to CH₃CO₂H and D to CH₃CO₂D. ||Upper limit on atoms of D/molecule of starting material (n.m.r.). ¶Amarine was isolated in 80% yield. ** <0.5% p-Cl-4 but 1% of p-Cl-3 was observed.

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isolated. As seen in runs 1 and 2, where the entire reaction was run at -78° and quenched with excess acetic acid at the times indicated, the reaction is proceeding slowly and the rates are not highly reproducible except that not more than 1% of 4 is produced.

These observations can be generalized to p-CH₃, p-Cl, and p-CN-1 (runs 4, 5, and 6) although there is a definite substituent effect upon the observed rate of reaction. This is exemplified by run 6 where p-CN-1 is completely consumed in 1 min. The apparent order of reactivity is p-CN-1 > p-Cl-1 > 1 > p-CH₃-1.

The singular feature of all these reactions was the appearance of an intense color when the phenyllithium reagent was added. The color varied with the substituent and the visible spectrum obtained for 1 showed a long wavelength absorption maximum at 592 nm. The color faded to a light yellow when the reaction mixture was warmed to ambient temperature. It is tempting to ascribe the color to an anionic intermediate in the cyclization reaction and in an attempt to assess this hypothesis three experimental approaches were used: (a) quenching with CH_3CO_2D ; (b) quenching with CH₃CO₂H with careful product analysis; and (c) irradiation of the colored solution. These are summarized in Scheme 2.

Runs 7, 8, and 9 report on the results obtained when the colored solutions obtained from 1, p-Cl-1, and p-CN-1 were quenched with CH₃CO₂D before complete conversion had occurred. Again the accelerating effect of the cyano grouping is observed (run 9), for even at -130° , with immediate quenching (at 1 min) about 50% reaction had occurred. The reaction mixtures were analyzed for deuterium incorporation into 1 and surprisingly none could be detected (<0.15 atoms D/molecule). These results require that the rate of proton abstraction from 1 by phenyllithium be slow at these temperatures and also if significant quantities of anionic intermediate are generated that quenching does not lead back to 1.

In an attempt to obtain further information on the character of the possible carbanionic intermediate, the colored solutions obtained from 1 and p-Cl-1 were quenched while cold after a short reaction period (run 14 for p-Cl-1) with excess acetic acid. An examination of the reaction product by n.m.r. revealed that about 1% of p-Cl-3 was present and on work-up a sample of N-p-chlorobenzyl-p-chlorobenzamidine was isolated. The n.m.r. spectrum of the reaction mixture from 1 did not show 3 but a trace of N-benzylbenzamidine was observed upon hydrolysis.

The base-catalysis, the substituent effect, the color, and the quenching results with CH_3CO_2H all support the intermediacy of an anion generated by proton abstraction from 1. However, from the small amounts of 3 and *p*-Cl-3 isolated and from the lack of deuterium incorporation into 1 upon quenching with CH_3CO_2D , the concentration of anion must be small but still large enough to give an intense color. Assuming an extinction coefficient of about 10^5 (5), amounts of anion in the 1 to 0.001% range are suggested.



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				Rate	constants†
Run	Substrate	[Base] (M)	3/2‡	$k_1 ({ m s}^{-1} imes 10^5)$	$k_2 (M^{-1} \text{ s}^{-1} \times 10^4)$
17	p-CH ₂ -1	0.23	1.2 ± 0.1	6.4	2.8
18	1	0.23	0.8 + 0.1	34	15
19	ī	0.21	0.9 + 0.1	26	12
20	1	0.097	0.75 + 0.05	13	13
21	1	0.14	0.7 + 0.1	31	22
22	p-Cl-1	0.023	0.5 + 0.1	73	320
23	3	0.21	—	0.046	0.022

TABLE 2. Kinetic runs in CH₃OH*-CH₃OK at 60 °C

*0.6 M in THF.

†Based upon three points for run 17, five for run 18, six for run 19, five for run 20, three for run 21, four for run 22, and five for run 23; $k \pm 10\% k$. ‡Average value for all points. §Assuming first order in added base (6).

||Contains 1 equiv of dibenzo-18-crown-6-ether.

As further evidence of an anionic intermediate, the colored solution due to the reaction of 1 was irradiated with appropriate filters to isolate the long wavelength absorption band (runs 10, 11, 12, and 13). For the first time significant amounts of 4 now appeared and up to 10% of 4 in the cyclized products could be obtained by extended irradiation at -78° . The relative amount of 4 obtained was temperature dependent and by -20° the thermal cyclization of the anionic intermediate was sufficiently facile to exclude significant photochemical reaction. As reported in runs 15 and 16, both 2 and 4 are largely unaffected by irradiation under these conditions.

In summary, the reactions with phenyllithium suggest that the cyclization of 1 to 2 can occur through a carbanionic intermediate whose concentration is never large. This intermediate is formed by proton abstraction and can be trapped by protonation or irradiation. These results are summarized in Scheme 2.

Reactions with Methanol-Methoxide

A study of the reactions of 1 and substituted-1 in methanol-potassium methoxide (0.02-0.2 M) mostly at 60° was made primarily in an attempt to further characterize any intermediates in the 1 to 2 conversion. As shown in Scheme 3, 3 was now observed as well as 2 and, as indicated by runs 17, 18, 19, 20, 21, and 22 of Table 2, 3 and 2 were produced in similar amounts although the ratio did depend upon the substituent.

The reaction proved to be first order in 1 over the range of concentrations studied, and as runs 18, 19, and 20 show both the ratio of 3 to 2 and the second order rate constant were reproducible within experimental error. From runs 17, 22 and runs 24 and 25 of Table 3, it is clear that electron-withdrawing substituents



SCHEME 3

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		Substrate		<i></i>			Р	roducts %	
Run	Nature	Concentration (M)	Solvent	Base concentration (M)	<i>T</i> (°C)	(min)	1	3 §	2
24	p-CN-1	0.008	CH ₁ OH	0.02	27	5	<0.5	< 0.5	100
25	p-CN-1	0.007	CHJOH	0.39*	24	30	40	< 0.5	60
26	· 1	0.13	CHJOD	0.19	60	15	59†	12	29
27	1	0.13	CHJOD	0.19	60	45	25	21	54
28	1	0.13	CHJOD	0.19	60	65	18	23	59
29	1	0.10	CHJOD	0.25	60	60	5	28‡	67
30	3	0.20	CHJOD	0.25	60	6870	<0.5	70±	30
31	3	0.19	CHJOD	0.25	60	11235	<0.5	70±	30
32	3-d¶	0.17	CHJOH	0.22	60	1715	<0.5	87±	13
33	3-d¶	0.14	CHJOH	0.22	60	3110	<0.5	84İ	16
34	3-d¶	0.15	CHJOH	0.22	60	4610	< 0.5	78‡	22
35	p-CH ₃ -1	0.08	CH ₃ OD	0.25	60	180	26†	27	47
36	p-CH ₃ -1	0.08	CHJOD	0.25	60	420	< 0.5	31	69

TABLE 3. Reactions in methanol and methanol-O-d with potassium methoxide

*Triethylenediamine was the added base.

p-Cl-1

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I rethylenediamine was the added base.
 †Contained <0.05 atoms D/molecule at the methine position (HA-100 n.m.r.).
 ‡N-Benzylbenzamidine obtained upon hydrolysis contained, for run 29, 0.86 atoms D/molecule; run 30, 0.08 atoms D/molecule; run 31, 0.10 atoms D/molecule; run 32, 0.65 atoms D/molecule; run 33, 0.64 atoms D/molecule; run 34, 0.62 atoms D/molecule by mass spectral analysis.
 §For those reactions of 1 in CH₃OD, the percentage of 3 was calculated from n.m.r. assuming 0.84 atoms D/molecule.
 [|Products showed for run 32, 65% d₁; for run 33, 66% d₁; and for run 34, 65% d₁ by mass spectral analysis.
 §Istarting material showed 77% d₁ by mass spectral analysis.

0.25

60

45

14†

CH₃OD

0.07

have an accelerating effect upon the rate of reaction. Using the data of runs 17-22 and σ values, a ρ of 3.8 is calculated for the trisubstituted molecule.

Treatment of 3 under the reaction conditions results in production of 2 but at a rate about 600 times slower than 1. Thus for most reactions of 1 reported here, any 3 produced should not react further to any significant extent.

By analogy with the extensive studies on allylic, pentadienyl (7), and particularly the azallylic systems (8), the conversion of 1 to 3must certainly involve an intermediate carbanion. The behavior of this intermediate was investigated using methanol-O-d and these results are included in Table 3. Of particular interest are runs 29, 35, and 37, for analysis of the recovered 1 for deuterium incorporation showed no observable uptake (<0.05 atom D/molecule) at >40% conversion. When 3 was analyzed for deuterium (run 29), only 0.86 atoms D/molecule were present showing that the isomerization had occurred with a low degree of intramolecularity (9). These results are consistent with an anionic intermediate(s)

Can. J. Chem. Downloaded from www.nrcresearchpress.com by 209.172.228.248 on 11/24/14 For personal use only. which protonates preferentially at the end carbon to yield 3 over 1. Once formed, 3 returns to the anion considerably more slowly as evidenced by slow deuterium uptake and cyclization (runs 30 and 31). Thus the reaction of 1 can be studied under conditions where the products 2 and 3 are not significantly reactive.

Reaction Schemes 4 and 5

One of the mechanisms considered, Scheme 4, has 1 lead only into a carbanion or carbanions which competitively reprotonate or cyclize. Since reprotonation (k_{-2}) should be occurring with rate constants of about 10^6 s^{-1} or greater in methanol (10), this scheme requires the cyclization rate constant (k_{-3}) to also be of this order of magnitude. This is several orders of magnitude greater than the rate constants which have been observed for electrocyclizations of other carbanions (*e.g.* heptatrienyl-lithium, $10^{-3} \text{ s}^{-1} \text{ at } -30^{\circ}(11)$; cyclooctadienyl-potassium or -lithium, 10^{-5} s^{-1} at $30^{\circ}(12)$; and pentadienyl not at all (13)) and thus the second mechanism was considered carefully.

In Scheme 5, the carbanions serve merely to



interconnect 1 and 3, and 2 arises from 1 not through an intermediate but a transition state. Thus possibly certain conformations of 1 would be more appropriate for cyclization with a bonding interaction across the 1 and 5 carbons occurring as the methine proton is being abstracted.

In an attempt to differentiate between these seemingly feasible mechanisms, the following results were obtained and analyzed.

Substituent Effects on the 3/2 Ratio

As the results of runs 17-22 and 25^1 indicate. the ratio of 3/2 depends upon the substituents in a systematic fashion with the more electronwithdrawing substituents resulting in a lower 3 to 2 ratio. Considering Scheme 5 first, the rate constants that determine the 3 to 2 ratio are k_3 and k_5 . It would seem unlikely that both k_3 and k_5 would respond to the same degree to changes in the substituent. Delocalization at the 1, 3, and 5 positions should stabilize the full charge that is developing in the anion more than in the transition state leading to 2 which has bonding developing across the terminal carbons. Thus this scheme would predict that the 3 to 2 ratio should increase with more electron-withdrawing groups contrary to the observation.

In Scheme 4, the ratio of 3 to 2 is determined by k_{-2} and k_{-3} . How k_{-3} would respond to substituent is uncertain but it does not seem unreasonable that k_{-2} would decrease as the anion becomes more stabilized. Thus Scheme 4 does not seem inconsistent with the observations and the substituent effects favor the mechanism in which both the prototropy and cyclization proceed through carbanionic intermediates (Scheme 4).

Solvent Isotope Effect on the 3/2 Ratio

As summarized in Table 4, when methanol is replaced by methanol-O-d, the ratio 3/2drops by about a factor of 2 for p-CH₃-1, 1, and p-Cl-1. Returning to Scheme 5, the ratio of 3 to 2 is determined by k_3 and k_5 of which neither should be directly affected by the solvent isotope. In Scheme 4, k_{-2} and k_{-3} are the important kinetic parameters and while the solvent is not directly involved in k_{-3} , the step which determines k_{-2} is reprotonation in which the OH or OD bond of solvent is being broken. In going from CH₃OH to CH₃OD, k_{-2} should

¹As run 24 indicates, p-CN-1 is so reactive that triethylenediamine was used as base. Controls were not run on p-CN-3 but presumably it is still less reactive than p-CN-1.

TABLE 4.Ratio of 3/2 obtained in methanol and
methanol-O-d at 60°

Runs	Substrate	Solvent	3/2
17	<i>p</i> -CH ₃ -1	CH ₃ OH	1.2
35, 36	p-CH ₃ -1	CHJOD	0.5
18-20	1	CHJOH	0.8
26-29	1	CH ₃ OD	0.4
22	p-Cl-1	CHOH	0.5
37	p-Cl-1	CH ₃ OD	0.3

be reduced to the extent of the primary isotope effect. Thus Scheme 4 is consistent with the results of Table 4 and a solvent isotope effect of about 2 is observed.

Effect of Methanol Concentration on the 3/2 Ratio

In a further attempt to distinguish between Schemes 4 and 5, the effect of diluting the methanol solvent with dimethylsulfoxide was observed and these results are collected in Table 5. As can be seen from runs 20, 38, 39, and 40, as the percentage of dimethylsulfoxide is increased from zero to 80 weight %, the ratio 3/2 drops to about zero. Runs 41 and 42 demonstrate that with 80 weight % dimethylsulfoxide, 3 is being rapidly converted to 2 but at a rate sufficiently slow to indicate that in run 40, the amount of 3 produced must still be quite small.

The effect of added dimethylsulfoxide in methanol should be twofold: the concentration of methanol is reduced and also the $\Delta p K_a$ between the methanol and substrate should be reduced, resulting in a reduced rate of reprotonation (10). Applying this reasoning to Scheme 5 where k_3 and k_5 are product determining suggests that both should be increased similarly by the enhanced basicity of the methoxide. However, in Scheme 4, while k_{-3} should be unaffected, k_{-2} should be systematically reduced as dimethylsulfoxide is introduced.

Again the experimental results are in accord with Scheme 4. Important, however, is the observation that 2 is produced to the exclusion of 4 and thus, any anionic intermediates generated must find their way to 2 alone.

Exchange and Cyclization of 3

If Scheme 4 is obeyed and there is a common anionic intermediate for cyclization and reprotonation, then the same k_{-2} and k_{-3} should be observed starting from either 1 or 3. Since $k_{-1} < k_{-2}$, k_{-3} , the ratio k_{-2}/k_{-3} can be

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TABLE 5. Reactions in CH₃OH-CH₃SOCH₃-CH₃OK at 60°

		Substrate	Colorado Colorado	Dene		Produc	ts
Run	Nature	Concentration (M)	weight % DMSO*	concentration (M)	Time (min)	% Substrate	3/2
50	-	0.067	0	0.097		 +	0.75 ± 0.05
38	1	0.073	25	0.097		++	0.55 ± 0.05
39	1	0.04	50	0.067		Ś	0.3 ± 0.05
40	1	0.04	80	0.030	8	<0.5	<0.5
41	e	0.03	80	0.030	5	0 9	
42	e	0.03	80	0.030	15	33	
*Sol †Alic ‡Alic §Alic	utions were 0 quots were re quots were re quots were re ruots were re rage ratio is	(5-1.0 M in THF. moved at 14, 27, 39, 46, and moved at 25, 40, 61, and 83 moved at 57 and 97% reacti reported.	1 55% reaction. % reaction. on.				

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calculated directly from the 3/2 ratio when 1 is the reactant. When 3 is the reactant k_{-2}/k_{-3} must be estimated from the rate of exchange of 3 relative to the rate of cyclization. The details of this calculation are included in the Appendix but in essence the results of runs 30 and 31 where 3 was reacted in CH₃OD were used to calculate the k_{-2}/k_{-3} ratio.

Beginning with 1 in CH₃OD, the k_{-2}/k_{-3} ratio is 0.4 and with 3 as substrate the ratio is 0.3 \pm 0.1. The agreement is sufficiently good to again support Scheme 4. Scheme 5 is not inconsistent with these results but would require the fortuitous equality $k_3/k_5 = k_4/k_6$.

Carbanion Geometries

Having apparently established that Scheme 4 best represents the reactions of 1, it is interesting to consider the possible character of the anionic intermediate or intermediates. Three basic skeletal geometries are available to a near planar carbanion, U, W and sickle, and each of these is shown in Scheme 6 with the phenyls arranged to give the most stable form.

If orbital symmetry restraints (14) are dominant, any concerted cyclization should occur in a disrotatory manner. Thus since only 2 is produced, the 'sickle' shape would not be the intermediate responsible for cyclization since it should lead to 4. This leaves the U and W shapes as candidates. While the U-shaped carbanion would seem to be ideal for cyclization, the W-shaped anion is undoubtedly much more favored energetically and should be formed in great preference to the U shape.

Whatever anion is generated in methanol, its lifetime must be quite short ($< 10^{-6}$ s) since reprotonation must be rapid (10). This brings into doubt the likelihood of geometric interconversions occurring prior to cyclization if the configurationally stable carbanions phenylallyllithium (15), 1-phenylbutenylpotassium (16), and pentadienyllithium (13) can be used as analogies. Life-times for rotational isomers in these molecules are of the order of $10^2 - 10^{-2}$ s near room temperature; considerably longer than the 10^{-8} s which might be needed to interconvert the W- and U-shaped anions. However, the rotational barrier around the 2,3bond in this system might well be lower² since the two isolated parts are relatively stable.

²As emphasized by a referee.



A second factor bears on the question of initial formation of the thermodynamically more stable W-shaped carbanion followed by conversion to the U-shaped carbanion which cyclizes. The pathways from the W-shaped anion to the U-shaped anion or from the sickleshaped anion to the U-shaped anion and from the U-shaped anion to the cyclized product were analyzed using molecular models. It is apparent that the energy surfaces for these processes cross and that the W-shaped anion or sickle-shaped anion could be diverted to cyclized products before reaching the U-shaped species.

Thus consideration of the possible geometries leads to the conclusion that the W-shaped anion is the one produced and rapid cyclization occurs either directly from this form or perhaps with prior conversion to the 'sickle' and then the U shape.

A complicating feature of direct cyclization from either the W or sickle shape is the recognition that the one or both nitrogen atoms rotate through 180° during the cyclization process. Orbital symmetry selects an initial disrotatory motion but if 1,5-bonding has not progressed to an important extent by the time the π -system is destroyed, symmetry rules need no longer apply. The possible involvement of a lone pair on nitrogen might complicate this simple picture.

Ion-pairing

Carbanions of different selectivity in their relative rates of cyclization and reprotonation are possible if ion pairs and dissociated carbanions were both being generated. In order to test whether the counterion might be affecting the relative amounts of cyclization and repro-

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tonation, two experiments were run. In runs 18, 19, and 20 the base concentration was varied by a factor of 2.4 and resulted in no change in the ratio 3/2. In run 21, the potassium ion was complexed with dibenzo-18-crown-6-ether (17) and again no change in 3/2 was observed. Again one carbanion is favored for both reprotonation and cyclization.

Reactivity of the Intermediate

If as has been considered above, the W-shaped anion is responsible for cyclization then the rate for this process must be high and the barrier to deformation must be low. In fact as discussed before, the barrier must be considerably lower than that observed for rotation around partial double bonds in other delocalized carbanions. The factor responsible for enhanced rotation in this system might well be thermodynamic, for rotational interconversions in phenylallyllithium and related compounds lead to products of the same or similar energy. The cyclization reaction of the carbanionic intermediate from 1 is undoubtedly highly exothermic. As a result 1,5-bonding interaction might account for the reduced barrier to cyclization.

Isotope Effects on Protonation and Deprotonation

The conversion of 1 to 2 and 3 provides one of the few opportunities to estimate a solvent isotope effect on the protonation of a shortlived carbanion in protic solvent. As was shown in Table 4 and discussed in the Solvent Isotope Effect section, the change in the ratio 3/2 should directly measure the primary isotope effect on k_{-2} . Within the accuracy of the 3/2ratio a $k_{\rm H}/k_{\rm D}$ of 2 ± 0.3 is observed.

The primary isotope effect for the conversion of 3 to carbanion has also been estimated from the results of runs 32, 33, and 34 of Table 3 (Appendix) and is $k_{\rm H}/k_{\rm D}$ is ≥ 5 . In summary then the primary deuterium kinetic isotope effect on k_2 is ≥ 5 and on k_{-2} is 2.³

Experimental

Solvents and Bases

Phenyllithium in tetrahydrofuran (THF) was prepared (19) as 0.7-0.8 M solutions. Methanol-O-d (0.99 atoms D/molecule) as analyzed by n.m.r. was prepared from dimethyl carbonate (20). Methanol was dried (<0.001 M in H₂O) and purified by distillation from magnesium (21). Dimethyl sulfoxide was distilled from lithium amide onto Molecular Sieves (freshly baked 4A). Tetrahydrofuran was freshly distilled from lithium aluminum hydride before use (<0.001 M in H₂O). The n.m.r. spectra were obtained in chloroform-d with TMS internal standard. Potassium methoxide in methanol (methanol-O-d) was prepared by reaction of freshly cleaned potassium with the alcohol and was stored under an argon atmosphere (<0.001 M in H₂O). All solvents and base solutions were analyzed for water using an Aquatest automatic Karl-Fisher titrator.

Compounds

The preparation and characterization of the substituted 1, 2, 3, and 4 are to be found in the preceding paper (4).

Isomerization with Phenyllithium

To a degassed solution of 1 (0.1-0.05 M) in THF under an argon atmosphere at the indicated temperature was added dropwise the THF solution of phenyllithium. The characteristic blue color formed on addition of the first drop of base to the stirred solution. After complete addition ($\sim 2 \min$) the reaction mixture was stirred for the time indicated and then quenched by adding ~ 1.1 equiv of a 10 volume % solution of acetic acid in THF.

The THF was removed with a rotary evaporator and the residue worked-up with ether-water, extracting the ether layer twice with water. Drying and solvent evaporation yielded the crude reaction mixture. Products were analyzed by n.m.r. and t.l.c.

Samples for irradiation were treated in a similar manner, except the reactions were run in a cell with provision for cooling. A Hanovia 1000 W high pressure mercury lamp was used for irradiation. The long wavelength absorption band was isolated using a soft glass plate for primary filtering and either a Corning glass filter (type 2-62) or a combination of solution filters (cupric chloride and potassium dichromate (22)).

Isomerization and Exchange with Methanol-Methoxide

To the stirred, degassed methanol – potassium methoxide solution held at a constant temperature and under an argon atmosphere was added a THF solution of the substrate. The resulting solutions were $2-4 \mod \%$ in THF. At the time indicated, aliquots were removed and treated with ether-water. The ether layer was washed twice with water, dried, and solvent evaporated. The residual oils were analyzed by n.m.r. and t.l.c.

Mixtures of 2 and 3 could be separated by multiple extraction of 2 from the ether solution using 1 M potassium dihydrogen phosphate solution.

Samples of 3 were converted to N-benzoyl-N'-benzylbenzamidines for isotopic analysis by mass spectrometry. The procedure involved basic hydrolysis of 3 to N-benzylbenzamidine by treatment of the reaction mixture or isolated 3 with excess water. The N-benzylbenzamidine could be extracted from ether using saturated sodium bicar-

³The authors wish to thank R. D. Guthrie, University of Kentucky, for providing a preprint of electron-transfer results which also yielded a primary deuterium kinetic isotope for reprotonation of a carbanion. For the anion of 9-methoxyfluorene in methanol at 30° , $k_H/k_D = 5.3$. Although the reasons for the difference between the two systems are not established there may be a solvent isotope effect on the cyclization reaction.

bonate. The aqueous layer was made basic with 6 N sodium hydroxide and extracted with ether. After washing, drying, and solvent removal the N-benzylbenzamidine was isolated. This product was reacted with 1 equiv of benzoyl chloride in benzene. Ether, saturated sodium bicarbonate, and water were used for extraction. The product was recrystallized from (1:1) benzene-hexane (m.p. 139-142°).

Analytical Procedures

The composition of mixtures of the hydrobenzamides, amarines, and N-benzylidene-N-benzylbenzamidines was normally determined by n.m.r. from the average of five integrations of the benzyl protons of each molecule. The complicating N—H protons were exchanged for deuterons where necessary.

Deuterium analyses of the isolated products or their derivatives were by mass spectrometry (Varian M-66) under conditions where P-1 peaks were absent. Usually the average of three scans of maximum scale expansion was obtained. In some cases n.m.r. integration was used for deuterium analysis again with maximum scale expansion.

The authors wish to thank the National Research Council of Canada for their financial assistance.

Appendix

Calculation of the ratio k_{-2}/k_{-3} of Scheme 4 using 3 as the substrate requires three separate pieces of evidence.

(a) Intramolecularity

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Since 1 can be converted to 3 in CH_3OD without complete exchange occurring (run 29), the use of hydrogen-deuterium exchange as a quantitative measure of carbanion formation probably results in an underestimation of the extent of carbanion formation. One simplifying assumption is that the observed 14% intramolecularity (run 29) is a feature common to the carbanion whether formed from 1 or 3. Thus in the following calculations it was assumed that exchange measured only 86% of the reacted material.

(b) Kinetic Deuterium Isotope Effect

In order to estimate the primary kinetic deuterium isotope effect, a sample of monodeuterio-3 was employed (runs 32, 33, and 34) which had been isolated from a run similar to run 29. By deuterium analysis of the 2 generated at low conversion, the isotope effect could be estimated (see Scheme 7).

As expected the isolated 2 contained primarily d_1 material, but to make a more accurate determination of the isotope effect, it was necessary to correct for the fact that the



starting material (3) was only 77% d_1 and its composition changed to 66% d_1 during the reaction. This correction was applied crudely as follows: To obtain 2 of the observed isotopic composition (~65% d_1) from 3 of the composition of the starting material, an isotope effect of about 5 would be required; 3 of the composition observed at the end of the reaction (~66% d_1) would require a very large isotope effect. Thus the actual isotope effect is described as $k_{\rm H}/k_{\rm D} > 5$.

(c) Relative Rates of Exchange and Cyclization

The method employed to estimate k_{-2}/k_{-3} used the results of runs 30 and 31 to compare the relative amounts of cyclization and exchange. The results were fit to a scheme which allowed for the isotope effect and the further reaction of exchanged 3. The technique is essentially that employed in an earlier study (18) and will not be described further. A ratio of 0.3 ± 0.1 for k_{-2}/k_{-3} fit the data best and proved to be insensitive to isotope effect.

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