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Direct ESR Evidence for Sodium Selective, Intramolecular Ion Pairing in Redox-Switched Nitrogen-Pivot Lariat Ethers

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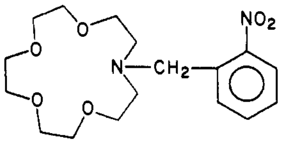
Abstract: *N*-(2-Nitrobenzyl)aza-15-crown-5, **1**, and the sidearm hexadeuterio analogue **2** have been reduced electrochemically to their corresponding radical anion forms and analyzed by ESR. Addition of Li^+, Na^+, or K^+ to the solutions leads to changes in the ESR spectra but the changes are most marked when Na^+ is present Essentially no change is observed in the ESR spectrum of 2-nitrotoluene, confirming that both macroring and sidearm must be involved for the intramolecular ion pair to be stable. The radical anion sidearm complexes must be relatively rigid species since the strongest sidearm interaction is observed with Na^+ cation which is closest in size to the cavity formed by the cooperating macroring and sidearm.

The binding of metallic and organic cations by a variety of macrocycles and macropolycycles is an increasingly important and well-studied phenomenon.[1] Our special interest in this area has been the chemistry of compounds we call lariat ethers:[2] macrocycles containing pendant sidearm-bearing functional groups. Such structures exhibit enhanced cation binding due to cooperativity between sidearm and macroring.[3] This enhancement can be further increased by altering some property of the system such as the charge state of the sidearm. Examples of this approach include photochemical processes,[4] changes in pH,[5] chemical reduction,[6] and electrochemical reduction.[3] The latter studies have generally involved cyclic voltammetry to quantify the overall binding enhancement observed upon reduction.

Spectroscopic characterization of such phenomena has been limited to two examples, one involving primarily ENDOR[7] and the other utilizing ESR.[8] The reducible species in these cases were quinone residues, and metal splittings between 0.28 and 1.74 G were observed. We report here a detailed, quantitative ESR study of the interaction between *N*-(2-nitrobenzyl)aza-15-crown-5 and Li^+, Na^+, and K^+ which demonstrates Na^+ cation selectivity and metal splittings far larger than anything previously reported for such species.

Results and Discussion

Syntheses. Aza-15-crown-5 was obtained in 98% yield[9] by hydrogenolysis (H_2, Pd–C, trace HCl) of *N*-benzylaza-15-crown-5. The latter was prepared (46% yield) as previously described[9] by the reaction of *N*-benzyldiethanolamine with triethylene glycol ditosylate in the presence of NaH/THF. Aza-15-crown-5 was then alkylated by 2-nitrobenzyl chloride (Na_2CO_3, CH_3CN, reflux) to afford *N*-(2-nitrobenzyl)aza-15-crown-5, **1**, in 96% yield.



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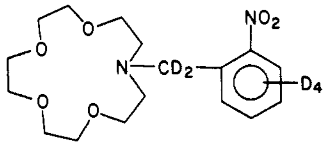

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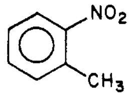

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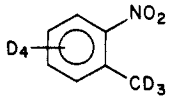

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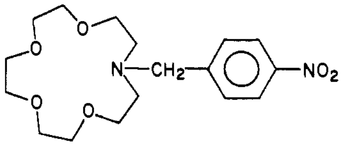

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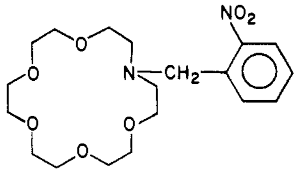

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The hexadeuterio analogue of **1**, i.e., **2**, was prepared in a similar fashion. Perdeuteriotoluene was nitrated[10] (HNO_3, HOAc, EtOAc) to afford a mixture of 2- (**4**) and 4-nitrotoluene-d_7 in a total yield of 42%. Bromination (NBS, CCl_4) afforded perdeuterio-2- and 4-nitrobenzyl bromides (50%). The bromide mixture was allowed to react with aza-15-crown-5 as described above. The lariat ether mixture was separated by column chromatography (alumina). Hexadeuterio crown **2** was obtained in 36% yield and was characterized by comparison with the all protio compound. 2-Nitrotoluene, **3**, was obtained commercially. Its perdeuterio analogue was obtained by nitration of toluene-d_7 (Merck Stable Isotopes). Nitro-crowns **5** and **6** were obtained in analogy to the synthesis of **1** from either aza-15-crown-5[9] or aza-18-crown-6.[11]

ESR Measurements. ESR spectra were recorded on MeCN solutions of **1**–**6** using tetra-*n*-butylammonium perchlorate as supporting electrolyte. Radicals were generated by using controlled-potential electrolysis directly in the ESR cavity. Spectra were recorded at 25 °C in the absence, and then in the presence,

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Table I. Table of Coupling Constant Values[a]

compd no.	metal[c]	NO_2	coupling constants[b]							line width
			M^+	A_N	A_2	A_3	A_4	A_5	A_6	
1	none	10.90		0.63	3.27	1.12	3.83	1.12	3.27	0.15
1	Na^+	12.40	2.50	1.40	1.30	1.00	3.95	1.00	3.18	0.40
2	none	10.85								2.12
2	Li^+	11.21								4.85
2	Na^+	12.40	2.45	1.45						1.70
2	K^+	11.10								2.21
3	none	10.87			3.14	1.08	3.90	1.08	3.14	0.20
4	none	10.95								2.0
4	Li^+	10.98								4.70
4	Na^+	11.04								2.13
4	K^+	11.08								2.10
5	none	10.90		0.63	3.27	1.12	3.85	1.12	3.27	0.15
5	Na^+	11.50								0.83
5	K^+	11.82								2.40

[a] All values in G. [b] The subscripts in $A_{\text{subscript}}$ refer to positions on the benzene ring; 2 is ortho to the nitro group, etc. [c] As the perchlorate.

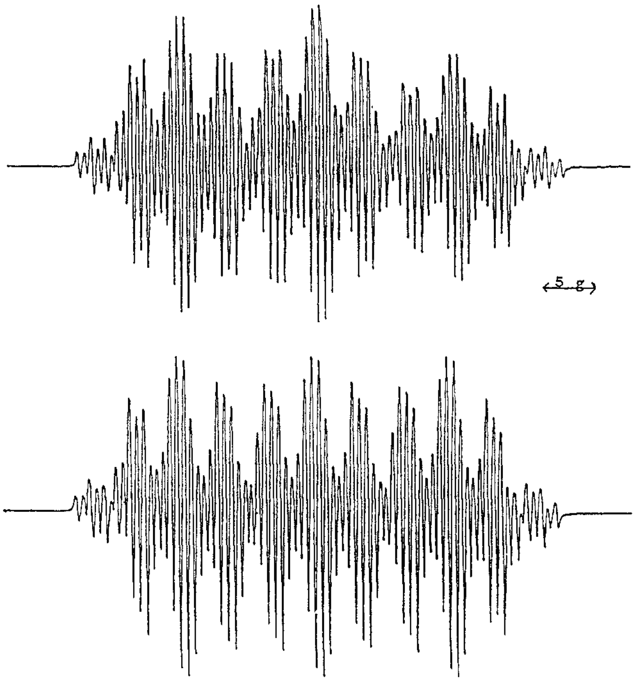

Figure 1. Experimental (A) and simulated (B) ESR spectra of anion radical **1** in MeCN solution.

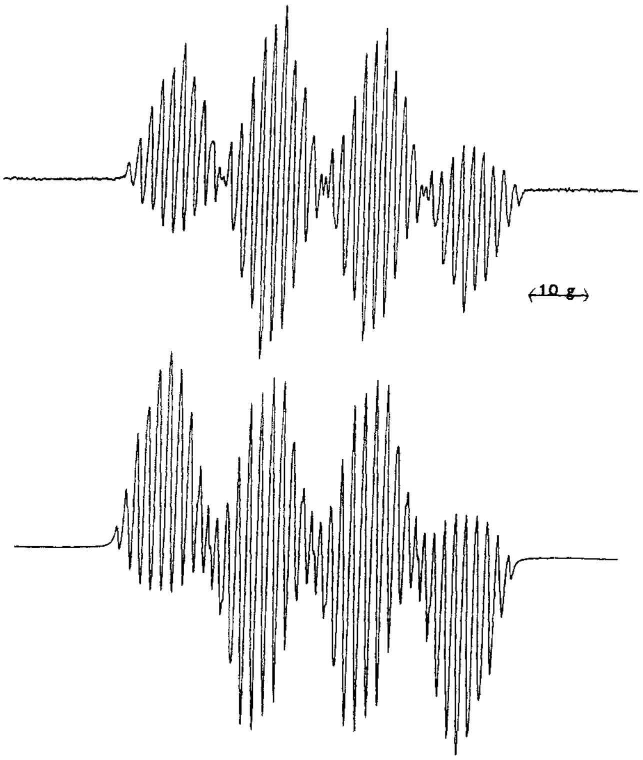

Figure 2. Experimental (A) and simulated (B) ESR spectra of anion radical **1** in MeCN solution in the presence of 1 equiv of $NaClO_4$.

of an added equivalent of the metal (Li^+, Na^+, or K^+) perchlorate salt. Spectral simulations were accomplished as described in the Experimental Section.

The experimentally observed ESR spectrum of *N*-(2-nitrobenzyl)aza-15-crown-5 (**1**) is shown in Figure 1A. The simulation shown in Figure **1B** was obtained by using the following coupling constants: A_{nitro}, 10.90 G; $A_{\text{ring-N}}$, 0.63 G; A_{2H}, 1.12 G; A_{3H}, 3.27 G; A_{1H}, 3.83 G (see Table I: subscripts here refer to number of equivalent hydrogens). The line width was 0.15 G. The agreement between the experimental and simulated spectra is excellent except for the slight asymmetry observed in the high field lines. This is because the simulation program does not incorporate g-tensor anisotropic effects.

The coupling constant values obtained are nearly identical with those reported in the literature for the model compound, 2-nitrotoluene (**3**).[12] The macroring does not appreciably influence the ESR spectrum in the absence of a cation. The most notable difference between the ESR spectra of **1** and **3** is the appearance in the former of a β nitrogen coupling (0.63 G). To our knowledge, this is the first observation of such a β nitrogen coupling in nitroaromatic systems.

Results. The ESR spectra of **1** were recorded in the presence of 1 equiv of $LiClO_4$, $NaClO_4$, or $KClO_4$. When either Li^+ or K^+ cations were present, no significant changes in the spectra were apparent. In contrast, when Na^+ was present, the dramatic changes shown in Figure 2 were observed. Our best simulation (Figure 2B) of the experimental spectrum (Figure 2A) is not perfect although the agreement is generally excellent. It (Figure 2B) was obtained by using the coupling constants shown in Table I. The imperfect simulation is caused by the complexity of the problem: seven different coupling constants must be simultaneously varied in the calculation. One important thing which is obvious from this work is that no reasonable simulation can be obtained without including a super-hyperfine splitting due to the sodium nucleus.

A comparison of the ESR spectra for **1** and the model compound, 2-nitrotoluene, **3**, shows clearly that both sidearm and ring must be present for a cation effect to be observed. Further evidence of this is obtained from the ESR study of *N*-(4-nitrobenzyl)aza-15-crown-5, **5**. When the sidearm is localized far from the macroring, no interaction with Li^+, Na^+, or K^+ cations was observed. This fact clearly demonstrates that geometry as well as the macroring presence are important for the occurrence of

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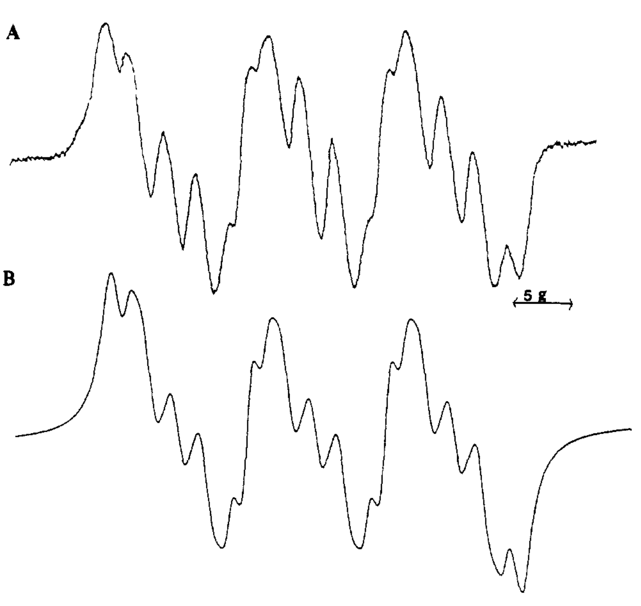

Figure 3. Experimental (A) and simulated (B) ESR spectra of anion radical **2** in MeCN solution in the presence of 1 equiv of $NaClO_4$.

this ion-pairing phenomenon. It is obvious that the interaction of **1** with sodium cation is intramolecular and that there is ring–sidearm cooperativity. Furthermore, when [2.2.1]-cryptand is added to the solution containing compound **1** and sodium cation, the ESR spectrum in the absence of cation (Figure 1A) is obtained. This reversibility is the key feature of a switch mechanism, where binding is enhanced during reduction and reverts upon oxidation. Moreover, there is clear evidence for Na^+ selectivity over either Li^+ or K^+ cations. This is especially interesting but not inconsistent with (see below) our previous observations based on cyclic voltammetry which gave an *overall* binding enhancement order of $Li^+ > Na^+ > K^+$.

In order to resolve the spectral simulation difficulty alluded to above, we prepared two deuterated analogues of **1** and **3**, compounds **2** and **4**, respectively. In the absence of any cation, the ESR spectrum of **2** simplifies to the expected triplet, with a coupling constant value of 10.85 G. It should be noted, however, that due to unresolved splittings, the line width for **2** is 2.1 G compared to a line width of 0.2 G for **1**. Addition of Li^+ or K^+ cations to **2** caused small changes in the nitro coupling constant, but line broadening is observed for Li^+. The coupling constant changes could be quantified more easily in the case of **2** than for **1** because of the simplified spectra. For the case of Li^+, A_{nitro} is 11.21 G, and the line width is 4.9 G. The corresponding values for K^+ are 11.10 and 2.21 G.

On the basis of our previous electrochemical studies, it might have been intuitively anticipated that the ESR spectral changes would follow the same decreasing trend of $Li^+ > Na^+ > K^+$. The apparent conflict can be resolved by considering that the two measurements involve very different quantities. The ESR changes caused by the presence of the metal ions come from complex formation with the crown radical anion while the electrochemical shifts result from a ratio of the binding affinities of the oxidized and reduced crowns for that metal ion. Thus the ESR experiment measures the changes in nonthermodynamic parameters such as the coupling constants for the anion radical in the absence and presence of cation. The electrochemistry measures a ratio of thermodynamic binding constants for the neutral and the charged crowns. Sodium cation could therefore form the strongest complexes with the radical anion crown without causing any shift in redox potential at all, if it forms an equally strong complex with the neutral crown. Thus, the ESR changes reflect differences in sidearm localized spin densities, while the electrochemistry reflects overall differences in ligand charge upon reduction.

As in the case of **1**, addition of Na^+ to **2** causes the largest changes in spectra (see Figure 3A). The nitro coupling constant has a value of 12.4 G, and both ring nitrogen and metal splittings are observed. The simulation shown in Figure 3B was obtained by using $A_{\text{nitro}} = 12.4$ G, $A_{\text{ring-N}} = 1.45$ G, $A_{Na^+} = 2.45$ G, and a line width of 1.7 G.

A striking feature of the spectrum shown in Figure 3A is the large metal atom splitting ($A_{NA} = 2.45$ G) which is observed, as it is for compound **1**. This shows unequivocally that there is cooperativity in cation binding between the macroring and sidearm. Although solvent dependent, it is notable that this coupling constant is the largest metal splitting yet reported for any crown ether compound. Such a value demonstrates substantial spin delocalization. In addition, the ring nitrogen splitting is considerably increased, probably due to spin delocalization through the metal cation. The absence of K^+ super-hyperfine splittings is not surprising in view of its much smaller magnetic moment.

A very interesting aspect of the present results is the Na^+ selectivity observed for **1** and **2**. In crown ether chemistry, selectivity is often accounted for in terms of a "hole-size" relationship.[13] We have shown that flexible macrocycles like 15-crown-5 and 18-crown-6 do not adhere to any such rule. Of course, less flexible ligand arrays such as those present in cryptands or spherands show clear size (geometric) relationships in their binding selectivities. Between the two extremes of "flexible" and "rigid" lie a continuum of states, and it is currently a problem to quantitatively designate a ligand's position on a line between these two extremes.

All of the evidence we have accumulated to date suggests that the neutral (uncharged) lariat ethers are quite flexible. Indeed, the neutral lariats generally exhibit the expected $K^+ > Na^+ > Li^+$ binding order which corresponds to increasing charge density on the cation. When the sidearms are reduced and become charged, the strong, combined interaction of ring and sidearm donors with the bound cation makes the system rigid compared to the neutral species. We have previously reported ^{13}C NMR T_1 measurements which show that Ca^{2+} complexation results in a rigid cryptate-like complex with *N*-[(2-methoxyethoxy)ethyl]-aza-15-crown-5.[14] A more rigid system is expected to show a greater sensitivity to geometric constraints. We therefore anticipate the Na^+ selectivity observed for **1** and **2** and predict that the 18-membered ring analogue (*N*-(2-nitrobenzyl)aza-18-crown-6, **6**) of **1** should be K^+ selective. Our experimental results were in accord with this expectation. The ESR spectrum of **6** is nearly identical with that of **1**. It is altered considerably by the presence of Na^+, but it is changed dramatically (to three broad lines) by addition of 1 equiv of $KClO_4$. The nitro coupling constant in the presence of Na^+ cations is 11.50 G and in the presence of K^+ cation is 11.82 G.

For redox active crown ethers, reduction/oxidation of the electroactive group affords a switching mechanism. By using this, it will be possible to affect the binding process as well as the selectivity offering a possibility of ion transport enhancement. The general problem of interplay between flexibility and selectivity is one we hope will yield to studies based on a combination of variable temperature cyclic voltammetry and variable temperature ESR. Such studies should permit us to assess the thermodynamic parameters which control these interactions, and appropriate experiments are currently underway in our laboratories.

Experimental Section

ESR Measurements. Solutions of **1**–**6** (10^{-3} M) in dry MeCN 0.1 M in tetra-*n*-butylammonium perchlorate were submitted to controlled potential electrolysis directly in the ESR cavity. Flat quartz cells were used, and a Hg pool served as the working electrode. The potential was controlled between −1.0 and −1.5 V by using a Hewlett-Packard model 6200B constant voltage supply. The supporting electrolyte was twice recrystallized from EtOAc, dried in a vacuum oven, and stored in a vacuum desiccator until use. The metal perchlorate salts were obtained from Alfa Inorganics, were recrystallized from aqueous ethanol, then

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dried, and stored as above. Acetonitrile (reagent grade, MCB) was distilled under vacuum from CaH_2, immediately prior to use. All spectra were recorded by using the X-band of an IBM ER-200D SRC spectrometer. Spectral simulations were done by using either the spectrometer's Aspect computer and the commercial IBM software package or an IBM PC using the simulation program developed by Stevenson and Reiter.[15]

Ligand Syntheses. Aza-15-crown-5 and aza-18-crown-6 were prepared as previously described.[9,11] 2-Nitrobenzyl chloride, 4-nitrobenzyl chloride, and *N*-bromosuccinimide were obtained from Aldrich Chemical Co. and were used without further purification. 2-Nitrotoluene (**3**) and 4-nitrotoluene were obtained from Aldrich and were distilled prior to use. Toluene-d_8 was obtained from MSD Isotopes and was used without further purification.

***N*-(2-Nitrobenzyl)aza-15-crown-5, 1.** Aza-15-crown-5 (3.03 g, 0.014 mol), Na_2CO_3 (2.91 g, 0.027 mol), MeCN (60 mL), and 2-nitrobenzyl chloride (2.70 g, 0.016 mol) were stirred at reflux for 24 h, cooled, filtered, and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (50 mL) and extracted with 6 N HCl (2 × 50 mL). The combined aqueous phases were adjusted to pH 8–10 with Na_2CO_3 and extracted with $CHCl_3$ (2 × 100 mL). The organic phases were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica gel 60, $CHCl_3$) gave 4.78 g (96%) of **1** as a yellow oil with physical properties identical with those previously reported.[3b]

***N*-(2-Nitrobenzyl)aza-15-crown-5-d_6, 2.** 2-Nitrotoluene-d_7 was prepared from toluene-d_8 (10.0 g, 0.1 mol), HNO_3, HOAc, and Ac_2O according to a literature procedure.[10] Kugelrohr distillation of the crude material (27–30 °C, 0.05 torr) gave a mixture of 2- and 4-nitrotoluene-d_7 (6.0 g, 42%). The mixture (2.0 g) was separated by column chromatography (120 g silica gel 60) to give 2-nitrotoluene-d_7, **4** (0.5 g, 3.6% total yield). The remaining material (1.5 g) was recovered after chromatography as a mixture of 2-nitrotoluene and 4-nitrotoluene.

The deuterated nitrotoluene mixture described above (2.88 g, 0.02 mol) was treated with *N*-bromosuccinimide (3.56 g, 0.02 mol) in CCl_4 according to a literature procedure.[16] A mixture of hexadeuterio-2- and hexadeuterio-4-nitrobenzyl bromides (2.21 g, 50%) was obtained by crystallization from hexanes.

The above described mixture of bromides (0.62 g, 0.028 mol) was treated with Na_2CO_3 (0.24 g, 0.046 mol) and aza-15-crown-5 (0.50 g, 0.023 mol) in MeCN (5 mL) at reflux for 24 h. The reaction mixture was cooled, filtered, and concentrated in vacuo. The mixture of 2- and 4-nitro lariat ethers was separated by chromatography (alumina, 2-PrOH/hexanes) to give **2** (36%) which was characterized as described for **1** above.

***N*-(4-Nitrobenzyl)aza-15-crown-15, 5,** was prepared from aza-15-crown-5 (3.03 g, 0.014 mol) and 4-nitrobenzyl chloride (2.39 g, 0.014 mol) as described for **1**. Column chromatography (silica gel 60, $CHCl_3$) gave 4.2 g (85%) of **5** as a yellow oil with physical properties identical with those reported.[3b]

***N*-(2-Nitrobenzyl)aza-18-crown-6, 6,** was prepared from aza-18-crown-6 (3.06 g, 0.012 mol) and 2-nitrobenzyl chloride as described for **1**. Column chromatography (silica gel 60, $CHCl_3$) gave **6** (3.9 g, 82%) as a yellow oil: ^1H NMR ($CDCl_3$, PPM) 2.73 (t, 4 H, NCH_2), 3.53 and 3.66 (t and m, 20 H, OCH_2), 3.98 (s, 2 H, benzyl), 7.3–7.9 (m, 4 H, Ar); IR (neat) 2840, 1520, 1440, 1350, 1300, 1240, 1110, 980, 940, 850, 780, 720 cm^{-1}. Anal. Calcd for $C_{19}H_{30}N_2O_7$: C, 57.26; H, 7.60; N, 7.03. Found: C, 56.96; H, 7.78; N, 7.00.

Summary

Electrochemical reduction of nitroaromatic lariat ethers leads to strong intramolecular ion pairing between the macroring bound cation and the anionic sidearm. The strength and specificity of the interaction is related to the cation radius and the cavity size. This dependence is the result of increased coulombic interaction which confers added rigidity on the complex.

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The [4 + 4] Dimerization of 2,3-Dimethylene-2,3-dihydrofuran: Secondary Deuterium Kinetic Isotope Effect Evidence for a Two-Step Mechanism[1]

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Abstract: 2,3-Dimethylene-2,3-dihydrofuran (**1a**), prepared by the flash vacuum pyrolysis of 2-methyl-3-furylmethyl benzoate (**2a**), rapidly dimerizes to form almost exclusively the [4 + 4] head-to-head dimer **3a**. Rate constants k_a, k_b, k_c, and k_d were measured at several temperatures for the dimerization, a [4 + 4] cycloaddition, of **1a**, 2-methylene-3-dideuteriomethylene-2,3-dihydrofuran (**1b**), 2-dideuteriomethylene-3-methylene-2,3-dihydrofuran (**1c**), and 2,3-bis(dideuteriomethylene)-2,3-dihydrofuran (**1d**), respectively. At −30.0 °C these rate constants in L mol^{-1} s^{-1} were found to be $k_a = 6.223 \pm 0.458 \times 10^{-4}$, $k_b = 1.147 \pm 0.087 \times 10^{-3}$, $k_c = 6.750 \pm 0.602 \times 10^{-4}$, and $k_d = 1.169 \pm 0.086 \times 10^{-3}$, which indicates that $k_a \cong k_c$ and $k_b/k_a \cong k_d/k_a = 1.86$. It was found that the [4 + 4] dimerization rate of **1a** is virtually the same in solvents ranging from 5:1 to 1:5 $CS_2/CDCl_3$, a result not consistent with the involvement of a zwitterionic intermediate. The secondary deuterium kinetic isotope effect results and the insignificant solvent effects lead to the conclusion that the [4 + 4] dimerization of **1a** proceeds via a stepwise mechanism involving a diradical intermediate. The activation enthalpy, ΔH^*, for the [4 + 4] dimerization of **1a** at 25 °C is 10.2 ± 0.3 kcal mol^{-1} and the activation entropy, ΔS^*, is −30.9 ± 1.2 entropy units.

Recently, we reported that 2,3-dimethylene-2,3-dihydrofuran (**1a**), generated by the flash vacuum pyrolysis (FVP) of 2-methyl-3-furylmethyl benzoate (**2a**), dimerizes quantitatively (>95%) to 4*H*,5*H*,9*H*,10*H*-cycloocta[1,2-*b*:6,5-*b′*]difuran (**3a**), the head-to-head, [4 + 4] dimer of **1a**.[2] As a rationalization of the formation of the high yield of **3a**, a stepwise mechanism involving diradical intermediate **4a** was proposed.[2] The dimerization of **1a** is an example of a facile, well-behaved thermal [4 + 4] cycloaddition. Cycloadditions can proceed in either a

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[2] (2) Trahanovsky, W. S.; Cassady, T. J.; Woods, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 6691.

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