Comparison of Free Energy Changes for Nitrogen Inversion and Electron Loss. 2. 8-Azabicyclo[3.2.1]octyl and 7-Azabicyclo[2.2.1]heptyl Systems

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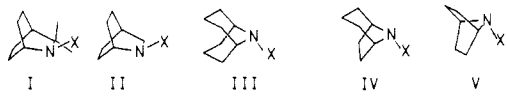
Abstract: Formal potentials for one- and two-electron oxidation of the 2-tetrazenes azo-8-azabicyclo[3.2.1]octane (**2**) and azo-7-azabicyclo[2.2.1]heptane (**11**) and hydrazine 7,7′-bi-7-azabicyclo[2.2.1]heptane (**14**) are compared with those of related compounds; **11** and **14** are especially hard to oxidize. The nitrogen inversion barrier of **11** is about 9.2 kcal/mol at −90 °C, and that for **14** is 16.6 kcal/mol at 62 °C. Comparison with literature data verifies the relationship between ease of oxidation and nitrogen inversion barrier for amino nitrogen compounds. Any special destabilization caused by orbital symmetry for the cation radicals, which is significant for cation radical center 7-methylene- and 7-oxanorbornyl units, is too small to be significant for 7-azanorbornyl-containing cation radicals.

R_2N groups that lower the nitrogen inversion barrier (eq 1) usually make electron loss (eq 2) thermodynamically easier. The reason for this parallel behavior is that a similar geometry change, flattening at the nitrogen atom, takes place during both processes.[1] If the resonance interaction between the nitrogen lone pair and X is not large, the nitrogen of neutral R_2NX is pyramidal; its lone-pair orbital has some s character. The transition state for nitrogen inversion is planar at nitrogen,[2] where the lone-pair AO has pure p character. For quantitative consideration[1a] of the relationship between eq 1 and 2, it is useful to consider Figure

(1)

(2)

1. Here the free energy of ionization has been artificially separated into two parts, that of flattening at nitrogen (the transition state for R_2NX inversion if X is cylindrically symmetrical, and hence labeled $\Delta G^{\ddagger}_{i}$) and that of a nearly vertical ionization of flat R_2NX, labeled ΔG^{*}_{e}. It is experimentally impossible to directly measure ΔG^{*}_{e}, but we suggested[1] that this energy gap should be affected by changing R groups in the same manner as vertical ionization potentials, vIP (which are enthalpies of ionization instead of free energies), which are experimentally available from photoelectron spectroscopy (PES) experiments.[3] $\Delta G^{\ddagger}_{i}$ values measured by dynamic NMR experiments were compared with changes in ΔG°_{e} measured by cyclic voltammetry (CV) for I(X)–III(X) and found to exhibit the parallel behavior expected from Figure 1. $\Delta G^{\ddagger}_{i}$ is highest for X = Cl among the X groups studied, and III(Cl) has a 6 kcal/mol higher N inversion barrier than I(Cl). The range in ΔG°_{e} is 4.6 kcal/mol for the X = Cl compounds but drops to 2.7 kcal/mol for the 2-tetrazenes [N=N linking two R_2N groups], and to 0.5 kcal/mol for the very low $\Delta G^{\ddagger}_{i}$ nitroxides [X=O•].



I II III IV V

Table I. Cyclic Voltammetry Data[a] for Some Bicyclic R_2NX Derivatives

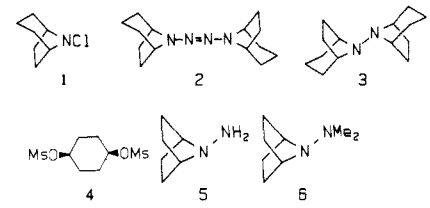
X	compd	R_2N = IV	compd	R_2N = V
Cl	**1**	E_p^{ox} 1.77	**13**	E_p^{ox} 1.93
N=NNR$_2$	**2**	0.51 [0.070]	**11**	0.83 [0.083]
		1.28 [0.065]		1.25 [0.069]
NMe$_2$		not studied	**6**	0.34 [0.070]
NR$_2$	**3**	0.13 [0.07]	**14**	0.45 [0.082]
		1.01, 1.14[b]		E_p^{ox} 1.35

[a] Reported numbers are $E^{\circ\prime}$ (average of oxidation and reduction waves observed, [peak separation, $E_p^{ox} - E_p^{red}$], V for reversible waves. Both first and second oxidation waves are reported for the dimeric hydrazines and the 2-tetrazenes. E_p^{ox} values only are reported for compounds showing only irreversible oxidation (no reduction wave observed). Conditions: acetonitrile containing 0.1 M n-Bu$_4$NClO$_4$ as supporting electrolyte, 200 mV/s scan rate, Pt electrode, reported vs SCE. [b] The cation radical has syn and anti forms, which oxidize at different potentials; see ref 6.

In this work we extend the range of bicyclic R_2N groups examined to include the CNC angle restricted 8-azabicyclo[3.2.1]octyl IV(X) and 7-azabicyclo[2.2.1]heptyl V(X) series.[4]

Results

Synthetic work in the IV series allowing preparation of **1**–**3** has been reported previously.[5] Several routes were used to prepare V derivatives. The bisalkylation of hydrazine by *cis*-1,4-cyclohexanedimesylate (**4**) via the procedure of Dervan[6] gave **5** in low yield, which was dimethylated to **6**. A slight modification of the



1 2 3

4 5 6

route of Hoesch and Dreiding[7] was later employed. Addition of "phthalimidonitrene"[7c] (generated in situ by lead tetraacetate

(1) (a) Nelsen, S. F.; Cunkle, G. T.; Gannett, P. M.; Ippoliti, J. T.; Qualy, R. J. *J. Am. Chem. Soc.* **1983**, *105*, 3119. (b) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev.* **1978**, *78*, 243.

(2) (a) Lehn, J. M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311–377. (b) Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219. (c) Lambert, J. B. *Top. Stereochem.* **1971**, *6*, 19.

(3) For discussion of alkyl group substituent and pyramidality effects on PE spectra of amino nitrogen compounds, see: (a) Nelsen, S. F. *Isr. J. Chem.* **1979**, *18*, 45. (b) Nelsen, S. F. *J. Org. Chem.* **1984**, *49*, 1891.

(4) Nelsen, S. F.; Ippoliti, J. T.; Frigo, T. B.; Petillo, P. A. *J. Am. Chem. Soc.*, in press.

(5) Nelsen, S. F.; Cunkle, G. T.; Evans, D. H.; Haller, K. J.; Kaftory, M.; Kirste, B.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 3829.

(6) We thank Prof. P. B. Dervan for private communication of the experimental details of this preparation.

(7) (a) Hoesch, L.; Dreiding, A. S. *Chemia* **1972**, *26*, 629. (b) Hoesch, L. Ph.D. Thesis, University of Zuerich, 1974. We thank Prof. Dreiding for a copy of this thesis. (c) See: Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1362 for revision of the structure of their intermediate.

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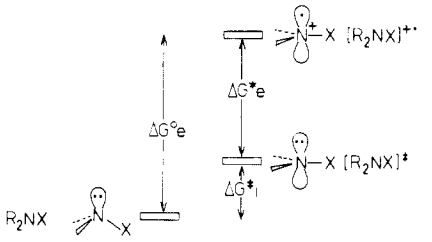
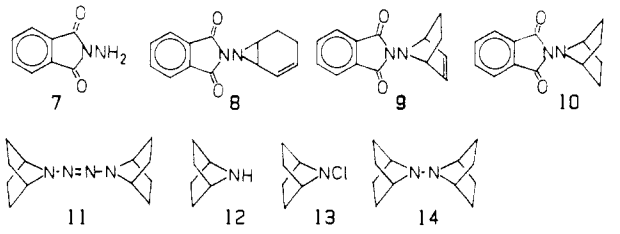


Figure 1. Diagram illustrating artificially dividing the free energy for electron loss from a pyramidal R_2NX compound, which gives a planar cation radical into a component for flattening at N and one for ionization of the planar neutral compound.

oxidation of aminophthalimide **7**) to cyclohexadiene gave vinyl aminoaziridine **8**, which was pyrolyzed to **9** and catalytically reduced to **10**. Hydrazinolysis gave **5**, which was oxidized to 2-tetrazene **11**. Conversion of **12**[8] to the chloroamine **13** and its coupling to the dimeric hydrazine **14** proceeded as well as it does with the higher homologues.[5]

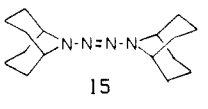


7 8 9 10 11 12 13 14

CV data for the compounds of interest are summarized in Table I.

The dimeric IV hydrazine, **3**, has an average nitrogen inversion/rotation barrier of about 12.3 kcal/mol.[6] The 50.1-MHz ^{13}C NMR spectrum of the dimeric V hydrazine **14** is frozen on the NMR timescale at room temperature, showing CH_2 peaks at δ 27.27 and 27.79 and a CH peak at δ 59.59 at 37 °C in DMSO-d_6/$CDCl_3$. The methylene peaks broaden as the temperature is raised and coalesce at 62 °C, corresponding to $\Delta G^{\ddagger}_i$ (62 °C) = 16.6 kcal/mol (employing $\kappa = 1/2$). The PE spectrum of **14** shows only a single peak at IP = 7.35 eV, which was resolved from the broad σ envelope, rising from 9.5 eV. The large separation between the bonding and antibonding lone pair MO's that the PE exhibits is consistent with **14**, like the dimeric hydrazines in the II–IV series, existing in the anti (lone pair, lone pair dihedral angle $\theta = 180°$) conformation. The ESR spectrum of $(\mathbf{14})^{\bullet+}$ shows splittings for two equivalent nitrogens of 14.52 G and for two sets of eight equivalent hydrogens that were reasonably fit by using couplings of 0.51 and 0.37 G, with a line width of 0.08 G; its g factor was 2.0031. A 2 N splitting of 14.60 G was observed in propionitrile, and no temperature variation was detected between −100 and 60 °C.

In our previous work,[1] we estimated from its $E^{\circ\prime}$ value that the 2-tetrazene in the III series, **15**, had a nitrogen inversion barrier of about 5 kcal/mol, which if true, would require that **11** have a high enough barrier to detect by dynamic NMR. This proved



15

to be the case. Its room temperature spectrum in CD_2Cl_2 shows the CH carbon at δ 58.8 and the CH_2 at δ 28.2. The methylene peak broadens at low temperture and shows coalescence at −90 °C and a partially resolved doublet with peaks at δ 26.76 and 27.05 at −93 °C, the lowest temperature at which we were able to record a spectrum. Use of the observed $\delta\nu$ of 14.6 Hz (presumably too small a frequency difference because the spectrum was not completely frozen out) gives a $\delta G^{\ddagger}_i$ value of 9.1 kcal/mol, while that

(8) (a) Fraser, R. R.; Swingle, R. B. *Can. J. Chem.* **1970**, *48*, 2065. (b) We thank Prof. J. B. Grutzner for a generous sample of $5H_2Cl$ prepared by this route by S. Thornburgh.

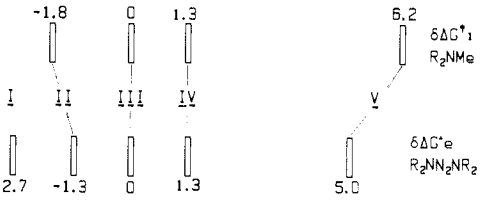


Figure 2. Changes in nitrogen inversion barrier, $\delta\Delta G^{\ddagger}_i$, for methylamines compared with half the change in electron loss thermodynamics, $\delta\Delta G^{\circ}_e$, for tetraalkyltetrazenes with R_2N groups I–V, relative to III.

calculated with the 23.9 Hz observed for the corresponding methylene carbons of frozen **14** gives $\Delta G^{\ddagger}_i$ of 9.3 kcal/mol. We conclude that nitrogen inversion is indeed being frozen out for **11**, making this the first 2-tetrazene for which this process has been observed, and that the barrier is about 9.2 ± 0.1 kcal/mol. Only a quintet splitting for two nitrogens of 12.16 G, $g = 2.0034$, was resolved in the ESR spectrum of $\mathbf{11}^{\bullet+}$ (CH_3CN/0.1 M n-Bu_4NClO_4).

Discussion

Correlation of $E^{\circ\prime}$ Values with n(eff). The parallel effects of R_2N on inversion barriers and ET thermodynamics also extend to the smaller bicyclic ring compounds investigated in this work, as is demonstrated in Figure 2. As before,[1] we compare changes in free energy relative to the azabicyclononane R_2N group III. We were unable to get free energy data for the smaller ring chloroamines; the minor conformation could not be detected for **1**, **13** decomposed too rapidly to allow measurement of its inversion barrier, and both cation radicals were too unstable to allow determination of $E^{\circ\prime}$. We therefore show the inversion barriers for the methylamines, using eq 3, and the free energy differences for Et in the tetrazenes, using eq 4, in which the difference in $E^{\circ\prime}$

$$\delta\Delta G^{\ddagger}_i = \Delta G^{\ddagger}_i(\text{obsd}) - \Delta G^{\ddagger}_i(\text{III}) \quad (3)$$

$$\delta\Delta G^{\circ}_e = 23.06[E^{\circ\prime}(\text{obsd}) - E^{\circ\prime}(\text{III})]/2 \quad (4)$$

(volts) is converted to kilocalories/mole and divided by two because two bicyclic rings are present. As Figure 1 makes evident, one cannot expect the spreads in $\Delta G^{\ddagger}_i$ and ΔG°_e to be equal, because ΔG^{*}_e is also affected by changing the alkyl groups.

In our earlier work, we had no reasonable way to estimate how ΔG^{*}_e ought to change with alkyl group substituents, nor a way of dealing with solvation energy changes in solution, where the thermodynamics of electron transfer are determined by using CV. We used the expedient of measuring ΔG°_e for bicyclic nitroxides, assuming that their $\Delta G^{\ddagger}_i$ values were negligible. We have subsequently realized that there is a more direct way of dealing with alkyl group change effects, which allows considering bicyclic, monocyclic, and acyclic alkyl groups together.[3b] Vertical ionization potentials for tetraalkylhydrazines are sensitive both to pyramidality at nitrogen and θ. These parameters are believed to be constant for n-alkyl compounds, for which the change in vertical ionization potential from that of the parent Me_4N_2, δvIP (eq 5),

$$\delta\text{vIP} = \text{vIP} - \text{vIP}(Me_4N_2) = \text{vIP} - 8.26$$

is experimentally linear with an alkyl group "inductive" parameter, n(eff). n(eff) is derived from changes in vIP caused by substituting larger alkyl groups for methyl in compounds with p hybridized lone pairs such as alkyl halides.[3b] For 18 n-alkyl hydrazines a plot of δvIP versus n(eff) is a straight line, slope −0.086 eV, with average deviation from the linear regression of 17 meV; the plot is shown as the diamonds in Figure 3. Accuracy was estimated at ±30 meV for vIP values derived from the PE experiments, so the linearity observed is excellent. Examining n(eff) values shows that one is simply counting α, β, γ, and δ carbons, with a decrease in effectiveness from the simple sum if more than one is present in a given alkyl group. n(eff) may be simply estimated for cyclic and bicyclic alkyl groups having more than one site of attachment to the heteroatom and accurately represents the experimentally observed changes in vIP for compounds that have pure p lone pairs that are ionized, such as ethers.[3b] Correlation of vIP for amino

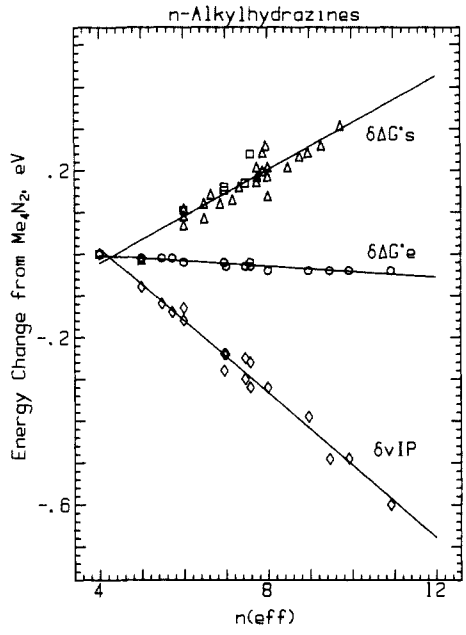


Figure 3. Plot of changes in the thermodynamics for one-electron oxidation, $\delta\Delta G°_e$, changes in vertical ionization potential, δvIP, and changes in solvation energy, $\delta\Delta G°_s$, versus the sum of the n(eff) values for the alkyl substituents for tetra-n-alkylhydrazines.

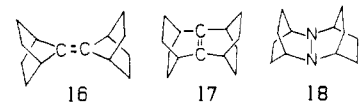
nitrogen compounds with n(eff) allows estimation of the effects of the rehybridization of the lone pair, which accompanies CNC angle restriction. The straight line obtained for δvIP of n-alkyl hydrazines in Figure 3 is experimental verification that the degree of pyramidality at N and θ remain quite constant for these 18 compounds. Changes in $E°'$ for these 18 n-alkyl hydrazines from that of Me_4N_2 are also within experimental error of being linear with n(eff) and are shown as the circles in Figure 3. Accuracy for the $E°'$ values is estimated at 10 mV, and the average deviation observed from the line shown is 4 mV, slope −0.006 eV. The larger change in vIP than in $E°'$ is clearly influenced both by the fact that one measurement is in the gas phase and the other is in solution and that one measurement is vertical and the other adiabatic.

Solvation energies for 30 tetraalkylhydrazine electron transfer equilibria have recently become available[9] through equilibrating mixtures of hydrazines and their cations in the gas phase by variable-temperature high-pressure mass spectrometry, extrapolating the gas phase numbers to room temperature, and comparing the changes in $\Delta G°_e$ in the gas phase with those in acetonitrile solution. We display these data as changes in solvent stabilization from that for the Me_4N_2 equilibrium, $\delta\Delta E°_s$ (a positive number means acetonitrile solvates the components, presumably mostly the hydrazine cation radical, less effectively than it does for Me_4N_2). Only six of the 30 compounds were n-alkylhydrazines, but the change in solvation energy from that of Me_4N_2 is described by n(eff) even for cyclic and branched alkyl groups. The squares in Figure 3 are the six n-alkyl examples (slope 0.057), and the triangles, the 24 branched and cyclic examples (slope 0.060); the line drawn is a linear regression through all 30 tetraalkyl hydrazines, slope 0.056, average deviation 20 mV. We believe this empirically establishes that the correlation of $\delta\Delta G°_s$ with n(eff) is linear within experimental error.

It is clear that the low slope of the $\delta G°_e$ line in solution is principally caused by cancellation of the decrease in vIP as the alkyl groups are lengthened by the poorer solvation of the cation radicals with larger alkyl substituents. The difference in slopes of the regression lines is −0.030 eV. We believe that this number is possibly within experimental error of the observed $\delta G°_e$ slope of −0.006 eV. The $\delta G°_s$ data were extrapolated about 150 °C by using variable-temperature measurements taken over a 100–170 °C temperature range, which we might well introduce statistical error of this magnitude. Other effects may also contribute, however.

From these data, we suggest that vertical deviations of $E°'$ from the n-alkyl line in plots of $E°'$ versus n(eff) ought to represent changes in the ease of electron removal caused by geometrical effects imposed by the alkyl groups, effectively eliminating solvation and "inductive" vIP effects.

Inversion Barriers and Oxidation Potentials. Hoffmann, Mollere, and Heilbronner[10] showed that 7-oxa- and 7-methylenenorbornane are unusually difficult to ionize in the gas phase and assigned this effect as caused by orbital symmetry. The highest several σ MO's of the boat cyclohexane portion of the norbornyl framework have the wrong symmetry to interact with a p orbital centered at position 7. This lack of mixing destabilizes species in which the π orbital at position 7 is not filled because the filled σ orbitals are less stabilized than is "normal". We found that 7,7'-binorbornylidene (**16**) has an $E°'$ 9.2 kcal/mol higher than that of its isomer **17**, showing that there is a substantial destabilization of 7-norbornyl cations in solution as well as in the gas phase.[11] If **16** is about 9 kcal/mol harder to oxidize than **17** because of norbonyl group orbital symmetry, how large is this effect for the diaza analogue of **16**, **14**$^{\bullet+}$? The diaza analogue of **17** is the sesquibicyclic hydrazine **18**, which is 22.6 kcal/mol easier to oxidize than **14**. Despite this large difference in ease



16 17 18

of oxidation, it is not clear that any of it is caused by orbital symmetry effects. The olefinic carbon atoms are probably planar in both **16** and **17**, and little if any pyramidalization is expected to occur upon electron removal. In contrast, substantial changes in the amount of pyramidality at the nitrogen atoms upon electron loss occur for the hydrazines. Steric interaction between the dimethylene bridges of neutral **18** (α(av) 112.8° by crystallography;[12] AM1 calculations[13] give[14] 113.9) is relieved in the flatter cation radical (α(av) 118.3° by X-ray; 118.1 by AM1 calculation); **14** and **3** have similar conformations for their neutral forms and cation radicals and less exagerated strain differences between them. The difference in $\Delta G^{\ddagger}_i$ for **14** and **3** is about 4.8 kcal/mol (at 20 °C, using $\Delta S^{\ddagger}$ of 5 eu), which is close to the 4.9 kcal/mol difference for the corresponding N-methylamines[4] (see Figure 2). An increased inversion barrier for hydrazines, which have a second nitrogen lone pair adjacent to the inverting nitrogen was not seen (a large increase is observed in 6-membered ring hydrazines when the second nitrogen's lone pair is at 180° to that of the inverting nitrogen[15]), but the dihedral angle of the lone pairs at the transition state for N inversion is not known for these structures; **14**$^{\bullet+}$ is doubtless slightly more pyramidal at N than is **3**$^{\bullet+}$; AM1 calculations predict α(av) at 115.5° for **14**$^{\bullet+}$, and 116.6° for **3**$^{\bullet+}$ (X-ray α(av) is 115.6°[6]) and the ESR N splitting constants (which increase as pyramidality increases) are 14.52 and 13.73 G, re-

(9) (a) Nelsen, S. F.; Rumack, D. T.; Meot-Ner (Mautner), M. *J. Am. Chem. Soc.*, in press. (b) Structures of the n-alkylhydrazines (squares in Figure 3): $Me_2N)_2$, EtMeN)$_2$, n-PrMeN)$_2$, n-PeMeN)$_2$, n-Pr_2NNMe$_2$. Structures of the branched acrylic hydrazines: i-BuMeN)$_2$, noePeMeN)$_2$, t-BuMeNNMe$_2$, i-Pr_2NNMe$_2$. Structures of the N,N-cyclic hydrazines = $(CH_2)_n$NNMe$_2$ (n = 3–7), $(CH_2)_4$NN$(CH_2)_4$, $(CH_2)_5$NN$(CH_2)_5$, $(CH_2)_5$N-N$(CH_2)_4$. Structures of the NN'-cyclic compound: 1,2-dimethylpyrazolidine; 1,2-dimethylhexahydropyridazine, *cis*-1,2,3,6-tetramethylhexahydropyridazine, 1,2,3,3,6,6-hexamethylhexahydropyridazine, 1,2-dimethyl-1,2-diazacycloheptane; 1,5-diazabicyclo[3.3.0]octane, 3,3,7,7-tetramethyl-1,5-diazabicyclo-[3.3.0]octane, 1,6-diazabicyclo[4.4.0]decane, 2,3-dimethyl-2,3-diazabicyclo-[2.2.1]heptane; 2,3-dimethyl-2,3-diazabicyclo[2.2.2]octane, *anti*-diazasesquinorbornane.

(10) Hoffmann, R.; Mollere, P. D., Heilbronner, E. *J. Am. Chem. Soc.* **1973**, *95*, 4860.

(11) Nelsen, S. F.; Kapp, D. L. *J. Org. Chem.* **1985**, *50*, 1339.

(12) Nelsen, S. F.; Blackstock, S. C.; Haller, K. J. *Tetrahedron* **1986**, *42*, 6101.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healey, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(14) Nelsen, S. F.; Frigo, T. B.; Kim, Y.; Thompson-Colon, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 7926.

(15) Nelsen, S. F. *Acc. Chem. Res.* **1978**, *11*, 14.

Table II. Deviations from the *n*-Alkyl Line for Mono- and Bicyclic Tetraalkyl-2-tetrazenes [$R_2NN{=}NNR_2$] (kcal/mol)

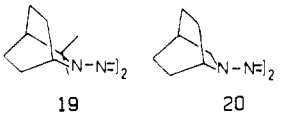
R_2N	Dev[a]	R_2N	compd	Dev[a]
$(CH_2)_3N$	+2.1	I	19	−1.1
$(CH_2)_4N$	−0.3	II	20	−0.4
$(CH_2)_5N$	+1.6	III	15	+1.3
$(CH_2)_6N$	−0.5	IV	2	+2.4
$(CH_2)_7N$	−1.3	V	11	+5.9

[a] Linear regression through *n*-alkyl compounds, $E^{\circ\prime}$(reg) = −0.0177*n*(eff) + 0.527; Dev = [23.06($E^{\circ\prime}$ − $E^{\circ\prime}$(reg)]/2.

spectively. We would therefore expect the pyramidality contribution to their ease of oxidation to be smaller than the 4.8 kcal/mol difference in their $\Delta G^{\ddagger}_i$ values. $\delta\Delta G^{\circ}_e$ for **14** is 4.0, and it is −3.3 for **3**. This 7.3 kcal/mol energy difference would correspond to approximately a 3.65 kcal/mol barrier difference at each nitrogen if complete flattening were occurring. We see no evidence from this comparison for detectable special destabilization of $\mathbf{14}^{\bullet+}$ relative to $\mathbf{3}^{\bullet+}$. If $\mathbf{16}^{\bullet+}$ is so clearly destabilized relative to other tetraalkyl olefin cation radicals of similar substitution, why do we not see a similar effect for $\mathbf{14}^{\bullet+}$ relative to other hydrazine cation radicals? One factor is that the pyramidality at N in $\mathbf{14}^{\bullet+}$ makes the symmetry factor inhibiting upper σ orbital mixing with the lone pair electrons less important than it is for $\mathbf{16}^{\bullet+}$. A second factor that will decrease destabilization of $\mathbf{14}^{\bullet+}$ is less efficient lone pair, σ orbital mixing for hydrazine cation radicals compared to those from olefins because the energy gap between the singly occupied MO of a hydrazine and the σ orbitals of its substituents will be substantially higher than that for those of a olefin.

Consideration of the relationship between ease of oxidation and inversion barrier is considerably easier for 2-tetrazenes than it is for hydrazines because of their geometry differences.[1] The amino nitrogen lone pairs are expected to be at a 0° dihedral angle with the azo π bond in both oxidation states, and nonbonded steric interactions between the R_2N groups should not change substantially when the NN bond length and pyramidality change, as they certainly do in hydrazines. We show a plot of $E^{\circ\prime}$ versus *n*(eff) for tetraalkyl-2-tetrazenes as Figure 4 and will discuss the deviations from the line for the *n*-alkyl compounds shown. The six *n*-alkyl compounds examined (R_2N = Me_2N, EtMeN, *n*-BuMeN, Et_2N, *n*-Pr_2N, and *n*-Bu_2N) give a linear correlation with *n*(eff), average deviation 5 mV, encouraging us to believe that deviations from this line are caused by energy differences resulting from the flattening that occurs upon electron removal, as discussed above. Because there are two R_2N groups that flatten upon electron removal, we have divided the deviation in $E^{\circ\prime}$ by two in converting it to Dev (see Table II). Dev values for the monocyclic compounds (diamonds in Figure 4) do not differ significantly from those previously discussed.[16] We note that the Dev values might be expected to represent nitrogen inversion barriers (maintaining lone pair, π overlap) for the neutral 2-tetrazenes relative to that of tetramethyl-2-tetrazene. Although this barrier has not been measured, we believe that the Dev values of Table II are internally quite consistent with the 9.2 kcal/mol inversion barrier measured for **11**. The total span in Dev for Table II is 7.2 kcal/mol, and if Dev represents 2-tetrazene nitrogen inversion barrier, this is entirely reasonable. Dev is 4.6 kcal/mol higher for **11** than for its bicyclo[3.3.1]nonyl (III) analogue **15**, for which we previously estimated a nitrogen inversion barrier on the order of 5 kcal/mol.[1]

The filled squares in Figure 4 are the second $E^{\circ\prime}$ values for the protected 2-tetrazenes **19**, **15**, **2**, and **11**, the only ones that show reversible second oxidation waves. There is no evidence in these



19 20

data for a specific, orbital symmetry caused destabilization of even

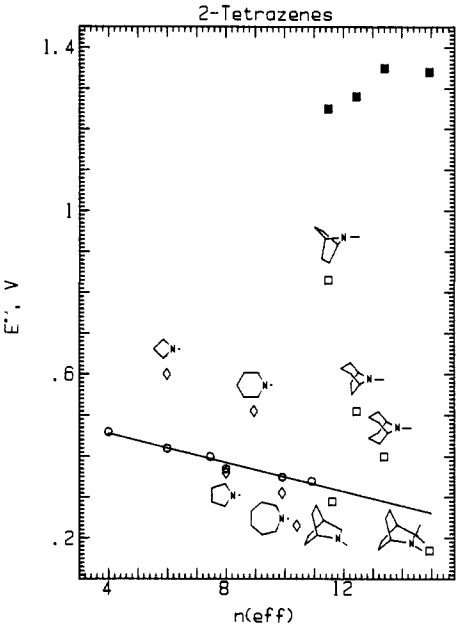


Figure 4. Plot of formal oxidation potentials, $E^{\circ\prime}$ versus *n*(eff) for some tetraalkyl-2-tetrazene. The line shown is a linear regression through the *n*-alkyl compounds (circles). the diamonds show cyclic R_2N-substituted compounds, and the squares, bicyclic R_2N-substituted ones. The filled squares are for the second oxidation.

the dication in the V series, $\mathbf{11}^{\bullet 2+}$; $E^{\circ\prime}_2$ for **11** is the lowest of the series. The nitrogens of 2-tetrazene cation radicals are presumably quite close to being planar. There may be is some pyramidality left, because the ESR nitrogen splitting constant of $\mathbf{11}^{\bullet+}$ is 12.16 G, and that of $\mathbf{15}^{\bullet+}$, 11.1 G. Tetramethyl-2-tetrazene cation radical has a value of 10.93 G.[17] This implies greater average pyramidality for the smaller CNC compounds but not necessarily a nonplanar energy minimum structure. We doubt that the nitrogen inversion barrier for 2-tetrazene cation radicals could be very large. AM1 calculations, which obtain a nitrogen inversion barrier for neutral **11** of 7.8 kcal/mol (compared with the observed value of 9.2 kcal/mol) get planar nitrogens even for $\mathbf{11}^{\bullet+}$.

The difference in formal potentials for second and first electron removal, $E^{\circ\prime}_2 - E^{\circ\prime}_1$, decreases greatly in the series **19**, **15**, **2**, and **11** (values are 1.17, 0.95, 0.77, and 0.42 V, a range of 17.3 kcal/mol). From Figure 4, the principal factor involved in lowering the difference in oxidation potentials is an increase in $E^{\circ\prime}_1$ as the CNC angle is restricted. If all of the pyramidality change at nitrogen occurred in the first electron transfer, steric differences as the NN bonds shortened were unimportant, and solvation differences as the alkyl groups were changed were also unimportant, the changes in the difference in $E^{\circ\prime}$ for the two oxidations would be twice the difference in $\Delta G^{\ddagger}_i$ for the neutral hydrazine. The observed values only roughly correspond to this behavior.

Conclusions

The difficult oxidation seen for V derivatives relative to R_2NX derivatives having less restricted CNC angles is caused by the increase in nitrogen inversion barrier for 7-azabicyclo[2.2.1]nonyl group. We were unable to detect a special destabilization for cation radicals containing the V R_2N group in the $E^{\circ\prime}$ values observed, or even for the 2-tetrazenes dication. Compound **11** has a nitrogen inversion barrier of about 9.2 kcal/mol by dynamic NMR and is the first 2-tetrazene for which nitrogen inversion has been frozen out.

Experimental Section

Azo-8-azabicyclo[3.2.1]heptane (2). A solution of 0.87 g of 8-nitroso-8-azabicyclo[3.2.1]heptane[5] in 25 mL of ether was added dropwise to a slurry of 0.75 g of LAH in 15 mL of ether over 2 h, the mixture

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was refluxed for 3 h, stirred at room temperature for 24 h, and quenched with 0.75 mL of H_2O, 0.75 mL of 15% NaOH, and 2.25 mL of H_2O. After the salts were washed with ether and dried over $MgSO_4$, the ether solution was cooled to 0 °C and treated with 0.5 mL of diethylamine, and a solution of 1.60 g of I_2 in ether was added dropwise until the yellow color persisted (about 90% of the solution was added). After filtration, washing with 50 mL of 10% $Na_2S_2O_3$ and 50 mL of H_2O, drying with $MgSO_4$, and concentration gave 0.52 g (68%) of **2** as a white solid, mp 103-106 °C. Empirical formula ($C_{14}H_{24}N_4$) was established by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 4.14 (br s, 4 H), 2.10-1.20 (m, 20 H); ^{13}C NMR δ 58.2 (d), 30.0 (t), 26.7 (t), 17.2 (t).

7-(Dimethylamino)-7-azabicyclo[2.2.1]heptane (6) was obtained in low yield by reductive methylation[18] of **5** prepared by the method of Dervan[6] and purified by preparative VPC. Empirical formula ($C_8H_{16}N_2$) was established by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 3.1 (m, 2 H), 2.5 (s, 6 H), 1.72-2.08 (m), 1.16-1.44 (m).

7-Phthalimido-7-azabicyclo[4.1.0]hept-2-ene (8) was prepared by the method of Hoesch.[7b] A slurry of 10.0 g (61.7 mmol) of *N*-aminophthalimide (7), 14.85 g (185 mmol) of 1,3-cyclohexadiene, 34.3 g (248 mmol) of K_2CO_3, and 30 mL of methylene chloride was mechanically stirred in a 250-mL three-necked flask while 25 g (185 mmol) of freshly recrystallized $Pb(OAc)_4$ was added in spatula-tip portions over 1.75 h. Methylene chloride was added as necessary to keep the slurry stirring. After 0.5 h of further stirring, the slurry was filtered, washed with methylene chloride, and stripped to a yellow residue. Filtration of a chloroform solution of this material through an alumina plug helps clean up later steps and gave 14.8 g of crude material. Recrystallization (hexane) gives a light yellow powder: mp 39-40 °C; ^1H NMR ($CDCl_3$) δ 7.75 (m, 2 H), 7.60 (m, 2 H), 6.25 (m, 1 H), 5.9 (m, 1 H), 3.15 (m, 1 H), 2.9 (q, 1 H), 2.4-2.65 (m, 1 H), 2.0-2.3 (m, 2 H), 1.6-1.8 (m, 1 H).

7-Phthalimido-7-azabicyclo[2.2.1]hept-2-ene (9).[7b] A mixture of 12.0 g of unrecrystallized **8** from the above reaction (50 mmol) was refluxed in 250 mL of xylene under N_2 for 48 h and stripped to a residue containing 10-20% **4**, 40-50% **8**, and 10-20% *n*-phthalimidopyrrole by ^1H NMR spectroscopy. Chromatography on a 500 × 7.5 cm column of preparative silica gel (60 PF) in CH_2Cl_2 separated **9**, which was recrystallized from hexane at -78 °C to give material melting at 118-122 °C: ^1H NMR ($CDCl_3$) δ 7.7-7.8 (m, 2 H), 7.6-7.7 (m, 2 H), 6.15 (t, 2 H), 4.95 (br s, 2 H), 2.0 (d, 2 H), 1.15 (q, 2 H).

7-Phthalimido-7-azabicyclo[2.2.1]heptane (10). Hydrogenation of 0.94 g (3.9 mmol) of **9** in 50 mL of ethyl acetate over 1.55 g of 5% $Pd/BaCO_3$ at atmospheric pressure took 1.5 h to take up the theoretical amount of H_2. After filtration, solvent removal gave 0.95 g of crude material, which was crystallized from hexane to give 0.67 g of bright yellow **10**: mp 102-104 °C; ^1H NMR ($CDCl_3$) δ 7.7-7.8 (m, 2 H), 7.6-7.7 (m, 2 H), 4.75 (t, 2 H), 1.8-2.0 (m, 4 H), 1.4 (m, 4 H).

Azo-7-azabicyclo[2.2.1]heptane (11). A mixture of 0.424 g (1.75 mmol) of **10** and 6 mL of hydrazine hydrate was stirred at room temperature. Solution of **10** occurred after 5 min, and after stirring an additional 10 min, the mixture was extracted with 4 × 10-mL portions of ether, and the ether was dried over NaOH pellets and stripped to give 0.095 g (48%) of **5** as a semisolid. This material was cooled to 0 °C in 5 mL of ether, treated with an excess of ethylamine, and stirred while 0.216 g (0.851 mmol) of I_2 in 10 mL of ether was added dropwise over 1.5 h. The mixture was filtered, washed with 15 mL of 10% $Na_2S_2O_3$, 15 mL of H_2O, dried over K_2CO_3, and concentrated to a solid residue, which was crystallized from acetonitrile to give 0.080 g (43%) of **11**. Empirical formula ($C_{12}H_{20}N_4$) was established by high-resolution mass spectroscopy: ^1H NMR (CD_3CN) δ 3.95 (br s, 4 H), 1.55 (m, 8 H), 1.30 (d, 8 H); ^{13}C NMR (CD_3CN) δ 58.91, 28.41.

7-Chloro-7-azabicyclo[2.2.1]heptane (13). The method of Coleman[19] was used to convert 0.50 g (3.7 mmol) of **12**·HCl[8] to 0.41 g (83%) of **13**, obtained as a yellow oil after Kugelrohr distillation. Empirical formula ($C_6H_{10}ClN$) was eastablished by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 3.68 (m, 2 H), 2.05-2.47 (m, 4 H), 1.24-2.08 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 67.57 (d), 27.99 (t), 27.27 (t).

7,7'-bi-7-azabicyclo[2.2.1]heptane (14). A 1.9 M *tert*-butyllithium solution (1.25 mL, 2.35 mmol) was added dropwise to a solution of 0.309 g (2.35 mmol) of **13** in 10 mL of dry THF at -78 °C. After being stirred for 1 h at -78 °C, the solution was allowed to warm to room temperature over 22 h. Concentration and Kugelrohr distillation gave 0.24 g of residue, which was sublimed at 3 Torr (80 °C bath temperture) to give 0.15 g (66%) of **14**, mp 111.5-112 °C. Empirical formula ($C_{12}H_{20}N_2$) was established by high-resolution mass spectroscopy: ^1H NMR ($CDCl_3$) δ 3.23 (m, 4 H), 1.92-2.28 (m, 4 H), 1.48-1.84 (m, 4 H), 1.10-1.36 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 60.79 (d), 28.27 (t), 27.93 (t).

Electrochemistry was done as previously described,[16] and low-temperature ^{13}C NMR experiments employed a JEOL FX-200 instrument. AM1 calculations were carried out on a VAX-8600, by using QCPE 506.

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Calixarenes. 22. Synthesis, Properties, and Metal Complexation of Aminocalixarenes

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Abstract: Calix[4]arene (**2**), readily accessible from *p-tert*-butylcalix[4]arene (**1**), is shown to react smoothly with formaldehyde and secondary amines to yield Mannich bases (**3**), which can be converted to the corresponding quaternary salts (**4**). Treatment of the quaternary salt with 2 equiv of a nucleophile (the first equivalent acting as a base) yields a para substituted calix[4]arene via a putative calixarene *p*-quinone methide intermediate. By means of this sequence of reactions a variety of functionalized calixarenes (**6**) have been prepared, including those carrying CN, OCH_3, N_3, SEt, $CH(CO_2Et)_2$, $CH(NO_2)CO_2Et$, and imidazolyl functions. Of particular interest are *p*-(2-aminoethyl)calix[4]arene (**7b**), obtained by reduction of *p*-(cyanomethyl)calix[4]arene (**6a**), and the amino calixarenes obtained directly from the Mannich reaction. On the basis of NMR, IR, and UV measurements, the aminocalixarenes are shown to exist as zwitterions in polar organic solvents and as aminophenols in nonpolar solvents. The interaction of the *p*-bromobenzenesulfonate of *p*-(2-aminoethyl)calix[4]arene (**11**) with several metal ions, including Ni^{2+}, Cu^{2+}, Pd^{2+}, Co^{2+}, and Fe^{2+}, has been investigated. The spectral and chemical characteristics of these complexes are interpreted as indicating that **11** is more flexible than had been anticipated, behaving more like four independent ethylamine moieties than a single trialkylenetetramine moiety.

Synthesis of Functionalized Calixarenes: the *p*-Quinone Methide Route. Calixarenes are cavity-containing macrocyclic compounds that have attracted our interest because of their potential for forming host-guest complexes and, if appropriately functionalized,

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