Acknowledgment. We wish to thank the Wisconsin Alumni Research Foundation, the National Science Foundation, and the National Institutes of Health for support of this work.

References and Notes

(1) For some alternative approaches, see (a) P. Barbier and R. Locquin, *C. R. Acad. Sci.*, **156**, 1443 (1913); (b) H. Wieland, *Z. Physiol. Chem.*, **161**, 80 (1926); (c) C. Meystre, H. Frey, A. Wettstein, and K. Miescher, *Helv. Chim. Acta*, **27**, 1815 (1944); (d) W. M. Hoehn and H. L. Mason, *J. Am. Chem. Soc.*, **60**, 1493 (1938); (e) G. Lehman, L. Koppe, and G. Hilgetag, *J. Prakt. Chem.*, **32**, 217 (1966); (f) J. Meinwald, A. Lewis, and P. G. Gassman, *J. Am. Chem. Soc.*, **84**, 977 (1962); (g) Y. Yanuka, R. Katz, and S. Sarel, *Tetrahedron Lett.*, 1725 (1968); (h) Y. Yanuka, R. Katz, and S. Sarel, *Chem. Commun.*, 851 (1968); (i) M. Fetizon, F. J. Kakis, and V. Ignatiadow-Ragoussis, *J. Org. Chem.*, **38**, 1732 (1973); (j) N. L. Allinger, T. J. Walter, and M. G. Newton, *J. Am. Chem. Soc.*, **96**, 4588 (1974).

(2) (a) L. F. Fieser and M. Fieser, "Steroids", Reinhold New York, N.Y., 1959; (b) E. H. Rodd, "Chemistry of Carbon Compounds", Vol. Ic, Elsevier, Amsterdam, 1965, p 129.

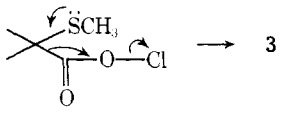
(3) For related work see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *J. Am. Chem. Soc.*, **96**, 5261 (1974); D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 121 (1972); E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Am. Chem. Soc.*, **93**, 4326 (1971); P. S. Wharton and B. T. Aw, *J. Org. Chem.*, **31**, 3787 (1966); P. K. Freeman, D. M. Balls, and D. J. Brown, *ibid.*, **33**, 2211 (1968); J. Paasivirta and H. Krieger, *Suom. Kemstilehti B*, **38**, 182 (1965); J. Paasivirta, *Suom. Kemstilehti A*, **39**, 120 (1966); H. Krieger and S. E. Masar, *ibid.*, **39**, 119 (1966); P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956).

(4) For a related independent study for conversion of nitriles to ketones see D. S. Watt, *J. Org. Chem.*, **39**, 2799 (1974); S. J. Sellkson and D. S. Watt, *Tetrahedron Lett.*, 3029 (1974). This method is limited to aryl substituted systems.

(5) P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972); P. L. Creger, *ibid.*, **37**, 1907 (1972).

(6) (a) B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973); (b) B. M. Trost, K. Hiroi, and S. Kurozumi, *Ibid.*, **97**, 438 (1975); (c) B. M. Trost and T. N. Salzmann, *J. Org. Chem.*, **40**, 148 (1975).

(7) The fragmentation of i also could form the intermediate **3**. This reaction



i

can be considered analogous to the decarboxylative elimination of β-halo acids. For leading references see H. E. Zaugg, *Org. React.*, **8**, 305 (1954).

(8) The use of thallium salts in the alkylation or catalysts in the Diels–Alder reactions are precluded by this approach. See E. J. Corey, U. Koelliker, and J. Neuffer, *J. Am. Chem. Soc.*, **93**, 1489 (1971).

(9) Camille and Henry Dreyfus Teacher Scholar Grant Recipient.

Barry M. Trost,*[9] Yoshinao Tamaru

Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received January 20, 1975

Electrochemical Detection of Conformational Equilibria in Tetraalkylhydrazines

Sir:

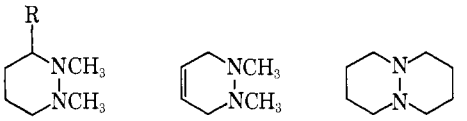
The potential at which electrochemical oxidation or reduction of a compound occurs is controlled by the E^0, rate of the heterogeneous electron transfer reaction, the rates of chemical reactions of the reactant preceding electron transfer, and rates of reactions of the product following electron transfer. Structural effects on observed oxidation/reduction potentials can appear through all of these factors. In particular, heterogeneous electron transfer rates have been discussed in terms of conformational and solvation changes accompanying electron transfer.[1] When it is considered, however, that different conformations of reactant species will often exist, and that these conformations could have different E^0 values and electron transfer rates, it seems possible that different electrochemistry for different conformations might be detectable.

Table I. Cyclic Voltammetry Data[a] for Hydrazines **1–4**

Compound	Temp (°C)	Scan rate (mV/sec)	E_p^{ox} (mV)	E_p^{red} (mV)	ΔE_p (mV)	$E_p^{ox'}$ (mV)
1	+23	100	352	273	79	unobsd
	−47	20	336	240	96	*a*
	−47	50	*a*	228		503
	−47	200	*a*	197		550
	−72	100	*a*	106		738
2	+23	100	372	292	80	unobsd
	−85	50	363	195	168	*a*
	−85	100	389	173	216	*a*
	−85	200	423	138	285	640
3	+23	100	468	380	88	unobsd
	−55	20	440	334	106	*a*
	−55	50	467	330	137	(ca. 700)
	−55	200	*a*	298		774
	−85	200	*a*	217		907
4	+23	100	418	341	77	unobsd
	−65	50	483	250	233	unobsd
	−65	200	578	205	373	unobsd

[a] Distortion due to this wave is apparent, but a clear maximum was not observed.

A variety of tetraalkylhydrazines show electrochemically reversible (or nearly reversible) oxidation at room temperature.[2] We have discovered that lowering the temperature allows the detection of two separate oxidation peaks by slow scan cyclic voltammetry (cv) in some cases. The cv of the six-ring hydrazines **1–4**, which illustrate this phenomenon, are discussed here.

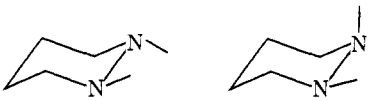


1, R = CH_3 3 4

2, R = H

When **1–3** were oxidized at a gold electrode in butyronitrile (an excellent low temperature electrochemical solvent[3]), they showed nearly reversible behavior[4] (Table I). At −47°, 20 mV/sec scan rate, for **1**, in addition to the wave observed at room temperature,[5] distortion was apparent at higher potential (Figure 1b), and at faster scan rates this grew into a clearly resolved peak (Figure 1c), designated as $E_p^{ox'}$ in Table I. At the faster scan rates, the first peak (E_p^{ox}) had greatly decreased in size, and $E_p^{ox'}$ had shifted to significantly higher values. Dimethylhexahydropyridazine (**2**) showed similar behavior, although appearance of distortion for the $E_p^{ox'}$ peak only became apparent at lower temperatures, and the $E_p^{ox'}$ peak remained clearly smaller than the E_p^{ox} peak, even at low temperatures and fast scan rates. Dimethyltetrahydropyridazine (**3**) showed behavior qualitatively similar to **1**, the E_p^{ox} peak becoming far smaller than the $E_p^{ox'}$ peak at fast scan rates and low temperatures. In contrast, diazadecalin **4** showed no sign of an $E_p^{ox'}$ wave at any temperature or scan rate.

These effects were all completely reversible, disappearing when the temperature was raised. We suggest that the only plausible cause for observing the $E_p^{ox'}$ peak is that a more difficultly oxidizable conformation of **1–3** is being oxidized at low temperature and/or fast scan rates than under slow passage, room temperature conditions. Different conformations must show different electrochemical behavior. We suggest that the conformations responsible for E_p^{ox} and $E_p^{ox'}$ may be assigned to ee and ae respectively,[6] on the



ee ae

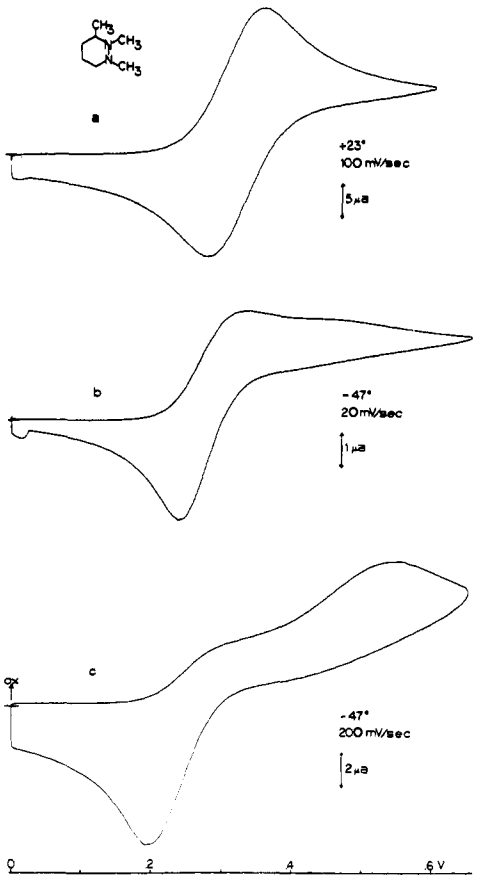


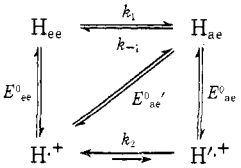
Figure 1. Cyclic voltammetry curves for 1,2,3-trimethylhexahydropyridazine (**1**), illustrating the appearance of the $E_p^{ox'}$ peak at low temperature, and its movement to higher potential at faster scan rates.

basis of the relative sizes of these waves at low temperature and fast scan rate.

Both **1** and **3** exist nearly exclusively in ae conformations, as has been shown by low temperature ^{13}C NMR[7] for **1**, and by proton NMR and dipole moment studies for **3**[8] (although the ee conformation of **1** is clearly not as high in energy as that of **3**, since it is easily observable as a minor contributor to the room temperature photoelectron spectrum of **1**[9]). The reason, then, that E_p^{ox} decreases in relative size at low temperature and fast scan rate is that the more easily oxidized ee conformation(s) are no longer being populated rapidly compared to the scan rate. For **2**, ee predominates over ae, as has been shown by low temperature ^{13}C NMR;[10] the E_p^{ox} peak remains larger than the $E_p^{ox'}$ peak even at low temperature and fast scan rate. Since hydrazine **4** exists completely in the ee conformation,[9] no $E_p^{ox'}$ wave is expected; none was observed.

The simplest kinetic schemes which will account for these data are shown in Scheme I, where H_{ee} and H_{ae} are the two

Scheme I. Six-Ring Hydrazine Redox Pathways



electrochemically different conformations of the hydrazine (H). A different heterogeneous electron transfer constant (k_s) and α value would characterize each electrochemical step. The major question to be answered is whether H_{ae} oxidizes directly to the stablest form of the radical cation (designated $H^{\cdot+}$ in Scheme I), or whether it gives a twisted radical cation closer in geometry to that of H_{ae} (designated $H'^{\cdot+}$ in Scheme I). If the oxidation were to $H'^{\cdot+}$ (the vertical oxidation labeled E^0_{ae} in Scheme I), E^0_{ae} could differ significantly from E^0_{ee}. INDO calculations on tetramethylhydrazine[11] held in a conformation resembling ee (lone pair–lone pair dihedral angle θ large, near 180° [9]) gave the energy of the highest occupied molecular orbital about 0.3 eV higher than that of the conformation resembling ae ($\theta \sim 55°$).[9] Since a higher energy should correspond to easier oxidation, this result would agree with the experimental observation of a higher oxidation peak potential for H_{ae} than H_{ee}. No reduction wave corresponding to the $E_p^{ox'}$ wave was observed; if $H'^{\cdot+}$ is formed, it must rapidly relax to the stable form of the radical cation $H^{\cdot+}$, which has been established by ESR studies[12] to have the two "lone pair" orbital axes nearly coplanar.[13] Alternatively, H_{ae} might oxidize directly to $H^{\cdot+}$, as is shown in the diagonal equilibrium $E^0_{ae'}$ of Scheme I. If this were the case, E^0_{ae} would have to be very close to E^0_{ee} for **1** and **2**, since the ee and ae forms are quite similar in free energy. Then the observation of the $E_p^{ox'}$ peak at a significantly higher potential than the E_p^{ox} peak would indicate slower electron transfer for H_{ae} to give $H^{\cdot+}$ than for H_{ee} to give $H^{\cdot+}$. Such a result is also plausible because of the large change in geometry which must occur upon removal of an electron from H_{ae} ($\theta \sim 55°$) to give $H^{\cdot+}$ (θ near 0 and 180° nearly equal in energy[13]), compared to electron removal from H_{ee} (θ near 180°). It is not yet possible to determine which type of pathway is being followed, but we hope to return to this interesting question in the future.

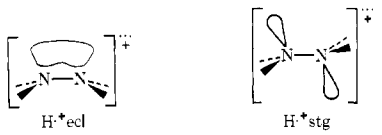
Different peak potentials for different conformations could very well be general for compounds which have more than one conformation available, since rotation about a single bond will quite generally change the amount of functional group interaction. An oxidation or reduction might well proceed from a conformation which is almost completely unpopulated in the neutral form, as is the case for **3**. Scheme I allows (and indeed, requires) a direct connection between electrochemical measurements and conformational changes in the neutral form. The 10 kcal/mol barrier between **2ee** and **2ae**[8] was largely frozen out at −85°, 200 mV/sec. Low temperature cyclic voltammetry seems to be a promising method for detecting conformational equilibria. Experiments and data treatment techniques designed to elucidate the rates and equilibria of Scheme I, and extend these studies to other systems, are in progress.

Acknowledgments. We thank the National Science Foundation and the Wisconsin Alumni Research Foundation for financial support of this work.

References and Notes

(1) J. M. Hale in "Reactions of Molecules at Electrodes," N. S. Hush, Ed., Wiley-Interscience, New York, N.Y., 1971, Chapter 4, p 229–258.
(2) S. F. Nelson and P. J. Hintz, *J. Am. Chem. Soc.*, **94**, 7108 (1972).
(3) R. P. Van Duyne and C. N. Reilley, *Anal. Chem.*, **44**, 142 (1972).
(4) PAR 170 instrument, at a planar gold electrode which was cleaned by polishing, in butyronitrile containing 0.05 *M* tetrabutylammonium perchlorate. All potentials are reported vs. SCE. Part of the increase of ΔE_p beyond the 57 mV expected for a completely electrochemically reversible reaction (at room temperature) is due to instrumental factors.
(5) A slight drop in $E_{1/2}$ is expected upon lowering the temperature.[3]
(6) For **3**, which exists in a half-chair instead of a chair conformation, pseudo-ee and pseudo-ae.
(7) G. R. Weisman and S. F. Nelsen, unpublished results.
(8) (a) J. E. Anderson, *J. Am. Chem. Soc.*, **91**, 6374 (1969); (b) R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J. Chem. Soc., Perkin Trans.*, **2**, 406 (1974).
(9) S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.*, **96**, 6987 (1974).
(10) S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.*, **96**, 7111 (1974).
(11) S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.*, **96**, 6982 (1974).
(12) S. F. Nelsen, G. R. Weisman, P. J. Hintz, D. Olp, and M. R. Fahey, *J. Am. Chem. Soc.*, **96**, 2916 (1974).
(13) Tetraalkylhydrazine radical cations were concluded to be slightly non-

planar, and eclipsed at the alkyl groups (see H·⁺ecl), although the staggered form (H·⁺stg) is not very much higher in energy, because "double nitrogen inversion" in H·⁺ecl, which presumably goes through H·⁺stg form as an intermediate, has a very low activation energy.[12] Twisting about the "three electron π bond" to move θ very far from 0 or 180° is costly in energy.



H·⁺ecl H·⁺stg

S. F. Nelsen,* L. Echegoyen, D. H. Evans
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706
Received March 3, 1975

Oligonucleotide Synthesis Catalyzed by the Zn^{2+} Ion

Sir:

Adenosine 5′-phosphorimidazolide (ImpA) is an activated derivative of adenylic acid that polymerizes on a polyuridylate template to form short oligoadenylic acids.[1] In the absence of a template or other catalyst, ImpA hydrolyzes to adenylic acid (pA) and imidazole. Here we report that the Zn^{2+} ion catalyzes the formation of oligonucleotides from nucleoside phosphorimidazolides in aqueous solution even in the absence of a template.

The imidazolides, ImpU and ImpA, were prepared by a modification of the procedures of Cramer et al.[2] Reaction mixtures (0.1 ml, pH 7.0), containing 0.025 *M* ImpA-*8*-^{14}C (specific activity 0.12 mCi/mmol), 0.025 *M* $ZnCl_2$, and 0.2 *M* *N*-ethylmorpholine as a buffer, were prepared at 0° and kept at 0–50°. In all cases some precipitation occurred. Aliquots were withdrawn at various times and treated with 30 μl of 0.25 *M* EDTA solution to break down Zn^{2+} complexes. The reaction mixtures were then subjected to paper chromatography in 1-propanol–15 *M* ammonia–water (55:10:35, v/v) and to electrophoresis in 0.03 *M* potassium phosphate buffer at pH 7.1. The yields of radioactive products were estimated by passing the chromatograms through a radiochromatogram scanner with integrator.

As the reaction progressed, ImpA disappeared from the reaction mixture, while adenylyl-adenosine 5′-phosphorimidazolide (ImpApA)[3] and oligoadenylic acids with chain length up to four (pApA, pApApA, and pApApApA) were formed. In addition, the usual products of ImpA hydrolysis, pA, and a small amount of P_1P_2-diadenosine 5′-pyrophosphate (AppA),[2] appeared. ImpApA and oligoadenylic acids were identified by cochromatography with authentic samples. The identification of ImpApA was confirmed by its clean hydrolysis to pApA and imidazole under slightly acidic conditions. The oligoadenylic acids obtained in this reaction were completely degraded to pA by venom phosphodiesterase.[4]

The yields of the products are given in Table I. The maximal yield of oligoadenylic acids including ImpApA was 25.2%. ImpApA was formed after short reaction times and disappeared at later times as pApA and pApApA accumulated. The formation of the various products is explained in Scheme I. Pyrophosphate formation (eq 2) was always a minor reaction.

The ratio of the yield of oligoadenylic acids to that of pA expresses roughly the efficiency of phosphodiester bond formation. The maximum ratio was 0.45 at 0° in the presence of Zn^{2+} ion. In the control experiments in which $ZnCl_2$ was omitted, the disappearance of ImpA was slow, and only small amounts of pApA and pApApA were formed. The Zn^{2+} ion increased the efficiency of phosphodiester-bond formation by a factor of as much as 10.

Table I. Yields of Products from Aqueous Solutions of ImpA in the Presence of $ZnCl_2$

Temp,[c] °C	Time (days)	(ImpA):($ZnCl_2$) (molar ratio)	Yield (%)							$(pA)_n$/pA	2′–5′ linkage of pApA (%)
			ImpA	pA	AppA	ImpApA	pApA	pApApA	pApApApA		
0°	1	1:1	76.0	15.8	1.2	5.9	1.1			0.45	
	3		46.9	38.5	1.7	8.4	4.2	0.3		0.34	
	10		18.3	54.8	1.6	8.3	13.0	3.7	0.2	0.46	90
r.t.	1		15.8	64.9	1.8	4.4	10.9	2.3		0.27	
	7		2.8	72.3	1.8	0.9	16.7	4.3	1.2	0.32	87
37°	5		1.7	73.8	2.2	0.7	15.5	5.0	1.1	0.30	78
50°	1		3.1	75.6	1.1	0.3	14.6	4.6	0.7	0.27	76
0°	1	2:1	62.5	25.5	0.9	9.6	1.5			0.44	
	3		41.6	41.3	1.7	10.4	4.6	0.4		0.37	
	10		18.9	55.2	1.5	9.2	12.9	2.3	0.3	0.45	91
r.t.	1		20.7	59.6	1.4	6.0	10.1	2.2		0.31	
	7		3.9	74.1	2.2	0.7	16.4	2.7		0.27	89
50°	1		1.6	77.0	1.1	0.2	16.4	3.3	0.3	0.26	83
0°	10	1:0[a]	56.5	38.9	2.6	0.9	1.1	Trace		0.05	
r.t.	7		9.3	86.2	1.6	0.5	2.1	0.3		0.03	
r.t.	7	1:1[b]	8.3	84.9	3.0	0.8	2.6	0.4		0.04	

[a] Control reaction. [b] $MgCl_2$ was used. [c] r.t. = room temperature.

Table II. Yields of Products from Aqueous Solutions of ImpU in the Presence of $MgCl_2$ or $ZnCl_2$[a]

(ImpU):($ZnCl_2$) (molar ratio)	Yield (%)						$(pU)_n$/pA	2′–5′ linkage of pUpU (%)
	ImpU	pU	UppU	ImpUpU	pUpU	pUpUpU		
1:1	5.8	81.4	3.6	0	8.8	0.4	0.11	86
2:1	3.2	83.3	1.9	0.2	10.1	1.3	0.14	86
1:1[b]	11.7	84.2	2.2	Trace	1.9	0	0.02	Not studied
1:0	13.9	80.3	3.8	0	2.0	0	0.02	Not studied

[a] At room temperature for 7 days. [b] $MgCl_2$ was used.