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Authors

Metzner, E.Kurt
Libertini, Louis J.

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E. Kurt Metzner and Louis J. Libertini

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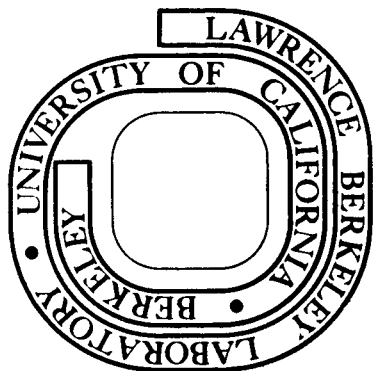
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Electron Spin Exchange in Rigid Biradicals

E. Kurt Metzner and Louis J. Libertini

Contribution from the Laboratory of Chemical Biodynamics,
Lawrence Berkeley Laboratory, University of California,
Berkeley, California 94720. Received

Abstract: Eleven rigid nitroxyl biradicals have been synthesized with distances between the radical groups of up to 12 Å. The electron spin resonance spectra were studied in a variety of solvents and over a range of temperatures. S-resonances, which permit the electron exchange interaction (J) to be determined with precision, were observed for all but one of the biradicals. Spectra corresponding to $J = 6$ G up to $J = 172$ G were obtained. The effects of structure on the exchange are complex and do not appear to be consistent with a simple direct (through space) mechanism. It is concluded that indirect (through bond) exchange occurs in these biradicals between nitroxyl groups separated by 10-11 sigma bonds, but the possibility of a combination of the direct and indirect mechanisms cannot be ruled out. Independent of mechanism, the exchange is found to be very sensitive to the structure of the biradical. The exchange can also be strongly dependent on solvent. Most of the biradicals show an increase in J with solvent polarity, although two show the opposite behavior and two have values of J which were independent of solvent polarity. The effects of solvent are attributed to changes in the distributions of the unpaired electrons as reflected by changes in the nitrogen hyperfine coupling constant. Increases in temperature can produce either an increase or a decrease in J depending on the solvent. The effects are generally small and probably result from changes in solvation as well as from changes in the vibrational state of the biradicals.

ref 1
A biradical may be defined as a molecule containing two unpaired electrons which are sufficiently separated and localized that they interact with one another only weakly.¹ The interactions which can occur between the electrons include the electron-electron dipolar interaction and the electron spin exchange interaction.

ref 2
The dipolar interaction is generally well understood, and, if the distance between the two radical centers is known, it may sometimes be accurately predicted by assuming the electrons to be localized at two points (the point dipole approximation).²

The exchange interaction (J) is much more complex and can be classified under two basic mechanisms.¹ That most commonly considered is the "direct" exchange mechanism which involves direct overlap of the molecular orbitals in which the unpaired electrons are localized. The character of direct exchange is sufficiently well understood that a calculation of the magnitude would be possible for a biradical if accurate wave functions for the free radical groups and their relative positions were known. Less well understood is the indirect mechanism of spin exchange which occurs as a result of the structure joining the two radical centers.

ref 3
Before the recent development of stable nitroxyl radicals, few examples of biradicals were available. A large number of nitroxyl biradicals have been prepared having a wide variety of structures joining the nitroxyl groups and with a wide range of interactions as determined from the esr spectra.³ The ease with which such biradicals can be prepared and their considerable stability in solution have led to efforts to use them in studies of membranes and membrane models,⁴⁻⁶ of isotropic and anisotropic liquids,^{4,7-10} and of intramolecular motion and conformational

ref 4,5,6
ref 7,8,9,10

ref. 11,12,13 analysis.^{8,9,11-13} Some of the studies relied on the dipolar interaction and others on the exchange interaction for useful information.

Because they can be prepared with a wide variety of structures, nitroxyl biradicals provide an excellent opportunity to study the electron spin exchange interaction and to try and estimate the importance of the direct and indirect mechanisms to the magnitude of the exchange. However, the great majority of known ^{nitroxyl} biradicals are of a flexible nature and can provide little information on the effect of structure on the spin exchange. The several rigid biradicals which have been reported all have exchange energies which are too large to be determined from the esr spectra.^{4,7,10,11,14,15}

We have synthesized and studied eleven rigid nitroxyl biradicals, most of which exhibit easily measurable exchange energy. Several of the molecules differ from one another only by small changes in the joining structure which would have little effect on the relative positions and orientations of the nitroxyl groups. The rigid nature of the biradicals has also permitted us to investigate the effect of solvent and temperature on the exchange interaction independent of ^{major} effects on molecular flexibility or conformation.

Measurement and Mechanism of Electron Spin Exchange

ref. 16
ref. 17 A theoretical discussion of the effects of spin exchange on the esr spectrum of a nitroxyl biradical has been given by Lemaire,¹⁶ Glarum and Marshall,¹⁷ and others.¹ The observed esr transitions can be classified into two groups distinguished by their responses to changes in the value of J. The S-resonances, which are transitions involving a state which is predominantly singlet in character, lose intensity as J becomes large and

move away from the center of the spectrum.¹⁷ When they are observed, the exchange energy can be accurately determined from the separation ΔH_J between the strongest S-resonance and the center of the spectrum:

$$\underline{J} = \Delta H_J - \frac{a^2}{\Delta H_J} \quad (1)$$

where a is the hyperfine splitting due to the nitroxyl nitrogen. However, for many biradicals, conformational changes in the molecule result in a broadening of the S-resonances beyond observation. This results from a modulation of the exchange interaction between two or more values.¹⁷

The remaining transitions are termed T-resonances, which are transitions involving a state which is predominantly triplet in character. They have positions and intensities which are much less dependent on the value of \underline{J} . When the S-resonances are difficult or impossible to observe, the magnitude of \underline{J} may sometimes be estimated from the positions of the T-resonances. Again, modulation of \underline{J} can broaden these transitions and caution must be observed.¹⁸

ref. 18

The mechanisms through which the spin exchange interaction occurs can be divided into two classes--direct and indirect. Direct exchange is that most commonly treated theoretically and occurs as a result of direct overlap of the molecular orbitals which contain the unpaired electrons. It is generally noted that the structure joining the two radical centers does not contribute to direct exchange. However, it should be apparent that if the joining structure is positioned such that it "shields" one radical center from the other, a considerable effect on (but not a contribution to) direct exchange can be expected.

Direct exchange is usually considered to be a short range interaction. It is very important in the theory of bond formation and also in the description of van der Waal's interactions but is rarely considered of

ref. 19 importance when the distance between electron centers is large.¹⁹ However, the exchange energies which can be determined directly from the esr spectrum of a nitroxyl biradical range from 3 to 300 G (8 to 800 x 10⁻¹⁰ kcal/mole) which is insignificant when compared to most energies of interest. Murrell and Teixeira-Dias¹⁹ have calculated the exchange energies for two hydrogen atoms in various states (2s, 2p) at distances between 7 and 11 Å. Even at 11 Å the calculated values of J can be greater than 1000 G, depending on the relative orientation of the hydrogen 2p orbitals. The electron distribution on a nitroxyl group is considered to be in a 2p_π orbital between the nitrogen and oxygen.²⁰ For the situation most closely approximating that of a nitroxyl biradical (two hydrogens in 2p states) their results indicate, as one should expect, that the magnitude of J varies strongly with gross changes in the relative orientation of the 2p orbitals. Small changes in distance, orientation or electron distribution can be expected to have small but significant effects on J.

ref. 20 Indirect exchange results through the structure which joins the two radical centers. It should be noted that this mechanism is not strictly limited to exchange transmitted only through bonds. Through space interactions between the radical center and the joining structure must also contribute to the magnitude of J. Calculation of indirect exchange is vastly more complicated than for direct exchange. The former requires a knowledge not only of the unpaired electronic distribution, but also of the distributions and interactions of the electrons in the structure joining the radical fragments. Efforts to calculate indirect exchange except for very simple systems can be considered only as order of magnitude estimates.²¹

Through bond spin exchange is also important to nuclear spin coupling in nmr²² and to electron-nuclear spin coupling in esr.²³

The bond polarization and hyperconjugation formalisms used to describe these situations²⁴ should also be important to electron spin exchange in

biradicals. Long range nuclear spin couplings (through 3 to 5 bonds) have been known for some time.²⁵ In some cases these long range interactions result from a through space coupling due to the close proximity of the nuclei involved.²⁶ Other long range couplings are usually associated with what is known as a W-plan arrangement of the bonds between the nuclei.²⁴

Unpaired electrons have magnetic moments more than one thousand times those of nuclei, and this in combination with their distribution in space allows them to interact with bonding electrons much more effectively than can nuclei. Thus it is expected that through bond electron-electron interactions can occur over distances much greater than 5 bonds, particularly if a W-plan bond arrangement exists between the radical centers. The through bond exchange magnitude will also depend strongly on the extent of overlap of the unpaired electronic orbital and the molecular orbitals of the joining structure. Thus one can expect that changes in the distribution of the unpaired electron on the radical center and changes in the orientation of the radical center with respect to the joining structure should affect the magnitude of indirect exchange.

Results

The structures of the biradicals studied are shown in Figure 1. Each was prepared from the corresponding steroid diketone by refluxing in xylene with a large excess of 2-amino-2-methyl-1-propanol and a catalytic amount of p-toluenesulfonic acid to give the 4',4'-dimethyloxazolidine precursor of the biradical. The oxazolidine precursors were then oxidized to the

ref. 22,23

ref. 24

ref. 25

ref. 26

Fig. 1

ref. 27
ref. 28
nitroxyl biradicals with m-chloroperoxybenzoic acid in ether.²⁷ The term "doxyl" has been used for the 4',4'-dimethyloxazolidine-N-oxyl derivative of a ketone²⁸ and will be used here (e.g., biradical I becomes 3,17-didoxyl-5 α -androstandane).

The nitroxyl groups at the 3-, 16-, 17- and 17a-positions are rigidly attached to the steroid structure, and space filling models indicate that molecular motion about the C₁₇-C₂₀ bond of biradicals VI-IX will be greatly restricted. Most of the biradicals fall into two main series: I through V and VI through IX. Within the two series, homologous changes in the trans steroid joining structure are introduced, including a change in stereochemistry at the 5-position (cis steroid biradicals II and VII), the introduction of a double bond between the 5 and 6 positions (III and VIII) and the subsequent oxidation of the double bond to the corresponding epoxide (IV and IX). Biradicals I and X bear an homologous relationship to V and XI where the major difference is in number of carbons in the steroid D-ring.

For each of the biradicals in Figure 1 except XI, S-resonances were clearly observed under all conditions of temperature and solvent examined. Before purification, several of the biradicals exhibited multiple sets of S-resonances with one set clearly predominant in intensity over the others. For reference purposes the compound designations in Figure 1 will be used with subscripts (e.g., V₂, V₃) to refer to the weaker sets of S-resonances in order of decreasing J. No subscript or a subscript 1 will be used to designate the predominant S-resonances. Except for X, the biradicals which could be recrystallized showed only one set of S-resonances corresponding to the strongest set in the crude compound. The relative concentrations of compounds producing the multiple sets of S-resonances could

be estimated from the height and width of the strongest transition in each set after correction for the effect of \underline{J} on the intensity. The crude biradicals were nearly always contaminated by varying amounts of mono-radical, and it is not possible to say whether a biradical with $\underline{J} = 0$ was present. Also a biradical with large \underline{J} and low concentration such that the S-resonances could not be detected could have been missed.

Values of \underline{J} ranging from 6 G (\underline{X}_1 in hexane) to 172 G (\underline{I}_1 in acetic acid) were determined using equation (1) and should be accurate to ± 1 G. Representative spectra are shown in Figure 2. Except for 2(d), only the high-field S-resonances are included. The T-resonance regions were generally symmetric, indicating that tumbling of the biradicals was sufficiently rapid to average anisotropic interactions such as the g-value, the hyperfine interaction, and the electron-electron dipolar interaction. Nevertheless, the linewidths of the S-resonances were 1.5-2.5 times those of the T-resonances, possibly due to modulation of \underline{J} by intramolecular motions. When the S-resonances were difficult to detect, the signal-to-noise ratio can be improved considerably by the use of high microwave power (100-250 mW) as in Figure 2(a). This results from the fact that transitions having very low transition probabilities can tolerate much higher microwave power before saturation effects become important. The S-resonance line widths were not strongly dependent on the microwave power used.

The effect of solvent on the exchange energy was studied in greatest detail for biradicals \underline{I} and \underline{VI} and in a variety of solvents for the remaining biradicals. The results are listed in Table I. Where more than one set of S-resonances were observed, \underline{J}_1 corresponds to the exchange

FIG. 2

TABLE I

Table I. Exchange energies for the reported biradicals in various solvents*

Solvent	Z	<u>I</u>			<u>II</u>		<u>III</u>				<u>IV</u>		<u>V</u>			
		J ₁	J ₂	a	J	a	J ₁	J ₂	J ₃	a	J	a	J ₁	J ₂	J ₃	a
Hexane	60	92.4	51.9	14.1	25.1	14.2	103.1	37.3	25.2	14.1	64.2	14.2	92.4	69.2	51.3	14.2
Ethyl acetate	--	109.6	59.9	14.4	--	--	--	--	--	--	--	--	--	--	--	--
THF	--	110.0	--	14.4	25.6	14.4	--	--	--	--	--	--	--	--	--	--
Xylene	63	113.2	61.8	14.3	27.4	14.3	116.8	38.9	26.9	14.2	52.9	14.2	103.1	75.4	60.3	14.2
Acetone	65.7	117.4	62.5	14.4	28.4	14.5	117.7	37.6	30.0	14.5	48.2	14.6	111.4	77.3	61.5	14.7
DMF	68.5	127.5	64.8	14.6	--	--	--	--	--	--	--	--	--	--	--	--
Acetonitrile	71.3	129.6	67.0	14.5	--	--	--	--	--	--	--	--	--	--	--	--
Pyridine	64	133.0	70.0	14.6	--	--	--	--	--	--	--	--	--	--	--	--
DMSO	71	133.2	69.0	14.6	30.1	14.6	124.3	37.2	30.7	14.6	43.2	14.8	126.3	85.5	67.9	14.8
Chloroform	63.2	155.6	75.7	14.8	22.0	14.8	148.0	37.3	22.7	14.8	28.4	14.9	136.9	95.2	75.3	15.0
Ethanol (95%)	81.2	155.0	77.2	14.8	--	--	--	--	--	--	--	--	--	--	--	--
Methanol	83.6	156.5	67.8	15.0	29.0	14.9	139.4	37.3	28.6	14.9	39.7	15.0	143.4	94.7	75.5	15.0

*The subscripts on J are used to designate results for minor epimers (or impurities) of the indicated biradicals in order of decreasing J. Absence of a subscript (or a subscript 1) implies the major epimer in each case.

Table I (cont.) Exchange energies for the reported biradicals in various solvents*

Solvent	Z	<u>VI</u>		<u>VII</u>		<u>VIII</u>		<u>IX</u>		<u>X</u>		
		J	a	J	a	J	a	J	a	J ₁	J ₂	a
Hexane	60	32.3	14.2	7.0	14.2	18.1	14.1	16.7	14.2	6.1	35.6	14.1
Ethyl acetate	--	35.3	14.5	--	--	--	--	--	--	--	--	--
THF	--	34.7	14.6	7.9	14.4	--	--	--	--	--	--	--
Xylene	63	36.0	14.5	5.7	14.5	19.5	14.2	17.6	14.2	6.5	33.7	14.4
Acetone	65.7	36.6	14.6	8.8	14.7	19.2	14.4	16.5	14.5	8.9	33.2	14.6
DMF	68.5	38.5	14.7	--	--	--	--	--	--	--	--	--
Acetonitrile	71.3	39.2	14.7	--	--	--	--	--	--	--	--	--
Pyridine	64	40.2	14.7	--	--	--	--	--	--	--	--	--
DMSO	71	39.6	14.8	8.0	14.7	19.8	14.6	16.5	14.7	9.3	34.0	14.8
Chloroform	63.2	43.9	14.9	7.2	15.0	19.6	14.8	16.1	14.8	15.4	25.0	14.9
Ethanol (95%)	81.2	43.4	14.9	--	--	--	--	--	--	--	--	--
Methanol	83.6	42.9	15.1	9.4	15.2	21.1	15.0	17.0	15.1	20.6	22.9	15.2

*The subscripts on J are used to designate results for minor epimers (or impurities) of the indicated biradicals in order of decreasing J. Absence of a subscript (or a subscript 1) implies the major epimer in each case.

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interaction determined from the strongest set and \underline{J}_2 and \underline{J}_3 were determined from the weaker sets in order of decreasing \underline{J} . Also included in Table I are the observed hyperfine interaction (\underline{a}) and the Kosower \underline{Z} value for each solvent.²⁹ The Kosower \underline{Z} is an empirical measure of solvent polarity based on the observed charge transfer energy of a pyridinium iodide complex in the various solvents. In general, the exchange energy is observed to increase with increasing solvent polarity, although for some biradicals little change in \underline{J} with solvent is seen (III₂, VII, IX) and in two cases \underline{J} decreases with solvent polarity (IV, X₂). Part of the results in Table I are plotted in Figure 3 for the two homologous series of molecules I through IV and VI through IX.

The exchange energies of most of the biradicals were also studied as a function of temperature in hexane and chloroform; the results are summarized in Table II. Variation of \underline{J} with temperature was essentially linear over the range examined. Temperature coefficients varied from -0.27 to +0.13 Gauss/degree, but were generally small in magnitude (<0.05) and negative. The effect of temperature was also studied in xylene, where results were essentially equivalent to those in hexane and are not included in the table. The S-resonances of biradical VI exhibited a singular behavior at high temperature in xylene. As illustrated in Figure 4, a new S-resonance appears from beneath one of the lines present at lower temperature and ^{appears to} increase in relative intensity with increasing temperature. The process is reversible and the new line may be the strongest S-resonance of a high energy conformation of the biradical.

ref. 29

FIG. 3

TABLE II

FIG. 4

Table II. Temperature coefficients of \underline{J} for biradicals \underline{I} through \underline{X} .

<u>Biradical</u>	<u>Temperature coefficient (Gauss/degree C)*</u>	
	<u>hexane</u>	<u>chloroform</u>
<u>I</u>	+0.05	-0.27
<u>II</u>	-0.05	-0.06
<u>III</u>	+0.13	-0.06
<u>III</u> ₂	-0.12	-0.12
<u>IV</u>	-0.12	+0.05
<u>V</u>	+0.10	-0.05
<u>V</u> ₂	-0.01	-0.11
<u>V</u> ₃	+0.03	-0.05
<u>VI</u>	+0.03	-0.02
<u>VII</u>	-0.01	-0.03
<u>VIII</u>	-0.03	-0.04
<u>IX</u>	-0.04	-0.02
<u>X</u>	-0.04	-0.11
<u>X</u> ₂	+0.04	+0.09

*The temperature range examined was generally 20 to 100° except for I, II, VI and VII in hexane and II, VI and VII in chloroform (-60 to 60°) and for I in chloroform (0 to 60°).

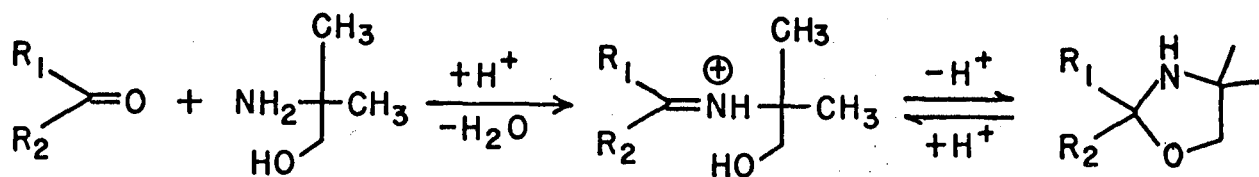
Discussion

Stereochemistry. The stereochemistry at the point of attachment of the doxyl group is of considerable interest since it determines the relative positions and orientations of the two radical subunits. Two epimers are possible at each of the 3-, 16-, 17- and 17a-positions of the steroids and also at the 20-position although in this case the additional problem of the conformation about the C₁₇-C₂₀ bond exists. Thus each biradical has a maximum of four possible epimers. Michon and Rassat³⁰ have studied the proton hyperfine interactions in 3-doxyl-5 α -cholestane and 3-doxyl-5 β -cholestane and concluded that in each case only the epimer which has the nitroxyl group in the equatorial position (3e-epimer) is obtained.

ref. 30
ref. 31
Marriot et al.³¹ have studied 3-doxyl-5 α -cholestane trapped in a thiourea host crystal and concluded from the observed anisotropy in the g-value that only the 3e-epimer was trapped. They further estimate that the 3e-epimer predominates at least 20-fold over the 3a-epimer. Consistent with these findings is the observation that the 3-oxazolidine methylene protons of the amine precursors of I, II, V, VI, VII and X appear as a sharp singlet in the nmr spectra near 3.5 δ .

Before considering the stereochemistry of the doxyl group at the 3-positions of biradicals III and VIII and at the 16-, 17-, 17a- and 20-positions, it will be useful to speculate as to the source of the stereochemical specificity observed during oxazolidine formation at the 3-position of cis and trans steroids. Neither Michon and Rassat³⁰ nor Marriot et al.³¹ have discussed this aspect of the problem. Oxazolidine formation proceeds most likely via an iminium ion intermediate following by ring closure resulting from attack by the alcohol OH on the iminium carbon.

-15-



The first step is driven toward completion by removal of water from the reaction. The reversibility of the second step would result in equilibrium concentrations of the two possible epimers with steric factors leading to the predominance of one epimer over the other. At the 3-position of a steroid (cis or trans) the axial position would experience the greatest steric interaction due to the axial protons at positions 1 and 5. Since the secondary amine group is larger than the ether, the nitrogen would be favored in the equatorial position. This simple and very probable mechanism can explain the reported results.

The synthesis of biradicals III and VIII was from the Δ^4 -diketo-steroids. During the formation of the oxazolidine at position 3 the double bond shifts to the Δ^5 -position, as evidenced by the fact that the olefinic proton in the resulting oxazolidine shows a complex splitting due to the protons at C_7 . Throughout oxazolidine formation there is no hydrogen at C_5 and the steric interactions which could result in predominance of the 3β epimer have been reduced to one axial hydrogen at C_7 . As one may predict from this observation, the ratio of 3α to 3β epimer formed appears to increase as evidence by the nmr of the 3-oxazolidine methylene protons. This is most easily seen for compound XII, which has only the 3-oxazolidine, where the nmr of the oxazolidine methylene protons indicates two independent sets of two non-equivalent protons in an approximate ratio 2:1.

One set of S-resonances were observed for biradical VIII, while III exhibited three sets; both III₂ and III₃ were estimated to be about 4% of

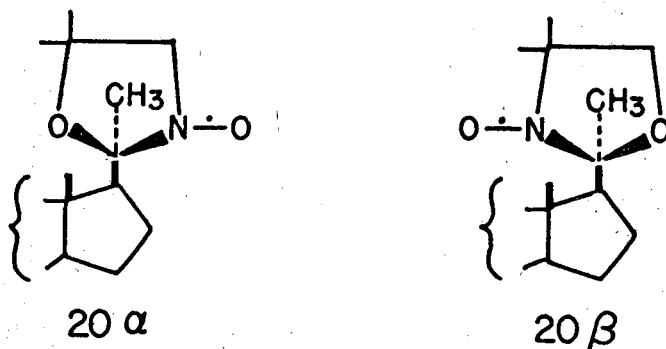
III. The dependence of \underline{J} on solvent is the same within experimental error for II and III₃ (the behavior in chloroform is unusual for both), and both may be due to the same biradical. It is unlikely that the precursor of II was present as an impurity in that of III. If not, then reduction of the double bond must have occurred, probably during the formation of the oxazolidine ring. If a biradical equivalent to I₁ were also produced during this process, it would not be detected because of the low yield combined with the very low intensity of the S-resonances for large \underline{J} .

Biradicals IV and IX were derived directly from III and VIII by treatment with m-chloroperoxybenzoic acid in chloroform. As the oxidation proceeds a new set of S-resonances appears, accompanied by the disappearance of those of the major isomer. In the case of III \rightarrow IV the S-resonances of III₂ also disappear while the major S-resonance of III₃ remains as a shoulder on that of IV. The intensity of the new S-resonances are too great to result from III₂. If the period of oxidation is extended, the S-resonances of IV disappear and the appearance of the T-resonance region begins to approach that of a nitroxyl monoradical.

The predominant epimer at the 17-position is not known. The nmr spectra of the amine precursors of biradicals I, II and of the monoradical 17-doxyl-5 α -androstan-3 β -ol (XIII) show the methylene protons of the 17-oxazolidine as one set of non-equivalent protons (one AB quartet around 3.5 δ). Thus one predominate epimer is indicated. Most steroids having a substituent at the 17-position exist as the 17 β isomer. Brutcher and Bauer³² have calculated that 17 β -methylandrostan-3 β -ol should be nearly 3 Kcal/mole lower in energy than 17 α -methylandrostan-3 β -ol, mainly resulting from repulsive interactions between the 17 α -methyl and the hydrogen at the 14 α -position. For the

17-oxazolidine, the bulkier amine group would therefore be expected to occupy the 17β -position, resulting in predominance of the 17β -doxyl in I through IV. Expansion of the D-ring to a six-membered ring (V) increases the diaxial interactions, and the situation is more similar to the 3-position. Biradical I exhibits two sets of S-resonances with I₁ predominating about fivefold over I₂. The ratio of I₂ to I₁ is much too large to be accounted for by the epimers at position 3 and more likely corresponds to the 3β - 17α and 3β - 17β epimers. Biradical II appears to have only one epimer, the other perhaps having $\underline{J} \sim 0$ or $\underline{J} \gg a$. Three sets of S-resonances are also observed for biradical V with V₁ predominating sixfold over V₂ and fivefold over V₃.

The two epimers of the 20-doxyl group of VI - IX can be designated in accordance with Fieser³³ as the 20α and 20β epimers.



Space filling molecular models indicate that rotation about the C_{17} - C_{20} bond is restricted and only certain conformations of the doxyl or of the oxazolidine can be expected. The sharp S-resonances at all temperatures for the 20-doxyl biradicals indicate that large amplitude oscillations about the C_{17} - C_{20} bond either do not occur, in agreement with the models, or are sufficiently fast as to completely average \underline{J} . Only one major set of S-resonances are observed for each of VI - IX, and the nmr of the 20-oxazolidine methylene protons consists of one AB quartet around 3.5 δ , both facts consistent with one major epimer and conformation. Unless the

shape of the iminium ion intermediate leads to other considerations, the equilibrium condition of oxazolidine ring formation at the 20-position should result in the epimer and conformation in which the fewest steric interactions are possible. Models indicate that, for either epimer, conformations (which will be designated A) in which the amine is below the plane of the steroid on the side opposite the 18-methyl will have fewer interactions than conformations B which have the amine above the plane. Molecular models of the iminium ion intermediates indicate no reason why the A conformation of either epimer could not be formed. One of the A conformations (A₁) of the 20 α epimer, in which the N-O bond of the final doxyl group is directed essentially perpendicular to the steroid plane, has somewhat fewer interactions than others (α or β) and should be favored. A very similar A₁ conformation of the 20 β doxyl is also possible. For either epimer other A conformations can be easily reached by rotation about the C₁₇-C₂₀ bond, but it is much more difficult to rotate an A into a B conformation.

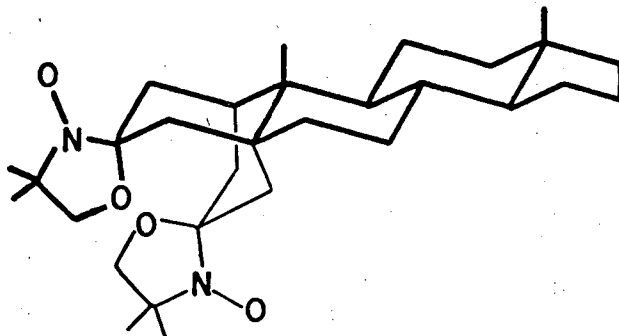
Biradical X has a doxyl group at the steroid 16-position. The nmr of the amine precursor of biradical X shows the 16-oxazolidine methylene protons as two AB quartets around 3.5 δ , one of the quartets predominating about fourfold. The biradical, even after recrystallization, showed two sets of S-resonances. The relative proportions could not be accurately determined but were estimated to be about 2:1.

Biradical XI is comparable to X but with the steroid D-ring expanded to six carbons. Sterically, the interactions which should lead to an equatorial nitrogen in the 17-oxazolidine are even stronger than those at the 3-position due to the 18-methyl group. Thus the 17 α epimer should

predominate. As expected, the 18-methyl also makes the formation of the 17-oxazolidine very difficult and the resulting dioxazolidine is produced in very low yield. Complete separation of the biradical from accompanying 3-doxyl monoradical was not possible. The best esr spectrum obtained for XI is illustrated in Figure 5. No S-resonances were observed under any conditions. The spectrum consists of a 3-line monoradical spectrum superimposed on a 5-line biradical spectrum with $\underline{J} \gg \underline{a}$.

FIG. 5

Effect of structure. For the cis biradicals II and VII the exchange is 4- to 6-fold lower than for the analogous trans compounds I and VI. The diagram below shows the major differences between the isomers.³⁰



The direction of the N-O bond at the 3-position is reversed and the nitroxyl groups are held closer together in the cis compounds. It is also apparent that the extent of W-plan arrangement of the sigma bonds is greater for the trans isomers and, if the W-plan arrangement is important to indirect exchange as suggested above, the higher values of \underline{J} for the trans isomers are quite consistent with an indirect exchange mechanism.

The β configuration has been assigned to the 17-doxyl group. The decrease in \underline{J} from I to II supports this assignment since for the 17 α -doxyl epimer the cis isomer has the nitroxyl oxygens separated by less

than 5 Å, which would certainly result in a very strong direct exchange interaction. For the A_1 conformation of the 20-doxyl group (see Stereochemistry) a similar argument should apply since the oxygen-to-oxygen distance in this conformation of VII would be 7 to 8 Å. The observed exchange, however, is small, indicating either that the 20-doxyl is not in the predicted A_1 conformation or that the contribution of the direct exchange is small even when the nitroxyl groups are closer together than in all the other biradicals studied here.

In several solvents (THF, acetone, DMSO) the ratio $\underline{J(I_1)}:\underline{J(II)}$ is essentially equal to $\underline{J(VI)}:\underline{J(VII)}$. This fact is intuitively acceptable on the basis of through bond exchange since the 17- and 20-doxyl groups are distant from the region involved in the change from the cis to trans steroid. The equivalent ratios are not expected for a through space mechanism unless the 20-doxyl group were oriented in a manner similar to the 17 β -doxyl. One of the B conformations of the 20 β -doxyl approximates this requirement. If this is the correct conformation, however, it is difficult to see why the exchange for the 20-doxyl series should be so much lower than that for the 17-doxyl series.

Introduction of the double bond between C_5 and C_6 (III, VIII) tilts the 3-doxyl N-O bond away from the 19-methyl group by more than 10° and at the same time brings the N-O group down nearer the plane of the steroid. If the magnitude of \underline{J} were mainly determined by the direct mechanism, one would expect a slight decrease in the exchange for III and VIII as compared to I and VI. In contrast, the exchange for III can be larger or smaller than for I, depending on the solvent, while $\underline{J(VIII)}$ is about half $\underline{J(VI)}$ in all solvents. These results also appear to be inconsistent with an

indirect mechanism since, as argued above for the cis-trans compounds, one could expect the ratios of \underline{J} in the two series to be comparable, particularly if the only effect of the unsaturation were distortion of the W-plan arrangement of the steroid sigma bonds. However, introduction of the double bond is in some ways a more drastic modification than the change to the cis steroid and may cause changes in the electronic distributions throughout the molecule.

The effect of oxidizing the double bond to the epoxide (IV, IX) on the relationship of the 3-doxyl group to the 17- or 20-doxyl is uncertain. However, the result most likely falls somewhere in between the saturated and unsaturated analogs. The exchange for IV is as much as threefold smaller than for I or III, while in contrast, there is little difference between $\underline{J}(\text{IX})$ and $\underline{J}(\text{VIII})$. Again the result is not readily explained by either exchange mechanism but is more consistent with indirect exchange.

Expanding the steroid D-ring from five (I) to six (V) carbons has two main effects. First, the NO bond of the 17 α -doxyl is tilted away from the 18-methyl group by about 30° more than for the 17 β -doxyl. Second, the angle between the planes of the two doxyl groups decreases by about 10°. It is difficult to predict what effect these changes should have on direct exchange since one should tend to counteract the other. The observation that $\underline{J}(\text{V})$ is less than $\underline{J}(\text{I})$ except in hexane where they are equal cannot be considered as more consistent with one exchange mechanism than another. However, the results in polar solvents do demonstrate that, whatever the mechanism, \underline{J} can be very sensitive to the spacial relationship of the nitroxyl groups, even when the distance between them is large (11 Å) and the bonding between them is changed very little.

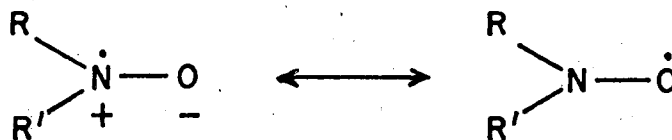
Biradical X is of interest independent of the other compounds studied here because the evidence clearly indicates two epimers at position 16. The interesting effect of solvent will be mentioned in the next section. The difference between the two epimers is only the configuration of the doxyl group about position 16. Yet the observed exchange can be either very different (e.g., in hexane) or nearly the same (methanol). It is very difficult to explain this latter observation on the basis of the direct exchange mechanism since the orientation of the nitroxyl is considerably different for the two epimers.

Biradical XI was obtained in very low yield and could not be isolated as a pure compound. It appeared to be contaminated by at least 50% mono-radical but high resolution mass spectral analysis gave the correct molecular ion for XI. This information is reemphasized here because of the very unusual result obtained for XI. In contrast to what one would expect by noting that the relationship between V and XI is analogous to that between I and X, namely, an exchange for XI of between 0 and 30 G, the only biradical evident has a very large J (>300 G). This result cannot be explained by a direct exchange mechanism. It is also difficult to accept on the basis of the indirect mechanism, since XI has one more bond separating the nitroxyl groups than V. However, it should be pointed out that the two nitroxyl groups in 3 β ,17 α -didoxyl-D-homoandrostane (the expected epimer of XI) are connected by an essentially symmetric W-plan arrangement of carbon-carbon sigma bonds which may account for the large exchange observed for this biradical.

Effect of Solvent. The dependence of the exchange interaction on solvent for the nitroxyl biradicals studied here is complex. The values

of $J(\text{III}_2)$ and $J(\text{IX})$ show no significant variation while other biradicals can have either an increase (e.g., I_1 and X_1) or a decrease (IV and X_2) in J with increasing solvent polarity. It has been suggested that such effects of solvent on J , which have also been observed with flexible biradicals, are the result of changes in the most probable conformation of the biradical.¹⁷ However, the rigid molecules presented here should be capable of only very limited conformational changes on which the solvent can be expected to have little effect. Yet the magnitude of the effect of solvent on J for I_1 , III_1 , and V_1 is greater than has been noted previously. An alternate explanation is that the changes in J are directly related to changes in the distribution of the unpaired electrons as is reflected in the well known dependence on solvent of the nitrogen hyperfine interaction (a).³⁴ Two resonance forms can be written for a nitroxyl group in which the unpaired electron is

ref. 34



either on the nitrogen or on the oxygen. Polar solvents stabilize the polar resonance form and lead to greater electron density on nitrogen than do nonpolar solvents. The situation may be considerably more complex than the above diagram indicates. Several nitroxides have been found by crystal structure determination to be non-planar and thus the hybridization of the orbitals on nitrogen is in question and may be affected by the solvent.²⁰

The Kosower \underline{Z} -value is an empirical measure of solvent polarity which was chosen because it had previously been shown to correlate linearly with the hyperfine interaction in several solvents.³⁴ Biradicals I and VI were studied in a number of solvents for which the results are not included in Fig. 3. The exchange interactions are listed in Table I. For both biradicals, plots of \underline{J} vs. \underline{Z} show good linearity with the exception of hexane, pyridine, and chloroform. The pyridinium iodide complex used to obtain \underline{Z} -values is rather insoluble in hexane, which may result in a high value of \underline{Z} due to dimerization or other interactions.^{35a} Dimroth et al. have used a different pyridinium compound to characterize solvent polarity, deriving an empirical parameter comparable to \underline{Z} which they call $E_T(30)$.^{35b} Values of $E_T(30)$ plot linearly against \underline{Z} -values for most solvents, hexane being an exception.^{35a} By extrapolating the $E_T(30)$ vs. \underline{Z} plot, one can estimate that \underline{Z} for hexane should be 52 rather than the value of 60 reported by Kosower. The use of $\underline{Z} = 52$ for hexane can be seen to considerably improve the linearity of the \underline{J} vs. \underline{Z} plots in Fig. 3.

In Fig. 3 the points for chloroform are consistently out of line with the other solvents whenever a significant variation of \underline{J} with solvent polarity is observed. This behavior may have to do with the ability of chloroform to form weak hydrogen bonds, a property to which the charge transfer transition of the pyridinium compounds may be insensitive. The results for methanol, which are consistent with other solvents, do not appear to support this suggestion; however, in alcohols, hydrogen bonding to other solvent molecules may be such that hydrogen bonding to solute molecules such as the biradicals is relatively weak.³⁶ Biradical I was examined in two other solvents in which hydrogen bonding is expected to

ref. 35

ref. 36

be important. In aniline ($\underline{Z} = 70$, estimated from a plot of $E_T(30)$ vs. \underline{Z}) the exchange interaction was 170 G, while in acetic acid ($\underline{Z} = 79.2$) a value of 172 G was determined. In each case the result falls well above the line defined by the other solvents.

Pyridine does not have a hydrogen capable of hydrogen bonding, and the reason \underline{J} in pyridine is not consistent with results in most other solvents is unclear. It may have to do with the structural relationship between pyridine and the pyridinium compounds from which \underline{Z} and $E_T(30)$ are derived. Solvent-solute interactions other than dipole-dipole interactions may be important (e.g., stacking of solvent and solute).

When \underline{a} is plotted vs. \underline{Z} , fair linearity is seen, but again the points in chloroform and pyridine fall clearly off the line defined by the other solvents. When \underline{J} is plotted vs. \underline{a} for biradicals \underline{I} and \underline{VI} , fair linearity is again obtained; however, the points for chloroform and pyridine (and aniline and acetic acid for \underline{I}) conform to the line defined by the other points. These observations provide strong evidence that the solvent dependence of \underline{J} and \underline{a} are closely related. In Fig. 6, $J(\underline{I}_1)$ is plotted against $J(\underline{VI})$. Very good linearity is obtained, strongly indicating that the mechanism by which solvent affects \underline{J} is the same in both biradicals. Other plots like Fig. 6 are much less linear (e.g., \underline{III}_1 vs. \underline{V}_1) indicating that other factors are also important.

A decrease in exchange with increasing solvent polarity has been previously reported for only one nitroxyl biradical.³⁷ Two further examples of such behavior are presented here, \underline{IV} and \underline{X}_2 . Biradical \underline{IV} should be little different from \underline{I} or \underline{II} in the spacial relationship of the nitroxyl groups, yet the presence of the epoxide at positions 5,6 results in an

Fig. 6

ref. 37

entirely different dependence of $\underline{J}(\underline{IV})$ on solvent polarity. For \underline{X} the two biradicals observed should correspond to the 16α - and 16β -doxyl epimers, yet the dependence of \underline{J} on solvent polarity is distinctly opposite for \underline{X}_1 and \underline{X}_2 . This observation does not generalize to the 3- or 17-positions since the minor biradicals ($\underline{I}_2, \underline{III}_2, \underline{V}_2, \underline{V}_3$) should also be epimers of $\underline{I}, \underline{III}$ or \underline{V} , yet the exchange interaction either increases with or is independent of solvent polarity.

The solvent trends in either the 3,17 or 3,20 series shown in Fig. 3 are not consistent with a direct exchange mechanism. Within either series the relative orientations of the doxyl groups should be similar for each member and one would expect that for direct exchange a qualitatively similar effect of solvent would be noted for each. In contrast, even the direction of the change in \underline{J} with solvent polarity is not the same.

Effect of Temperature. The temperature coefficients listed in Table II show many inconsistencies. The magnitude of the coefficient does not directly relate to the dependence of \underline{J} on solvent polarity as one can see by comparing $\underline{I}_1, \underline{V}_1$ and \underline{III}_2 . For a particular biradical, the coefficient in hexane can be smaller or larger than that in chloroform and the signs can be the same or different. Similar inconsistencies obtain when comparisons are made between the major and minor biradicals where multiple sets of S-resonances were observed.

The single consistency is seen in chloroform, where the sign of the temperature coefficient is positive only when \underline{J} decreases with increasing solvent polarity. A similar relationship can be noted for flexible biradicals at temperatures for which S-resonances could be clearly discerned (generally below 20°).³⁷ A plausible explanation would be that, because

-27-

the tumbling rate of both solvent and solute increases with increasing temperature, the ability of the solvent molecules to interact with the solute (either through hydrogen bonding or through dipole-dipole interactions) decreases, leading to a condition of decreasing polarity with increasing temperature. When \underline{J} decreases with increasing polarity, a positive temperature coefficient would result and vice versa. In hexane which lacks a dipole moment, no similar correlation is seen. Here the effect of increasing intramolecular (vibrational) motions with increasing temperature may predominate.

For biradical VI an extra S-resonance becomes apparent as the temperature is increased (Fig. 4) and most likely corresponds to the strongest S-transition of a second form of the biradical. This observation is possibly due to the presence of a second epimer of VI in which the effect of temperature on \underline{J} is much less than for the major epimer resulting in the resolution at higher temperatures. However, the extra S-resonance may actually be increasing in relative intensity as the temperature is raised and might correspond to a higher energy conformation of the biradical reached by rotation about the C₁₇-C₂₀ bond.

Conclusion

The biradicals reported here were synthesized in the hope that they might provide insight into the mechanism of electron spin exchange in nitroxyl biradicals. For the most part the results have been considered to be more in line with the indirect mechanism than with direct exchange. It should be emphasized, however, that the more complex indirect mechanism has in large part "won by default" on the basis that many of the results

appear inconsistent with the simpler direct mechanism. It is of course possible that both exchange mechanisms are of importance in these compounds and together lead to the rather complex dependence of \underline{J} on structure and solvent. The indirect mechanism itself may include contributions from several mechanisms such as spin polarization, spin delocalization and homohyperconjugation, and thus lead to complex behavior.

In discussing direct exchange, the W-plan arrangement of bonds, which appears to be important to long-range coupling in nmr and esr and is apparent in the rigid biradicals presented here, has been emphasized. The fact that $\underline{J}(\underline{XI})$ is greater than $\underline{J}(\underline{V})$ would not appear to follow from such considerations since the bonding is mainly the same for both, and \underline{XI} has one more bond separating the nitroxyl groups than does \underline{V} . The one property of \underline{XI} which stands out when compared with \underline{V} is the greater symmetry of \underline{XI} and suggests that symmetry may be of importance in determining the magnitude of \underline{J} .

The magnitude of \underline{J} was found to depend also on the solvent polarity and on the temperature. Depending on the structure of the biradical, the effect of solvent on \underline{J} may be large or small, and either an increase or decrease of \underline{J} with solvent polarity can result. The correlation of these changes in \underline{J} with changes in the nitrogen hyperfine interaction strongly suggests a cause-effect relationship between solvent-induced shifts in electron density on the nitroxyl groups and changes in \underline{J} . The reasons the exchange interaction depends on temperature probably include the kinetic aspects of solvation and changes in the vibrational state of the molecules.

Experimental

Nmr spectra were recorded on a Varian Associates Model HR-220 instrument. High resolution mass spectra were run on a AEI MS 9 spectrometer. Esr spectra were recorded on a Varian Associates E-3 spectrometer equipped with 100 KHz modulation and an X-band (9.5 GHz) klystron, and a Varian V-4502 variable temperature accessory was used for variable temperature work. Samples were prepared at 10^{-5} molar concentrations and degassed in 1 mm quartz tubes with nitrogen for 30 sec, frozen in liquid nitrogen while purging the tube with nitrogen and then sealed with a torch. Care was taken during sealing not to pyrolyze the solvent since this generated radicals which reacted with the sample.

Preparation of the Dioxazolidines. The general procedure for the conversion of the steroid diones to the dioxazolidines²⁷ was to reflux the dione with a 20-fold excess of 2-amino-2-methylpropan-1-ol (Aldrich Chemical Co.) in xylene (20 ml per mmole of steroid diketone) with 5 mg of toluene sulfonic acid monohydrate per mmole of steroid. A Dean-Stark trap packed with 4A molecular sieves was used for continuous water removal. The reflux time varied depending on the steric hindrance about the ketone group. The reaction progress could be easily followed by gas chromatography on a 6-foot column of OV-17. In general, complete conversion at the 3-position occurred in 3 days; however, a 3-week reflux was necessary to affect an 80% conversion at the 17- and 20-positions. Reaction at the 17-position of the precursor of XI was extremely slow and after 30 days only a small amount of the dioxazolidine was formed.

After refluxing, the reaction mixture was cooled and washed 4 times with equal volumes of cold saturated sodium bicarbonate solution and then

with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate the xylene was removed under reduced pressure. The crude dioxazolidines were obtained as viscous oils and not further purified prior to oxidation to the free radicals. In some cases the dioxazolidines could be obtained as crystalline compounds by recrystallization.

A similar procedure was used to prepare the mono-oxazolidine precursors of monoradicals XII, XIII and XIV.

Preparation of the Nitroxyl Radicals. The general procedure for conversion of oxazolidines to nitroxyl radicals²⁷ was to dissolve the oxazolidine in ether (10 ml per mmole). While stirring and cooling the solution on ice, a 1.5 mole excess of m-chloroperoxybenzoic acid in ether (5 ml per mmole) was added dropwise. This mixture (unless otherwise indicated below) was allowed to stand at room temperature for 48 hr. After this time the reaction mixture was washed 4 times with an equal volume of cold saturated sodium bicarbonate solution and then once with saturated sodium chloride solution. The ether solution was dried over anhydrous magnesium sulfate and the ether was removed at reduced pressure. All biradicals were obtained as oils and purified by column chromatography on silica gel, using a solvent of chloroform-hexane (10:1). Samples for esr study and high resolution mass spectroscopy were further purified by tlc on silica gel, using a solvent of chloroform-hexane (20:1). In some cases the biradicals could be crystallized from the appropriate solvent.

3,17-didoxyl-5 α -androstane (I). The dioxazolidine precursor prepared from 5 α -androstan-3,17-dione (Sigma) was oxidized to the biradical as described above. Crystallization from hexane-methanol yielded yellow plates; mp 200-201°. Anal. calcd. for C₂₇H₄₄N₂O₄: C, 70.40; H, 9.62;

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N, 6.10. Found: C, 70.57; H, 9.35; N, 6.23. Mass spec (M^+ 460.330869, for $C_{27}H_{44}N_2O_4$ $\Delta = -1.64$ ppm).

3,17-didoxyl-5 β -androstande (II). The dioxazolidine precursor prepared from 5 β -androstan-3,17-dione (Sigma) was oxidized to the biradical as described above. Crystallization from hexane-methanol gave yellow plates; mp 188-189°. Anal. calcd. for $C_{27}H_{44}N_2O_4$: C, 70.40; H, 9.62; N, 6.10. Found: C, 70.24; H, 9.44; N, 6.04.

3,17-didoxyl- Δ^5 -androsten-3,17-dione (III). The dioxazolidine precursor was prepared from Δ^4 -androsten-3,17-dione (Sigma). Oxidation to the biradical was done at 4° for 24 hr using two equivalents of m-chloroperoxybenzoic acid. The radical was obtained as a yellow oil. Mass spec (M^+ = 458.314930, for $C_{27}H_{42}N_2O_4$ $\Delta = -1.02$ ppm).

3,17-didoxyl-5,6 α -epoxyandrostande (IV). Method A: The dioxazolidine of Δ^4 -androsten-3,17-dione, when oxidized in the usual manner using a twofold excess of m-chloroperoxybenzoic acid, yields a mixture of biradicals III and IV which can be separated by tlc on silica gel. Method B: Biradical III was treated with one equivalent of m-chloroperoxybenzoic acid in chloroform. The reaction can be followed by esr and appears to be complete in 30 min. The biradical is isolated as a yellow oil. Mass spec (M^+ = 474.305247, for $C_{27}H_{42}N_2O_5$ $\Delta = 8.71$ ppm).

3,17a-didoxyl-5 α -D-homoandrostande (V). 5 α -D-homoandrostan-3,17a-dione, prepared by the method of Goldberg *et al.*,³⁸ was converted to the oxazolidine and oxidized to the biradical in the usual manner. Crystallization from methanol-water yielded yellow plates; mp 187-190°. Anal. calcd. for $C_{28}H_{46}N_2O_4$: C, 70.84; H, 9.76; N, 5.90. Found: C, 71.01; H, 9.76; N, 5.71.

3,20-didoxyl-5 α -pregnane (VI). 5 α -pregnan-3,20-dione (Sigma) was converted to the oxazolidine. The oxazolidine crystallized from hexane; mp 159-161°. Anal. calcd. for C₂₉H₅₀N₂O₂: C, 75.93; H, 10.98; N, 6.11. Found: C, 75.74; H, 10.77; N, 6.25. Oxidation yielded the biradical which could be crystallized from hexane-methanol; mp 202-203°. Anal. calcd. for C₂₉H₄₈N₂O₄: C, 71.27; H, 9.89; N, 5.73. Found: C, 71.40; H, 9.60; N, 5.50. Mass spec (M⁺ 488.359849, for C₂₉H₄₈N₂O₄ Δ = +3.21 ppm).

3,20-didoxyl-5 β -pregnane (VII). The dioxazolidine precursor was prepared from 5 β -pregnan-3,20-dione (Sigma) and oxidized in the usual manner. The biradical crystallized from hexane-methanol; mp 191-192°. Anal. calcd. for C₂₉H₄₈N₂O₄: C, 71.27; H, 9.89; N, 5.73. Found: C, 71.38; H, 9.69; N, 5.88.

3,20-didoxyl- Δ^5 -pregnane (VIII). Progesterone (Sigma) was converted to the dioxazolidine and oxidized at 4° for 24 hr with two equivalents of m-chloroperoxybenzoic acid to the biradical. Mass spec (M⁺ = 486.346892, for C₂₉H₄₆N₂O₄ Δ = -2.32 ppm).

3,20-didoxyl-5,6 α -epoxypregnane (IX). Prepared by either method A or B as described for biradical IV. Mass spec (M⁺ = 502).

3,16-didoxyl-5 α -androstane (X). Androstan-3,16-dione was prepared by the method of Bridgeman et al.,³⁹ converted to the dioxazolidine and oxidized in the usual manner. The biradical could be crystallized from hexane-methanol. Anal. calcd. for C₂₇H₄₄N₂O₄: C, 70.40; H, 9.62; N, 6.10. Found: C, 70.9; H, 9.4; N, 6.2.

3,17-didoxyl-17 α -methyl-5 α -D-homoandrostane (XI). 17 α -methyl-5 α -D-homoandrostan-3,17-dione was prepared by the method of Ramirez et al.⁴⁰ Conversion to the oxazolidine and oxidation yielded a very small amount of biradical. Mass spec (M⁺ = 488.358161, for C₂₉H₄₈N₂O₄ Δ = 6.66 ppm).

3-doxy1-testosterone propionate (XII). Prepared from testosterone propionate in the usual manner. Anal. calcd. for $C_{26}H_{41}NO_3$: C, 75.14; H, 9.94; N, 3.37. Found: C, 75.14; H, 9.88; N, 3.26.

17-doxy1-5 α -androstan-3 β -ol (XIII). 5 α -androstan-3 β -ol (Sigma) was converted to the oxazolidine and crystallized from hexane-methanol; mp 122-124°. Anal. calcd. for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87; N, 3.87. Found: C, 76.36; H, 10.61; N, 3.88. Oxidation gave the monoradical which was crystallized from hexane-methanol; mp 198°. Anal. calcd. for $C_{23}H_{38}NO_3$: C, 73.36; H, 10.17; N, 3.72. Found: C, 73.50; H, 9.92; N, 3.95.

20-doxy1-5 α -pregnan-3 β -ol (XIV). 5 α -pregnan-3 β -ol-20-one (Sigma) was converted to the oxazolidine and crystallized from hexane-methanol; mp 151-152°. Anal. calcd. for $C_{25}H_{43}NO_2$: C, 77.06; H, 11.03; N, 3.59. Found: C, 76.76; H, 10.82; N, 3.59. Oxidation gave the monoradical which was crystallized from hexane-methanol; mp 180° dec. Anal. calcd. for $C_{25}H_{42}NO_3$: C, 74.21; H, 10.46; N, 3.28. Found: C, 73.96; H, 10.18; N, 3.28.

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Figure Captions

Figure 1. Structures of the biradicals and monoradicals synthesized.

Figure 2. Representative esr spectra of biradicals in chloroform:

(a) I at 40°; (b) II at room temperature; (c) VI at room temperature;
(d) VII at room temperature. Except for (d), only the high-field S-resonances are shown.

Figure 3. Effect of solvent on J for I - IV (left) and VI - IX (right).

The solvent and biradical designations are given in the figure. The Kosower Z is a spectroscopic measure of solvent polarity (see text).

Figure 4. Effect of temperature on the S-resonances of VI in xylene.

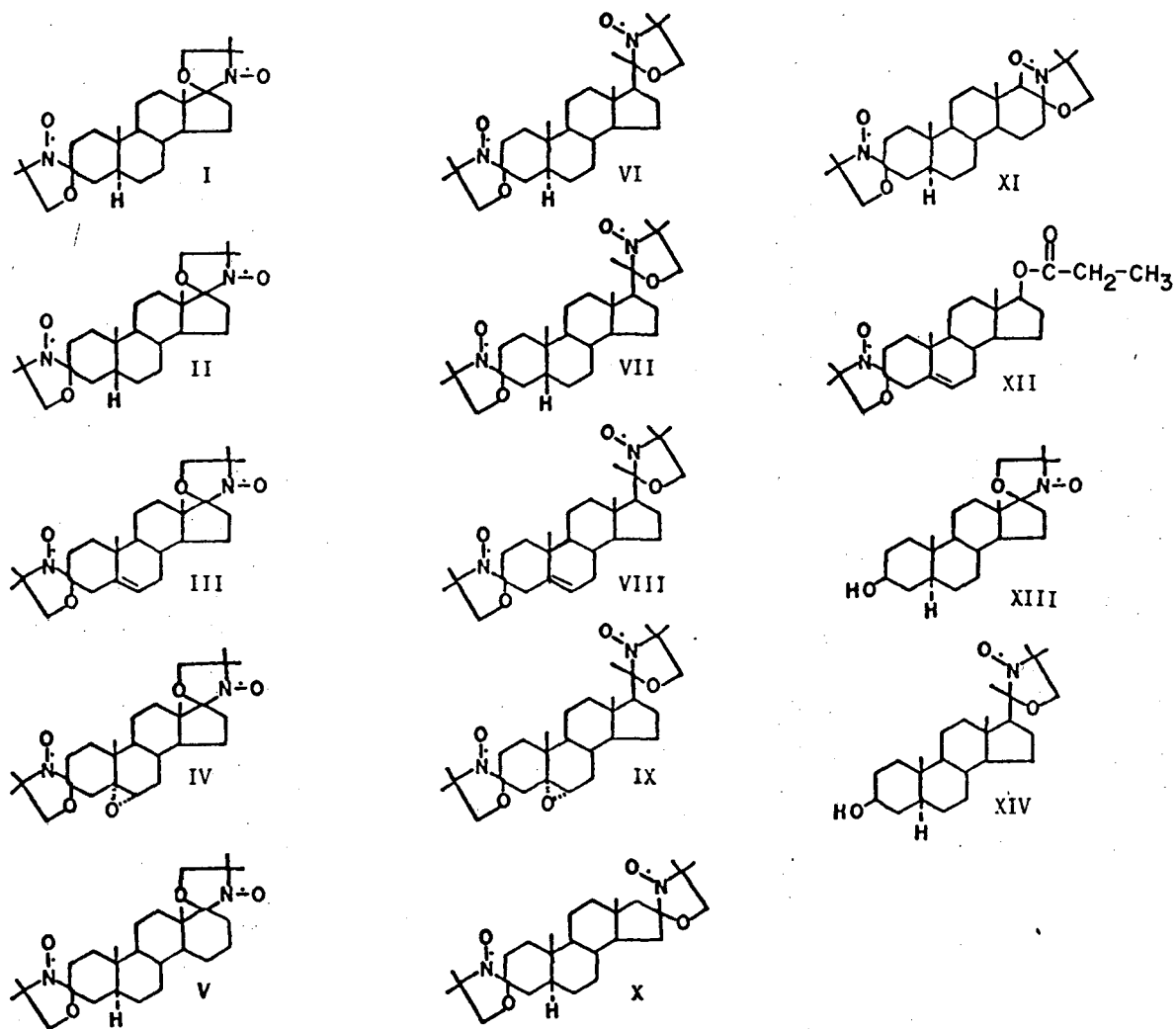
Only the high-field S-resonances are shown. The biradical was decomposing, slowly at 100° and rapidly at 200°, such that gain settings are different for each spectrum. The effect was reversible.

Figure 5. Esr spectrum of XI in chloroform at room temperature. The

spectrum appears to contain about 50% monoradical and 50% biradical with

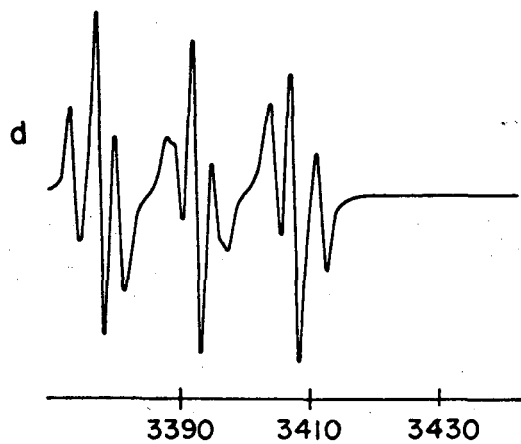
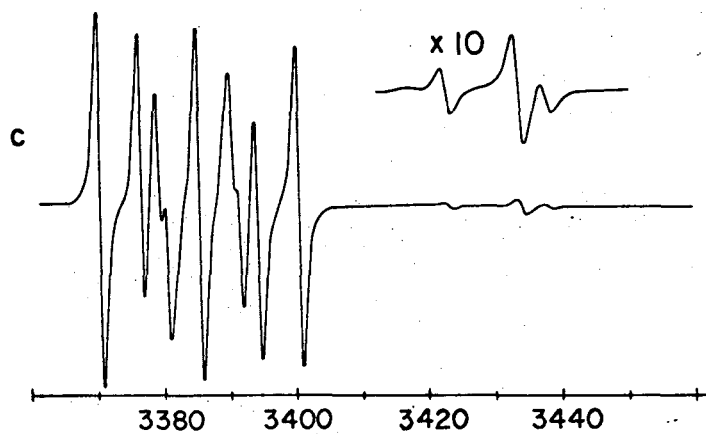
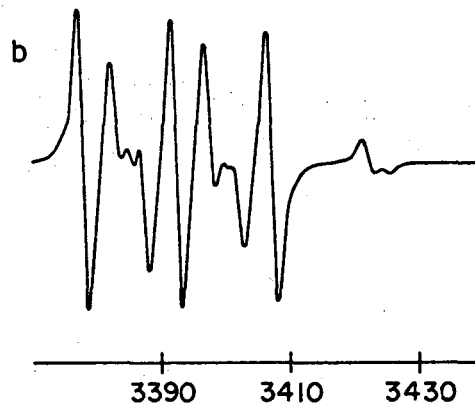
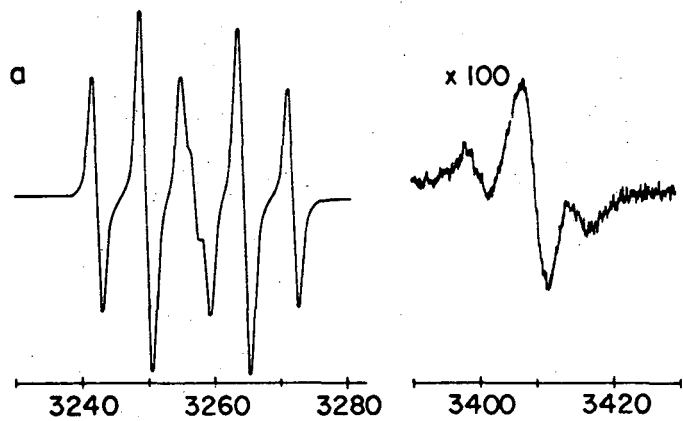
J >> a.

Figure 6. Plot of J(I) vs. J(VI) in different solvents.



XBL 7410-8062

Fig. 1.



GAUSS

Fig. 2.

XBL 7410-8063

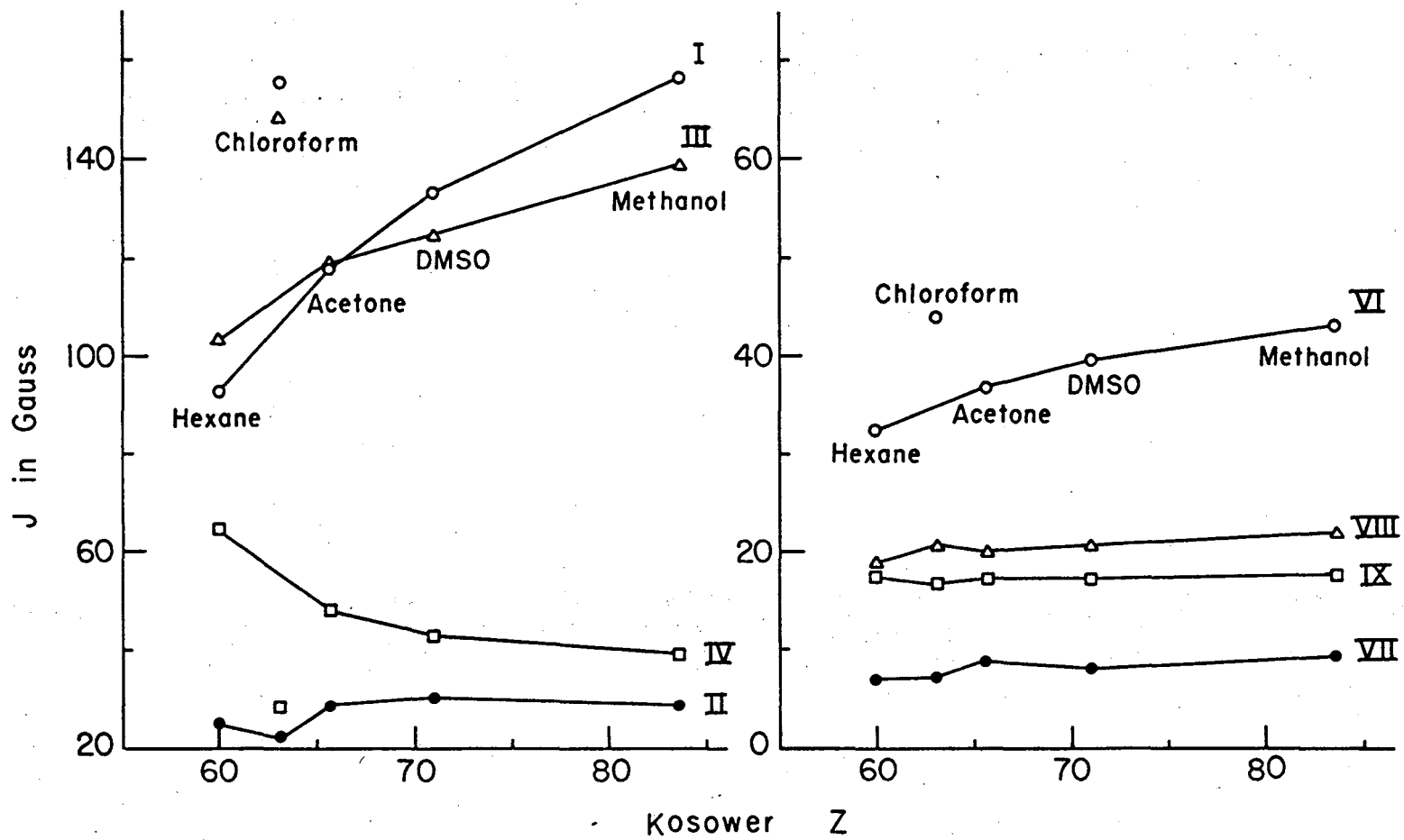
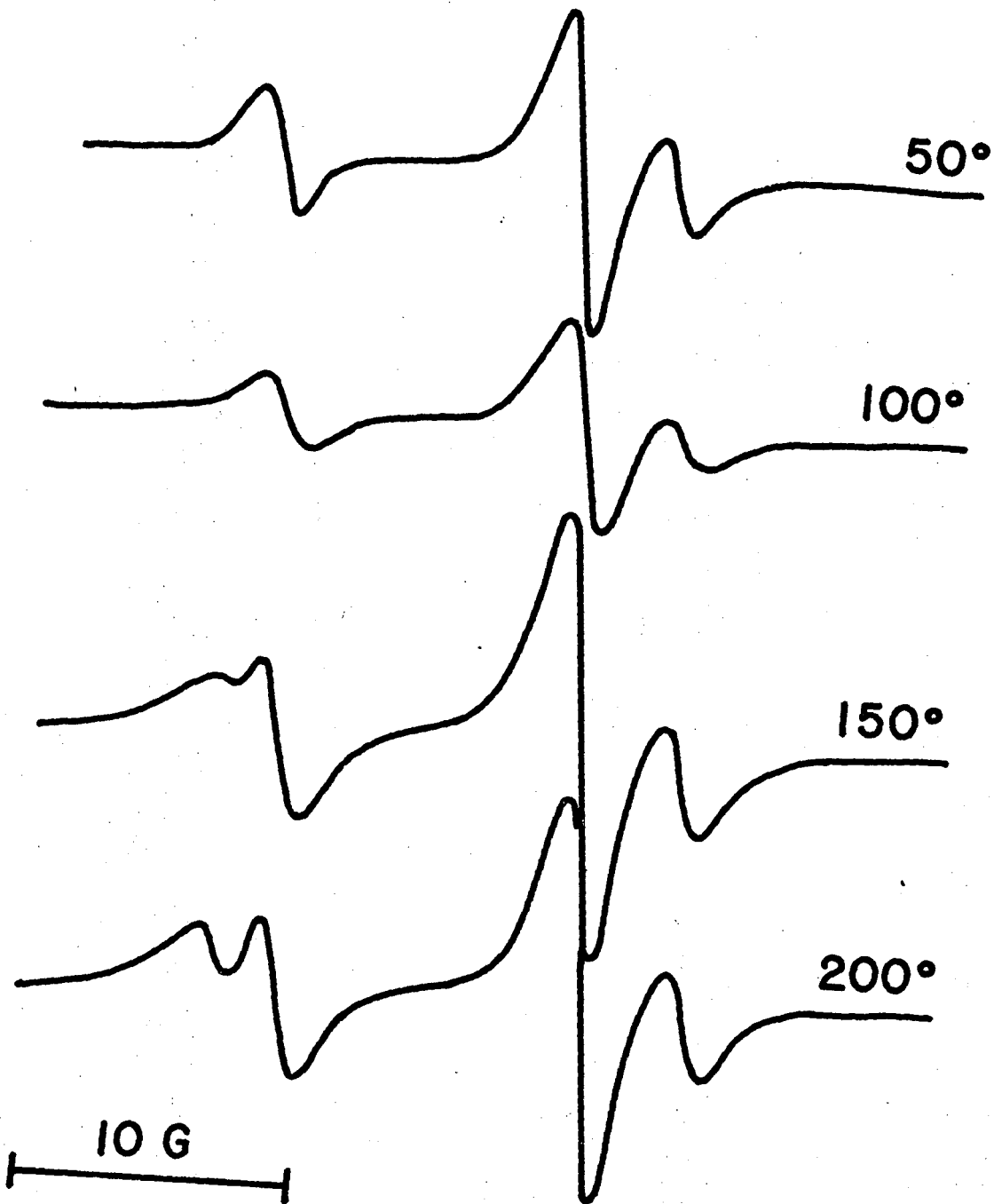


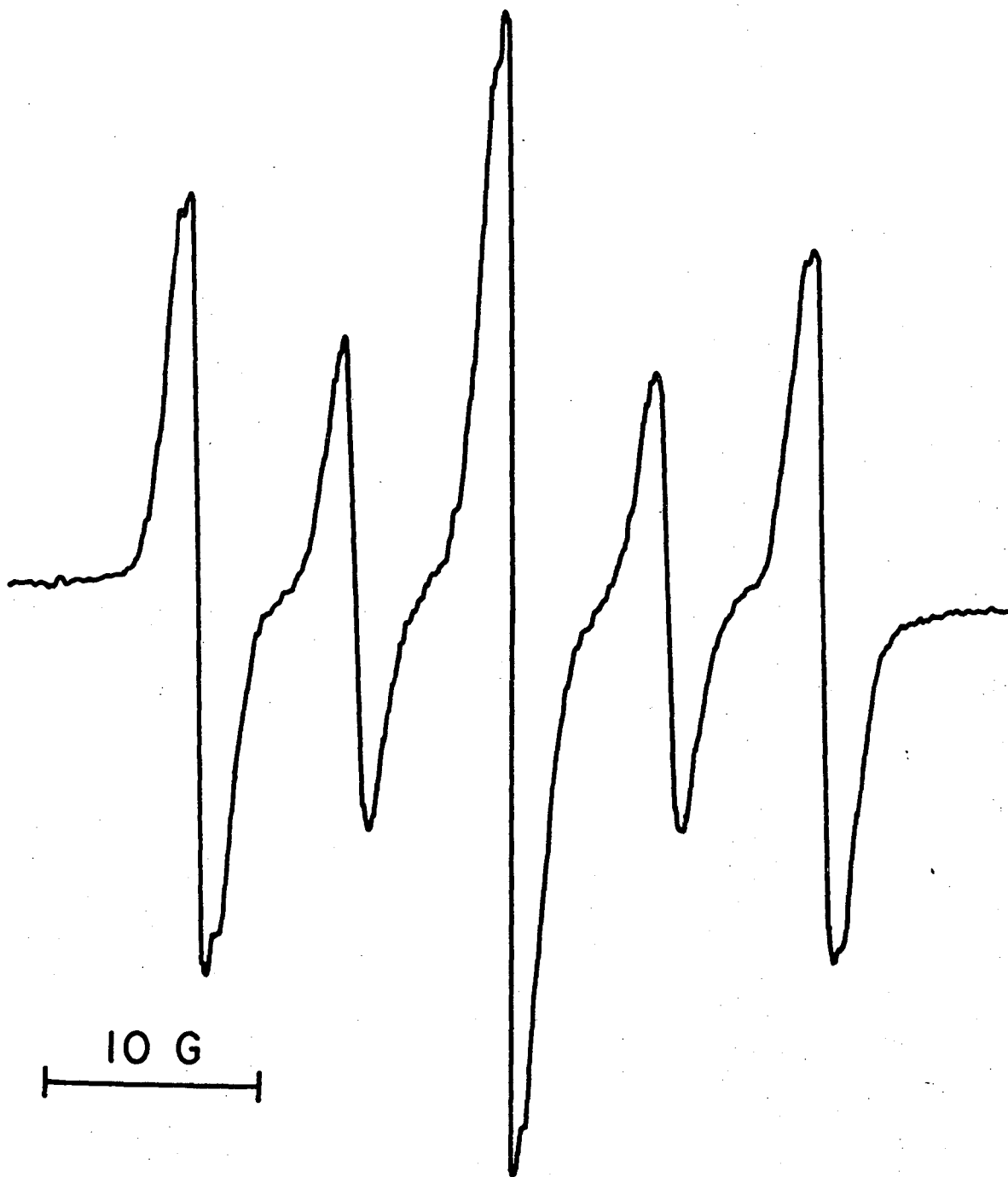
Fig. 3.

XBL746-5225



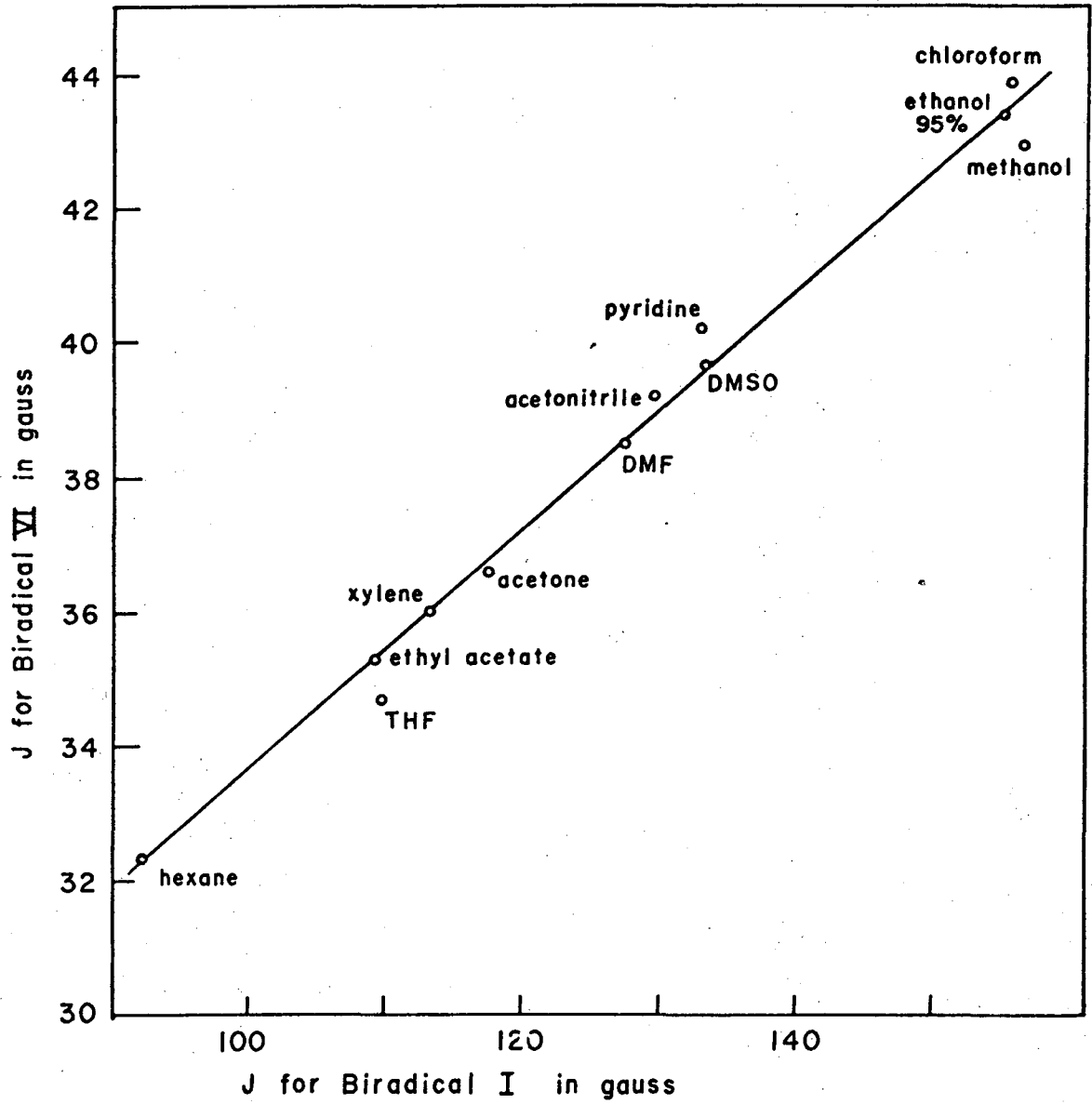
XBL7410-8052

Fig. 4.



XBL7410-8051

Fig. 5.



XBL742-5053

Fig. 6.

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