Orientation in Nucleophilic Substitution at the Cycloheptatrienone Nucleus: Failure of Predictions from Either Electron Spin Resonance Data or Molecular Orbital Treatments[1]

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Abstract: Reactivity in nucleophilic substitution of either chlorine or the tosyloxy group from the cycloheptatrienone nucleus by either dimethylamine in dimethyl sulfoxide or sodium methylmercaptide in absolute ethanol, via the addition–elimination mechanism, as measured kinetically, yields the reactivity sequence C(3) > C(2) ≈ C(4). The radical anions of the above cycloheptatrienones, generated electrolytically in dimethyl sulfoxide and studied by ESR spectroscopy, show the decreasing order of hyperfine splitting constants C(2)-H > C(4)-H ≫ C(3)-H. Lack of correlation between the site of the highest hyperfine splitting constant and that of highest reactivity shows the limitation of correlations of this type which have aroused great interest because reportedly they work well for aromatic substitution. Also extended perturbational treatments, as well as static procedures and localization methods, fail to predict correctly the orientation in substitution with troponoids. There is some indication that medium effects on the substitution reactions are largely responsible for unsuccess in such predictions with troponoids. This suggests that, in general, for the reactivity of ionic processes in solution, it is still the experimental (kinetic) method on which we must rely.

Recently reported success in relating preferential orientation in aromatic substitution with the position of highest hyperfine splitting constant in the aromatic free radical, via either the monoelectronic transfer mechanism[3] or the traditional bielectronic flow from the nucleophile to the substrate,[4] has generated great interest.

We became directly interested in this approach in connection with the reactivity of cycloheptatrienones. The scope of the investigation was twofold. On the one hand we hoped to arrive at a firm rationalization of why cycloheptatrienones (**1**)

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carrying an electron donating group at C(2) are attacked by nucleophiles, albeit slowly, at C(2) only, while those carrying heavy halogen,[5a] positive nitrogen,[5a,c,6] bivalent sulfur,[7] or positive, tricoordintated sulfur at C(2) are more reactive, being usually attacked by nucleophiles first at other ring carbons, most frequently at C(7),[5-8] but also at C(1),[5a,9] C(3),[9] and C(6).[5a,9] In fact, only intuitive explanations have been offered for this complex reactivity pattern.[5,9] On the other hand, this study would constitute a test of the validity of reactivity predictions from ESR parameters in a nonbenzenoid system.

To this end we provide here a set of consistent data for the orientations in nucleophilic substitution with cycloheptatrienones together with the ESR data for the radical anions of such substrates, which were unreported.

Results

Rate Data for Nucelophilic Substitution at the Cycloheptatrienone Nucleus. What is needed to determine the orientation in nucleophilic substitution at the cycloheptatrienone nucleus is at least one set of three isomeric cycloheptatrienones carrying an atom or group at either C(2), C(3), or C(4) which is replaceable by at least one nucleophile without any rearrangement. We have found two such sets of substrates, halo- and tosyloxytropones, which fulfill the above conditions toward both an amine like dimethylamine in dimethyl sulfoxide (DMSO) and sodium methylmercaptide in ethanol.[10]

All these reactions proceed with quantitative yield under kinetic conditions as shown in the Experimental Section. Reactions by the thiolate are simple overall second-order reactions, the relevant kinetic data being collected in Table I.

Reactions by the amine are generally more complex, the observed rate coefficient, k_{obsd}, obtained by dividing the pseudo-first-order rate coefficient by the amine concentration, being strictly independent of the amine concentration only for reactions by the C(2) substituted substrates. In all other cases a linear increase with the amine concentration is observed according to the equation

$$k_{obsd} = k_2 + k_3[\text{amine}] \qquad (1)$$

The relevant data are collected in Tables II and III. Table III also collects activation data computed from the k_2 coefficients.

Other observations which will prove useful later in discussing the reaction mechanism are: (a) the reactions of the tosylates of Table II are insensitive to the addition of a tertiary amine like quinuclidine; (b) while the reactions of 2-chloro- and 2-tosyloxytropone of Table II are only slightly sensitive to medium effects, being in a nonpolar solvent like benzene nearly as fast as in the strongly dipolar Me_2SO, all other substrates of Table II remained unreacted in the presence of dimethylamine in benzene; (c) also 4-iodotropone[11] remained unreacted in the presence of dimethylamine in benzene while in Me_2SO 4-dimethylaminotropone was rapidly produced; moreover, addition of *m*-dinitrobenzene had no noticeable effect on this reaction; (d) UV spectra showed the absence of important preequilibria for formation of adducts[6] between nucleophile and substrate for all cases in Tables I and II.

Distribution of Hyperfine Splitting Constants in Radical Anions of Cycloheptatrienones. At the onset of this study little was known about radical anions of cycloheptatrienones. In particular, nothing was known about radical anions of cycloheptatrienones carrying a replaceable group, which are just the cases where we need the distribution of the hyperfine splitting constants for the study proposed in the Introduction.

Table I. Kinetic Data[a] for Substitution of Chlorine or the Tosyloxy Group from Chloro- or Tosyloxytropones[b] by Sodium Methylmercaptide[c] in Absolute Ethanol

Group replaced	Second-order rate coefficient k, mol^{-1} L s^{-1} 15 °C	20 °C	25 °C	31 °C	32 °C	40 °C	$\Delta H^{\ddagger}$ kcal mol^{-1}	$-\Delta S^{\ddagger}$ at 25 °C, eu
2-Cl		2.0	2.4	3.5		5.6	8.9	27
3-Cl		3.0	3.7	4.6		5.6	6.4	34
4-Cl		2.3	2.8	4.1		6.8	7.9	30
2-OTs		2.8	3.5		7.0	12.3	13.4	11
3-OTs	178		227		268		3.7	35
4-OTs		3.7	4.8		9.4	14.8	12.4	14

[a] Kinetic data at any temperature are the mean of two runs except for the case of 3-tosyloxytropone, where they are the mean of six runs. [b] Initial concentrations range between 4×10^{-5} and 9×10^{-5} M. [c] Initial concentrations range between 6×10^{-4} and 2×10^{-3} M.

Table II. Kinetic Data for Substitution of Chlorine or the Tosyloxy Group from Chloro- or Tosyloxytropones[a] by Dimethylamine in Me_2SO

Group replaced	$(CH_3)_2NH$, M × 10^2	Observed rate coefficient k_{obsd}, mol^{-1} L s^{-1}, × 10^3 25 °C	31 °C	33 °C	35 °C	36 °C	45 °C
2-Cl	5.87	18.6			28.5		50.2
	8.57	18.6			28.5		50.2
3-Cl	0.960						170
	1.20						198
	1.35	100					200
	1.50	110					
	2.40						300
	2.68	190					395
	3.00	217					
	3.90						570
	5.13	330					
	5.90	380					
4-Cl	3.00	2.85				4.40	
	5.85	3.65				5.30	
	7.45						9.70
	8.50	4.20				6.20	
	11.3						11.5
2-OTs	1.55	113					239
	3.00	107	122				240
	6.00	107	122				
3-OTs	0.300	5200		6200			
	0.450	5200					
	0.650	5600		6400			
	1.00						8800
	2.00						9700
	2.10	6750					
	3.00						10500
	4.15	8400					
4-OTs	1.45	17.0					
	1.60						90.0
	2.85	27.0					
	2.95	29.5	42.0				
	3.10						94.0
	3.25	34.0	42.5				
	5.50		60.0				100
	5.90		62.0				
	5.95	49.0					
	6.30	54.0	63.0				

[a] Initial concentrations ranging from 4×10^{-5} to 8×10^{-5} M.

Table III. Kinetic Data at 25 °C for Reactions of Table II Computed by Equation 1

Group replaced	$10^3 k_2$, mol^{-1} L s^{-1}	$10k_3$, mol^{-2} L^2 s^{-1}	k_3/k_2 mol^{-1} L	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu
2-Cl	18.6	0	0	8.8	−37
3-Cl	23.3	60.7	260	0	−67
4-Cl	2.10	0.25	12	9.5	−39
2-OTs	109	0	0	7.1	−39
3-OTs	4950	8.38	17	3.7	−43
4-OTs	7.6	7.24	95	21.4	3.6

[a] Enthalpy and entropy of activation were computed from k_2 rate coefficients.

Later it became clear that while radical anions of cycloheptatrienones are often sufficiently stable to allow recording their ESR spectra, using electrochemical generation directly in the spectrometer cavity, just those needed for this study are very unstable because the mobile group, such as a halogen, is easily lost as an anion.[12]

However, following indications by cyclic voltammetry (Table IV, footnote *a*) we have been able to record the ESR spectra for the radical anions of both 2-chloro- and 4-chlorotropone by carrying out electrolyses directly in the spectrometer cavity at low temperature. The hyperfine coupling constants, which were assigned with the aid of a simulation program, via deuterium substitution (Table IV) and SCF MO calculations (Table IV, footnote *b*), are collected in Table IV.

In the case of 3-chlorotropone radical anion the ESR spectrum could not be obtained, as explained at Table IV, footnote *b*. However, since SCF MO calculations reproduced the trend of the experimental hyperfine coupling constants for the case of the two isomers of Table IV, as well as for all other anion radicals of cycloheptatrienones so far investigated,[12,13] which are mentioned below, we can safely take for 3-chlorotropone radical anion the hyperfine coupling constants, calculated by SCF MO methods, which are collected in Table IV.

The result is that the decreasing order of hyperfine splitting constants for all radical anions of chlorotropones is C(2)-H > C(4)-H ≫ C(3)-H. This is the order already found for the radical anions of tropone,[12,14] 3-methoxytropone,[13] 2-methoxytropone and several alkyl substituted 2-methoxytropones,[15] 2,7-dialkyltropones,[16] and 2-fluorotropone.[12] Moreover, investigations from these laboratories, to be reported later, have shown that the same trend of the spin density applies to the radical anions of various 2-, 3-, and 4-aminotropones, to various 2,6-diaminotropones, 2-, 3-, and 4-alkylthiotropones, and to the 2-dimethylsulfoniumtropone cation, where the assignment of hyperfine splitting constants to ring protons is supported by both deuterium substitution and SCF MO calculations.

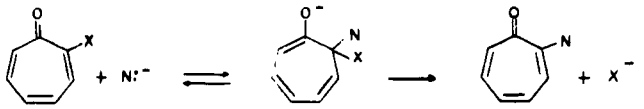
Only in the case of nitro-substituted tropones and tropolones a drastic change of the distribution of hyperfine splitting constants was observed because most of the unpaired electron is taken by the nitro group.[17]

The conclusion is that also for the radical anions of the three isomeric tosyloxytropones (the formation of which by monoelectronic reduction of the parent tosyloxytropones was unambiguously shown by cyclic voltammetry, but the mean life of which was too short even at low temperature to allow recording a satisfactory ESR spectrum[18]) the decreasing order of hyperfine splitting constants C(2)-H > C(4)-H > C(3)-H can be safely assumed. In fact, even if SCF MO calculations proved unfeasible in these cases, owing to the complexity of the molecules, it is unlikely that the tosyloxy function could capture most of the unpaired electron, since the positive sulfur of the sulfonio group proved unable to do so, as mentioned above.

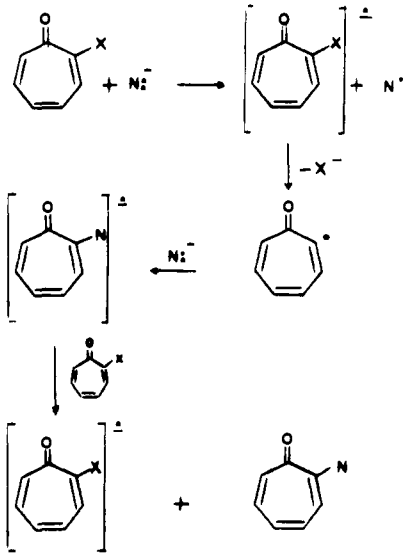
Discussion

Rate Data. Before we are in the position of assessing the predictive value of the ESR data obtained here in regard to the reactivity of cycloheptatrienones, the orientation in nucleophilic substitution at the cycloheptatrienone nucleus has to be unambiguously assessed from the rate data reported above. To this end we have to take the reaction mechanism into consideration, since any meaningful comparison about preferential

Scheme I



Scheme II



orientation has to be made through mechanistically homogeneous rate coefficients.

The two most likely mechanisms for the substitution reactions studied here are sketched in a simplified form in Schemes I and II for a substrate carrying a mobile group at C(2). The radical mechanism of Scheme II had to be taken into consideration after the recent observations as to the loss of halide anions from electrochemically generated radical anions of halotropones to give a troponyl radical which then abstracts hydrogen from the environment.[12]

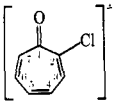
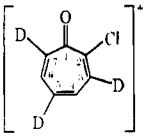
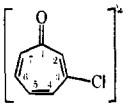
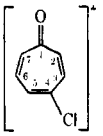
However, although the nucleophile could well do (homogeneously) the function of the cathode in affording electrons to the cycloheptatrienone,[19] the radical mechanism of Scheme II can be ruled out for the reactions of tosyloxytropones because work to be published from these laboratories has shown that electrochemically generated tosyloxytropone radical anions decay exclusively via O–S bond breaking.

Going to halotropones, the radical machanism of Scheme II is most conceivable for weakly bound X groups, such as iodine.[19,20] However, such a mechanism can hardly account for the strong solvent effect in the reactions of cycloheptatrienones carrying a mobile group at either C(3) or C(4) (points b and c above). More cogently, the radical mechanism is ruled out by the lack of any effect of a powerful radical trap like *m*-dinitrobenzene[19] (point c above).

This leaves under consideration only the ionic addition–elimination mechanism of Scheme I, which was already able to explain previous observations with cycloheptatrienones carrying a mobile group at C(2).[5a,15] Such a mechanism seems acceptable because it also explains consistently observations b and c above for all reactions of cycloheptatrienones carrying the mobile group at either C(3) or C(4) in terms of higher rates in more polar solvents for reactions involving charge development in the transition state.

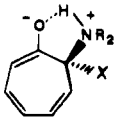
Going into details of the mechanism of Scheme I, the question of the timing of the proton removal during the reaction has to be considered. This is a question which has received great attention for the formally similar aromatic substitution by protic amines, where it has been suggested that higher values

Table IV. Hyperfine Coupling Constants (in Gauss) for Chlorocycloheptatrienone Radical Anions in Dimethylformamide Containing Tetra-*n*-butylammonium Perchlorate

		Expt[a]	Calcd[b]
	a_1^C		0.0
	a_3^H	0.0	1.93
	a_4^H	4.7	4.38
	a_5^H	4.7	5.04
	a_6^H	1.0	2.50
	a_7^H	8.1	7.13
	a_1^C		
	a_3^D	0.0	
	a_4^H	4.7	
	a_5^D	0.7	
	a_6^H	1.0	
	a_7^D	1.2	
	a_1^C		0.0
	a_2^H		8.9
	a_4^H		5.5
	a_5^H		6.9
	a_6^H		0.9
	a_7^H		7.6
	a_1^C		0.0
	a_2^H	8.7	7.4
	a_3^H	0.0	0.8
	a_5^H	5.4	6.9
	a_6^H	0.0	1.6
	a_7^H	8.7	8.3

[a] At −50 °C for 2-chlorotropone (−1.18 V) and at −25 °C for 4-chlorotropone (−1.20 V). In the case of 3-chlorotropone, even at low temperature, at the reduction potential indicated by cyclic voltammetry (−1.16 V) the behavior was that already described for experiments at room temperature (M. Martinelli, L. Nucci, L. Pardi, F. Pietra, and S. Santucci, *Tetrahedron Lett.*, 2089 (1975)); i.e., shortly after the beginning of the electrolysis the typical spectrum of tropone radical anion appeared. [b] Using the CNDO/2 program (J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970) for the regular heptagon planar geometry which was found to give the best fit for calculating the π-electron density (ρ_π) and the McConnell equation $a^H = Q\rho_\pi$ (H. M. McConnell, *J. Chem. Phys.*, 24, 764 (1956)). It must be noticed that the plot of a^H, directly obtained from INDO calculations (see Pople above), vs. ρ_π for tropone and 2-fluorotropone radical anions (M. Martinelli et al., above) gave $Q = -33$ G, which is considered to be more reliable than the value −23.7 G, as reported from examination of the only case of tropone radical anion (N. Trinajstic, *Bull. Chem. Soc. Jpn.*, 44, 3208 (1971)).

of the k_3/k_2 ratio (Table III) imply that more of the addition intermediate of the type at Scheme I decomposes into products via a catalyzed pathway involving a second amine molecule.[22] Following these ideas, substitution at C(2) gives simple first-order kinetics in amine (Table III) as expected for intramolecular assistance to the removal of a proton by the carbonyl oxygen[21] (**2**). In contrast, substitution at either C(3) or C(4),



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where the carbonyl group is far removed from the reaction center, in an addition intermediate of the type at Scheme I with a planar[23] seven-membered ring, gives complex kinetics according to eq 1 with a second-order component in amine (Table III).

However, such an interpretation of the trend of the k_3/k_2 ratio of Table III contrasts with both the lack of kinetic influence of a strong base like an unhindered tertiary amine

Table V. Energy Levels for Tropone and Chlorotropones

Compd	Energy[a] for levels, au		
	HOMO	LUMO	Next higher level
Tropone	−0.381	0.0116	0.0598
2-Chlorotropone	−0.4064	0.0167	0.0765
3-Chlorotropone	−0.4145	0.0233	0.0639
4-Chlorotropone	−0.4920	0.0162	0.0763

[a] Calculated by the CNDO/2 program for planar, bond alternate geometries, as established by x-ray diffraction analysis for tropone (M. J. Barrow, O. S. Mills, and G. Filippini, *J. Chem. Soc., Chem. Commun.*, 66(1973)) and 2-chlorotropone (D. J. Watkin and T. A. Hamor, *J. Chem. Soc. B.* 2167 (1971)).

(point a above) and the irregular trend of the k_3/k_2 ratios for the C(3) and C(4) substituted substrates.

Although we feel that the question of the origin of the k_3 terms of eq 1 would require more careful attention, remaining unanswered by the present investigation, nonetheless we have arrived at a set of mechanistically homogeneous rate coefficients (k_2 for the amine reactions, Table III, and k for the mercaptide reactions, Table I) which fulfill the scope set forth at the beginning of the Discussion. In fact, the above rate coefficients are mechanistically homogeneous not only insofar as reaction orders are concerned, but also because they are free from complications by side equilibria involving complexes of addition of the nucleophile to ring carbons other than the one which is finally substituted.[6,21b,24]

Therefore orientation in nucleophilic substitution at the cycloheptatrienone nucleus can be judged from the above rate coefficients. What emerges from such a comparison (Table I and II) is that both the amine and the thiolate do not show a marked preference at room temperature for any one of the three isomeric carbons of the tropone nucleus, except for C(3) when it is bearing the tosyloxy function, where a definitely enhanced rate is observed.

Lack of Correlation of Rate Data with ESR Data. Clearly the above results contradict predictions from the ESR data obtained here, according to which the expected order of decreasing preference for substitution at the cycloheptatrienone nucleus would have been C(2) > C(4) ≫ C(3).

This conclusion is important, being at variance with the success of correlations between hyperfine splitting constants and orientation in aromatic substitution.[4] Therefore it is worthwhile to examine possible causes of failure of such correlations in the present case. To this end let us briefly recall the successful treatment for aromatic substitution[4] in order to learn about its requirements. For nucleophilic aromatic substitution the preferential position of substitution, via the bielectronic flow from the nucleophile to the substrate (which is the case also here, as shown by the discussion above supporting the mechanism of Scheme I), is related to the position of highest hyperfine splitting constant in the radical anion of the substrate.[4] Because hyperfine splitting constants are related to the spin density, and therefore to orbital coefficients, via the McConnell equation (Table IV, footnote *b*), this is a perturbational treatment which has been restricted to the frontier orbitals.[4]

To have such a correlation it is required that:[4] (i) attack of the reagent to the substrate is the rate-limiting stage; (ii) the extent of bond formation between attacking reagent and substrate at the rate-limiting transition state is the same for isomeric positions of attack; (iii) atoms or groups to be replaced on the substrate do not alter the LUMO energy with respect to the unsubstituted substrate.

We can show that condition i is fulfilled for the reactions studied here. In fact, it has been found that the relative rates for substitution of the halogen from 2-halotropones by sodium *p*-toluenethiolate stand in the order 82:2.6:2.5:1 for, respectively, F, Cl, Br, and I.[21b] When it is recognized that such a reactivity range, from the fluoro to the iodo compound, is compressed by symbiotic effects[25] which, for a polarizable nucleophile like a thiolate, favor substitution of the more polarizable leaving group, iodine, it turns out that, intrinsically, fluorine is displaced much faster than iodine. Therefore there must be very limited bond breaking with the leaving group at the rate-limiting transition state; otherwise the most weakly bound atom, iodine, would be displaced more easily than the strongly bound atom, fluorine, contrary to what has been observed.

Going to point ii, it is conceivable that the exchange integral for attack at C(2) can greatly differ from those for attack at either C(3) or C(4). In fact, for a planar[23] addition intermediate (Scheme I), interaction between charges on the attacking species and on the carbonyl oxygen can be very substantial for attack at C(2), in contrast with the cases for attack at either C(3) or C(4). However, since ESR data, as shown above, also fail to predict correctly the relative rates for substitution at C(3) and C(4), where there is no obvious reason why exchange integrals should greatly differ from one another, we can also forget point ii.

Finally, data in Table V show that the halogens in place of hydrogen have little effect on the LUMO energy, condition iii thus being fulfilled.

Failure of Predictions from Extended Theoretical Treatments. Searching for other possible causes of failure of the ESR treatment[4] to predict correctly the orientation for substitution with cycloheptatrienones, it can be argued that even if it is assumed that delocalization methods apply to our problem, i.e., that the rate-limiting transition state is not too far from reagents along the reaction coordinate[26] and that the "noncrossing rule" holds,[26] the mere use of frontier orbitals, as implied by the ESR treatment,[4] is an inadequate oversimplification. However, calculations reported in Table V indicate that the next higher level to the LUMO is of so high energy that interaction among this orbital and the approaching nucleophile orbitals can only negligibly contribute to the stabilization energy. Therefore such extended perturbational treatments[26] do not help to solve our reactivity problem.

On the other hand, if we admit (what seems contradicted by the kinetic data[21b] discussed before) that the rate-limiting transition state for substitution on troponoids is far from reagents along the reaction coordinate, the orientation might be dictated by Coulombic attractions and interelectronic repulsions, as accounted for by extended treatments.[26] This is expressed by the equation

$$\Delta E = -\frac{q_s q_t}{R_{st}\epsilon} + 2\frac{(C_s C_t \Delta\beta_{st})^2}{E_m^* - E_n^*} \qquad (2)$$

where the second term represents orbital control and the first term charge control, q_s and q_t being the total charges of the two interacting atoms, R_{st} the distance between the two interacting atoms, and ϵ the dielectric constant of the medium.[26] In accordance with our suggestion above of an early transition state, calculations for the reactions of chlorotropones with sodium methylthiolate in absolute ethanol at Table I, taking for $\Delta\beta_{st}$ the mean value of 20 kcal mol^{-1} for benzene, result in a charge control term less important than the orbital control term by several orders of magnitude for every reasonable value of R_{st}.

Since delocalization methods have failed, as shown above, to predict correctly the orientation in substitution with troponoids, we have considered a static approach through the well-known free valence index of eq 3. We have thus obtained the reactivity order C(2) > C(4) > C(3), in contrast with what has been observed experimentally, as said above.

$$F_\mu = \eta_{max} - \eta_\mu \quad (3)$$

We are thus left to localization procedures.[26] Such an approach has been already attempted long ago leading to the prediction of the reactivity order C(2) > C(4) > C(3) for nucleophilic substitution on the tropone nucleus.[27] Our present data show that such predictions[27] are incorrect.

Lack of Correlation of ESR Data with Other Literature Rate Data. Since, as shown above, substitution with cycloheptatrienones fulfill the requirements for application of hyperfine splitting constants–reactivity correlations,[4] it must be concluded that failure of such predictions depends on oversimplifications in the perturbational treatments.

Probably inadequacy of the ESR treatment[4] is not merely due to the molecular complexity of troponoids. In fact, although the ESR treatment[4] in some cases is reported to predict correctly the orientation in aromatic substitution by both nucleophiles and free radicals,[4] it has already been noticed[28] that predictions from hyperfine splitting constants[4] for orientation in substitution by the electrophilic radical OH in toluene are incorrect.

We want to add that the rationalization, on the basis of higher hyperfine splitting constant at the unsubstituted position, for the faster rate of attack at the unsubstituted ring position in the addition of methoxide to 2,6-dinitro 4-cyanoanisole,[4] is not convincing. In fact, methoxide adds faster at the unsubstituted position also with methyl picrate,[29] where hyperfine splitting constants, as judged from the radical anion of *sym*-trinitroanisole, must be equal at the two isomeric positions (notwithstanding the resonable expectation, from what has been said above, that the methoxy group has a negligible effect on the spin density distribution in the radical anion of methyl picrate).

Another inconsistency has to be remarked upon. Thus, while orientation in nucleophilic substitution on halonitrobenzenes is said to be orbital controlled, and therefore predictable from the values of the hyperfine coupling constants for the aromatic radical anion,[4] as discussed above, the orientation in nucleophilic substitution on halo-substituted aromatic diazonium salts is reported to be charge controlled, and therefore predictable from the ^{13}C chemical shift values for the aromatic substrate.[30] This generates the suspected view that only ad hoc explanations have been offered.

Origin of the Failure of Predictions from Either ESR Data or Extended Theoretical Treatments. Because extended theoretical treatment proved unable to account for orientation in substitution with troponoids, there also must be some overcomplexity with these reaction systems which is not accounted for by such treatments. Just because both the ESR treatment[4] and the theoretical treatments above do not take medium effects into account, while the reactions investigated here are extremely sensitive to solvent effects (points b and c above), the suspicion arises that medium effects are largely responsible for unsuccess in such predictions with troponoids.

The reasoning is as follows. The solvent effects on the reactions studied here can be rationalized on the basis of transition states for substitution of either chlorine or the tosyloxy group by the amine, which requires strong solvation. Therefore, in a nonpolar, nonsolvating medium only substitution at C(2) can occur because of internal solvation owing to hydrogen bonding, as indicated by (**2**).

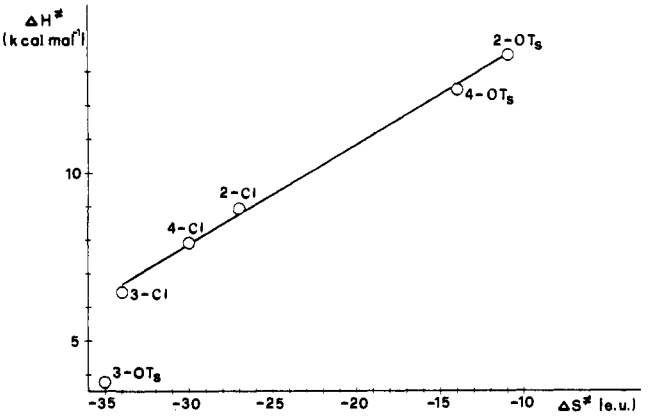

Figure 1. Plot of $\Delta H^{\pm}$ vs. $\Delta S^{\pm}$ for the reactions (Table I) of chloro- or tosyloxytropones with sodium methylmercaptide.

It can be argued that for substitution at either C(3) or C(4), as well as for the mercaptide reactions, such anchimeric effects are absent, as implied in the preceding discussion. However, because of the extreme sensitivity of these reactions to the nature of the medium, as said above, differential solvent effects at C(3) vs. C(4) cannot be excluded. On the same ground it is also to be expected that when orientation for substitution at the cycloheptatrienone nucleus in the same solvent is considered, solvent effects are involved to a different extent for substitution at the various ring positions, a situation which is not accounted for by either the ESR treatment[4] or the above theoretical treatments, which are then likely to lead to fallacious predictions, as observed here.

Therefore, until the effect of the medium cannot be included into theoretical calculations, it is still the experimental (kinetic) method on which we have to rely for the reactivity of ionic processes in general.

Before closing let us inquire to what extent the orientation observed in substitution with troponoids can be intuitively rationalized. Although we have made very little progress in this direction, we feel that the first step in the answer to this problem lies in the interpretation of the activation parameters in Tables I and III. If $\Delta H^{\pm}$ is plotted against $\Delta S^{\pm}$, it is seen that a isokinetic relationship[31] is followed in all cases except for 3-tosyloxytropone for both the mercaptide and the amine reactions. This is shown in Figure 1 for the mercaptide reactions: while in general a more favorable enthalpy factor is compensated for by an adverse entropic factor, thus resulting in a leveling out of the rates for different substrates, 3-tosyloxytropone shows an enhanced reactivity because a low enthalpy of activation is only poorly compensated for by an adverse entropic factor.

The difficulty lies in translating into molecular terms these extrathermodynamic observations because a delicate balance

Table VI. UV Data for the Products of the Reactions in Tables I and II

Product	Solvent	λ_{max}, nm	ϵ, mol^{-1} L cm^{-1}	λ (nm) at which the kinetics were followed
2-Thiomethyltropone	Absolute ethanol	343	8 600	385
3-Thiomethyltropone		284	18 000	272
4-Thiomethyltropone		344	8 700	370
2-Dimethylamiontropone	Me_2SO	354	7 600	405
		413	5 600	
3-Dimethylaminotropone		283	23 000	288
4-Dimethylaminotropone		362	13 900	375

of several effects, including solvent and steric[32] effects, is likely to be involved.

Experimental Section

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. UV spectra and all kinetics, except those for 3-tosyloxytropone, which were followed by the stopped-flow machine already mentioned,[6] were recorded on either a Unicam SP 800 or a Cary 14 spectrophotometer provided with a thermostated cell compartment. ^{1}H NMR spectra were run on either a Varian T-60 or a JEOL PS 100 spectrometer, with tetramethylsilane as internal standard. ESR spectra were obtained at 9.5 GHz by a machine assembled as already described,[13] always by the in situ electrochemical generation method at the appropriate constant potential as indicated by experiments of cyclic voltammetry. The electrolytic cell in the spectrometer cavity was cooled by a stream of cold nitrogen gas and the temperature was controlled by means of a thermocouple. Frequent cleaning of the platinum grid (cathode)[13] by means of hot nitric acid was essential to obtain good ESR spectra. All experiments, including sampling operations, were carried out under dry nitrogen.

Chemicals. Dimethylformamide and dimethyl sulfoxide were distilled over activated molecular sieves at reduced pressure directly in Schlenk tubes containing molecular sieves and stored at low temperature. Commercial absolute ethanol was utilized. Tetra-*n*-butylammonium perchlorate was dried in vacuo.

Troponoids available from previous work or reprepared according to published directions include 2-chlorotropone,[21a] 2-chloro-2,5,7-trideuteriotropone,[21a] 2-tosyloxytropone,[33] 3-chlorotropone,[34] 3-tosyloxytropone,[34] 4-chlorotropone,[35] 4-tosyloxytropone,[36] 2-dimethylaminotropone,[37] 3-dimethylaminotropone,[34,35] 4-dimethylaminotropone,[36] and 2-thiomethyltropone.[39]

3-Thiomethyltropone. To 0.034 g (0.122 mmol) of 3-tosyloxytropone dissolved in 1 mL of absolute ethanol was added, under N_2 and with stirring, sodium thiomethoxide (0.113 mmol). After 1 h the mixture was filtered, the solvent was evaporated in vacuo, and the residue was chromatographed on a 2-mm thick silica gel layer, eluent benzene–ethanol 80:20. The band at R_f 0.6 gave 3-thiomethyltropone, mp 64–66 °C from cyclohexane, with a 60% yield: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, CH_3, 3 H) and 6.9 (complex m, 5 H); UV $\lambda_{max}^{C_2H_5OH}$ 343 nm (ϵ 8600). Anal. Calcd for C_8H_8OS: C, 63.1; H, 5.3; S, 21.1. Found: C, 63.0; H, 5.4; S, 21.0.

4-Thiomethyltropone. The synthesis was carried out as described above for the 3-isomer. Chromatographic eluent benzene–ethyl ether–ethanol 75:20:5, R_f 0.3. 4-Thiomethyltropone was obtained in a 60% yield as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, CH_3, 3 H) and 7.0 (complex mult, 5 H); UV $\lambda_{max}^{C_2H_5OH}$ 344 (ϵ 8700), 292, 276, and 230 nm; picrate mp 118–119 °C (from ethanol). Anal. Calcd for $C_{14}H_{11}N_3O_8S$: C, 44.1; H, 2.9; N, 11.0. Found: C, 44.0; H, 3.0; N, 11.0.

Kinetics. All reactions in Tables I and II were followed by measuring the UV absorbance of the troponoidal substitution products free from interference from absorption by any other chemical. To this end wavelengths were chosen as indicated in Table VI. In any case the "mock infinity" prepared with authentic samples of the reaction products corresponded to the real infinity, according to practically quantitative yield. Moreover, both the nature and yield of the reaction products were further checked by carrying out large scale reactions under the kinetic conditions of Tables I and II, then evaporating the solvent in vacuo and chromatographing the residue by TLC on silica gel and finally isolating the troponoidal reaction products. UV analysis at λ_{max} (Table VI) established the practically quantitative yield of the substitution product, free from any side product.

Kinetics were carried out either by mixing the reagents into a quartz cuvette which was placed into the thermostated cell compartment of the spectrophotometer, or, for all reactions of 3-tosyloxytropone, by the standard stopped-flow technique already employed for similar cases.[6]

References and Notes

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