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Recent advances in the chemistry of stable simple enols

Zvi Rappoport*, Joseph Frey, Mark Sigalov and Elimelech Rochlin

Department of Organic Chemistry, The Hebrew University, Jerusalem 91904, Israel

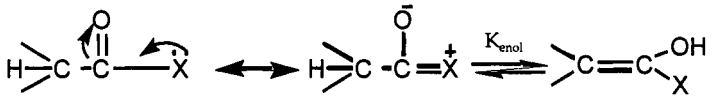
Abstract: Two new aspects of the chemistry of simple bulky-aryl substituted enols are described. (i) The reactions of amines such as Me_2NH, morpholine piperidine, or pyrrolidine with ditipyl ketene (tipyl = Tip = 2,4,6-tri-isopropyl-phenyl) generate the enol of the amide $Tip_2C{=}C(OH)NR^1R^2$ which is observed and characterized by NMR spectra. The addition reaction is reversible. Further tautomerization of the enol to the stable conformer of the amide is relatively slow and involves an additional NMR observable intermediate which is presumably the kinetically controlled unstable conformer of the amide. (ii) Di- and tri-bulky arylvinyl alcohols and their derivatives such as the ethers or acetates are chiral, having a propeller conformation. The enantiomerizations of triarylethenols usually proceed by a three ring flip, and the rotational barriers are mostly too low for resolution of stereoisomers. In the $Mes_2C{=}C(OH)$(2-X-9-anthryl) system where X = F, OMe, the α-ring lacks a C_2 symmetry and enantiomerization barriers in which this ring passes through the molecular plane are higher. Resolution on an optically active column is achieved when X = F, but fast enantiomerization then takes place. This is probably due to an E ⇌ Z enol interconversion which was observed in other systems.

This lecture deals with two topics in the chemistry of stable simple enols in which advances were achieved in the last two years. These are the generation and ^1H NMR observation of enols of amides and the successful attempt to make an optically active enol.

A background to the first topic is that simple enols, i.e. those substituted only by hydrogen, alkyl or aryl groups are usually short-lived compared with their carbonyl tautomers. For example, the acetaldehyde ⇌ vinyl alcohol equilibrium constant is $10^{-6.23}$ in water.[1] However, these enols were generated and studied extensively in recent years, especially by Wirz's and Kresge's groups.[2]

We had studied a different family of enols. Bulky-aryl (e.g., mesityl) substituted enols, were prepared as stable species by Fuson, more than 50 years ago,[3] but they were mainly forgotten. We prepared many new enols and studied many aspects of their chemistry. These involved their X-ray structures, substituent and solvent effects on the keto ⇌ enol equilibria, the conformation of the C=C-O-H moiety, their NMR spectra, gas phase reactions and other topics. A natural extension is to less stable enol species.[4]

Enols of carboxylic acid derivatives are much less stable than enols of aldehydes and ketenes. A recent calculation gives the equilibrium value for $AcOH \rightleftharpoons H_2C{=}C(OH)_2$ as 10^{-19} in water.[5] Nevertheless, several enols of acid were observed by Wirz and Kresge as short lived intermediates[6] and the equilibrium constants with their acids are indeed low. This is ascribed to stabilization of the tautomeric acid derivative by electron donation from the heteroatom attached to the carbonyl group (eq 1).



X = OH, OR, NHR, OCOR (1)

We applied our approach, which involve the use of bulky substituents to increase the stability and generated recently in solution the most persistent enol of acid known so far, i.e., 2,2-ditipyl-1,1-ethenediol (**2**, Tip = 2,4,6-tri-isopropylphenyl), by addition of water to ditipyl ketene (**1**)[7] (eq 2). Although **2** was not isolated, its spectral properties, the reversibility of its formation, and its reactions were investigated.

$$\underset{\mathbf{1}}{Tip_2C{=}C{=}O} + H_2O \underset{0\ ^\circ C,\ 8\ hr}{\overset{10{:}1\ DMF\text{-}THF}{\rightleftharpoons}} \underset{\mathbf{2}}{Tip_2C{=}C(OH)_2} \longrightarrow Tip_2CHCOOH \qquad (2)$$

Enols of amides are much less known that enols of acids and I will describe now our preliminary results in preparing them in solution by a reaction analogous to that in eq 2. A prerequisite of the study is the use of a secondary amine in order to avoid the possible enamine $\rightleftharpoons$ imine equilibria in the derivatives of primary amines.

Four amines were reacted with ditipyl ketene and strong ^{1}H NMR spectral evidence for the formation of the α-dialkylamino enol was obtained in each case. The simplest amine studied was dimethylamine which on reaction with **1** in 5:1 DMF-CCl_4 at 243 K gave immediately a new compound, whose spectrum differs from that of the ketene (3 singlets for the *o*-Me, *p*-Me and Tip-H protons and two heptets for the *o*- and *p*-CH). Part of the spectrum is shown in Figure 1. Especially revealing are several signals. (i) The high field two i-Pr-Me doublets at ca. 0 ppm, since i-Pr-Me groups at this field are characteristic of $Tip_2C{=}CR^1R^2$ systems ($R^1 = R^2$ = H, OH, $SiMe_3$; R^1 = H, R^2 = OH). [7](ii) The low field OH signal at δ 9.40, a position reminiscent of the enolic OH of **2** or simple aryl-substituted enols in DMF of DMSO. (iii) The four different Tip-H signals (two of which nearly overlap) and separate signal for each i-Pr-Me group indicate diastereotopicity for each pair of *m*-H and *o*-Me signals, reflecting a slow rotation of the tipyl ring around the Tip-C= bonds on the time scale of the NMR experiment. The reaction is depicted in the left hand side of equation 3, with a frozen propeller conformation for **3**, the enol of the amide.[8]

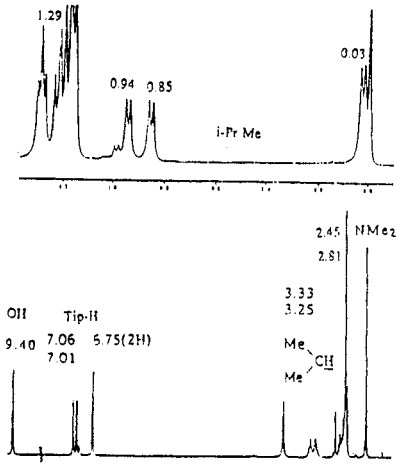


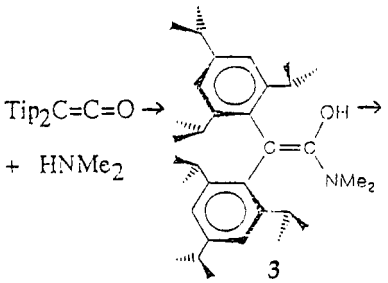
Fig. 1 ^{1}H NMR spectrum of **3** in 5:1 DMF-CCl_4 at 243 K.

The ^{13}C NMR spectrum display 12 signals for Tip-C carbons, corresponding to structure **3**, a low field C_β (157.43 ppm) and a high field C_α (82.98 ppm), at δ values close to those in

Table 1. Chemical shifts for $Tip_2C{=}C(OH)X$

X	Solvent	$\delta^{13}C_\alpha$	$\delta^{13}C_\beta$	δO^1H
NMe_2	5:1 DMF-CCl_4	157.43	82.98	9.40
	5:1 MeCN-THF		6.48	
	$CDCl_3$	156.23	82.86	
OH	DMF	157.02	80.4	9.65
OMe	2:1 MeOH-CCl_4	158.44	85.51	
H	DMSO	144.70	108.62	8.92

the 1,1-enediol **2** and in other enol amides, but at a lower field and higher field respectively, than in 2,2-ditipylethenol (Table 1), suggesting a contribution from the dipolar structure $Tip_2\overset{-}{C}\text{-}C(=\overset{+}{O}H)OH$. The enol was also observed in 5:1 CD_3CN-THF-d_8.

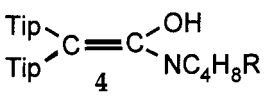


$Tip_2CHCONMe_2 \rightarrow Tip_2CHCONMe_2$ (3)

Amide I Amide II

On standing at 273 K, or faster at room temperature, **3** tautomerizes to the amide. However, this process is more complicated than the tautomerization of **2** to the acid. After 2 hr at 273 K **3** disappears completely and a spectrum of a new species appears. It displays a CH signal at δ 5.90 and several iso-Pr-Me signals, but on standing this species rearranges to the stable amide isolated from the reaction, which displays i-Pr-Me and C-H signals at different positions. As represented in eq 3 we believe that the first formed species is a less stable conformer (amide I) of the product amide (amide II).

Similar spectral changes are observed when the cyclic amines morpholine, piperidine and pyrrolidine are added to **1** in $CDCl_3$. In the initially formed products **4a-c**, which are formed very rapidly, even when the amine/**1** ratio for pyrrolidine is only 2, C_α and C_β are at positions similar to those in **3**, there are 12 Ar-C or 4 Ar-H signals indicating a hindered rotation around the Tip-C bonds, and high field i-Pr-Me at ca. δ=0 are observed.



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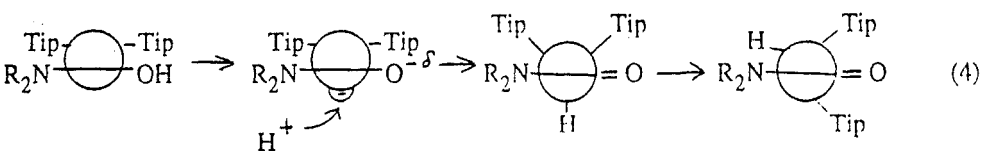
a NC_4H_8R = Morpholino (R = O)
b NC_4H_8R = Piperidino (R = CH_2)
c NC_4H_8R = Pyrrolidino (R = -)

The OH signal integrates as 1H for **4a**, but it is broad for **4b** and **4c** and it is not observed at several [amine]/[**1**] ratios, presumably due to exchange with free amine. In **4a** it disappears completely in D_2O, and in 1:1 H_2O:D_2O C_α split to two signals ($\Delta\delta$ = 0.25 ppm at 400 MHz), one C_o and the two C_{ipso} carbons also split but to a lower extent, while C_β split very little. We ascribe this splitting to an isotope effect of the D on the ^{13}C signals, e.g., Tip_2C-OH and Tip_2C-OD appear at different δ values. This behavior partially resembles that observed for **2**. In a single experiment such splitting was not observed for **4c**, whose OH proton seems to exchange in the medium.

Two amides, amide I and amide II were observed in each case. Whereas amide II was isolated, amide I was unstable and rearranged to amide II. Corroboration of the amide I structure is the C*H* signal at δ 5.84 and the ^{13}C=O signal at δ 172.67 ppm which at amide II appear at δ 5.73 and 173.31 ppm, respectively. There are differences in the chemical shifts of the proton signals α to the nitrogen in the two amides.

At present, we do not have enough data on the conformation of the two amides and we are waiting until we will have an X-ray data of the stable amide. 2D NOESY spectra show similarities among the spectra of the amide I of **4a-c** and similarities among those of amide II of **4a-c**. In the pyrrolidine amide, II but not in amide I the C-*H* shows cross peaks with the two CH_2 protons and with two methines of i-Pr groups.

A reasonable speculation concerning the conformation of both amides is possible. Tautomerization probably occur via initial ionization to the enolate ion (**5**) followed by protonation on the carbanionic orbital (equation 4) to give **6** which is then converted to

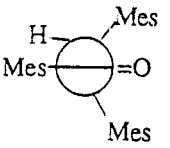


(4)

5 6 7

the unstable conformer of the amide. The stable conformer is **7** formed by internal rotation in **6**. In **7** the CH is in the vicinity of the NCH_2 protons and if the conformation is slightly unsymmetric, this is consistent with the NOESY correlation. The suggested structure of **7** is close to the X-ray structure (**8**) of

trimesitylethanone.[9] We note, however, that ditipylacetic acid, which is structurally related to **6** does not show a hindered rotation in the ^{1}H NMR spectrum.



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In conclusion, formation of enol amides with the bulky β-tipyl groups seems a rapid and easy process. The spectral data strongly corroborates the suggested structure. The tautomerization to the isolated amide proceeds via an initial formation of an unstable conformer of the final amide, which is slowly converted to the more stable conformer.

My second topic deals with the recent advance in our attempt to prepare an optically active simple stable enol.

Triarylethenols, like other triarylvinyl systems, exist in a chiral propeller conformation where all the rings are twisted in the same direction with respect to the double bond plane. The evidence comes from X-ray diffraction, MM calculations and dynamic NMR (DNMR) behavior.[4] When the aryl rings are bulky, e.g., mesityls, rotation around the Ar-C- bonds is hindered, and at room temperature or below, the NMR spectrum displays a frozen conformation where each proton or group exhibits a separate signal. On raising the temperature, rotation around the Ar-C- bonds becomes faster on the NMR time scale and coalescence of diastereotopic groups enables to calculate the rotation barriers. Analysis of the rotations in these vinyl propellers is in terms of flip processes. The rotation of the three rings in most cases is correlated, i.e., the three rings rotate concertedly. Such rotations can lead to helicity reversal of the propeller either when a ring passes through a plane normal to the reference $(C_{ipso})_2C{=}C$ plane (a flip process) or via this plane (a non-flip movement). Various combinations of conrotatory flip rotation of one or more rings and disrotatory rotation of the other ring(s) leads to helicity reversal and the mechanisms are dubbed "[n]-ring flips" where n is the number of the flipping rings. When all the rings are identical and have C_2 symmetry any flip route results in enantiomerization. The barrier to enantiomerization (threshold energy) is the flip route of lowest activation.

DNMR enables to follow a flip of a ring which leads to coalescence of diastereotopic groups. When all the rings have C_2 symmetry passage of a ring through the reference plane exchanges enantiotopic protons and is unrecorded by DNMR. The propeller enantiomers together with group labeling are shown for trimesitylethenol in Figure 2, which enables to corroborate the latter statement.

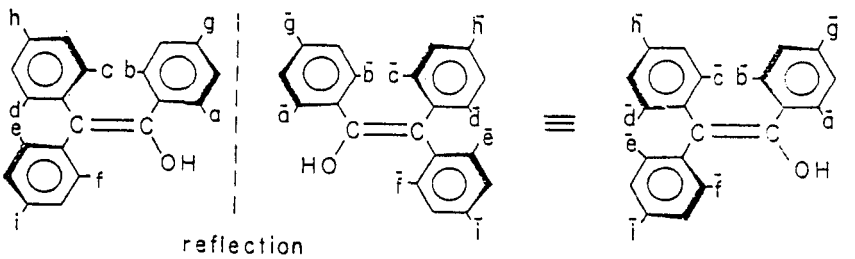


Fig. 2 Trimesitylethenol, a representative vinyl propeller

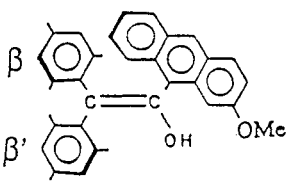
It was found experimentally that the threshold process for most tri(bulky-aryl) vinyl propellers, including the enols is the three ring flip. The enantiomerization barriers were < 20 kcal mol^{-1}.[4] These values are too low to enable isolation of one enantiomer at a reasonable temperature. How can we then isolate an optically active triarylethenol?

The obvious answer is to increase the enantiomerization barrier by devising a threshold enantiomerization route in which at least one ring passes through the reference plane. This can be done by breaking the C_2 symmetry of one ring. When a single *m*-substituent is introduced into a ring, the

substituent in the C_s-ring can be "up" (U) and "down" (D) in relation to the reference plane. Having "right-handed" (RH) and "left-handed" (LH) propellers result in two pairs of diastereomers. The three ring flip of a RH-U propeller leads now to a LH-U propeller, i.e. diastereomerization. Enantiomerization, i.e., RH-U → LH-D requires passage of the C_s ring via the reference plane, usually a higher energy process than a flip of this ring. We used this approach to measure the barriers for four types of ring flips in methoxy-substituted trimesitylvinyl isopropyl ethers[10] and found the following increasing order of barriers: [3-] < [α,β'-2] < [α,β-2] < [β,β'-2], where β- and β'- are the ring *trans* and *cis* to the non-aromatic vinylic substituent, and the ring which does not appear in the bracket is the ring passing through the reference plane.

The conclusion is that our desired enol should contain three bulky aryl groups, two identical C_2-ones at C_β and a C_s-one at C_α. Past experience and convenience in the measurement suggest the use of two β-mesityl (Mes) rings and a 2- or 3-substituted 9-anthryl ring. The latter resembles mesityl by being an *o,o'*-disubstituted phenyl, is less bulky then mesityl in a plane normal to the C=C plane, but is bulkier than mesityl when passing through the molecular plane.

We had studied α-9-anthryl-β,β-dimesitylethenol in the past by DNMR. The threshold process is a 3-ring flip with a threshold energy of 16.1 kcal/mol, measured at the three rings (16.0 at the anthryl ring, measured by coalescence of the peri-H), 16.1 and 16.3 for the β and β' rings, respectively (measured by coalescence of *o*-Me or *m*-H groups in each).[11] As an anthryl substituent we had chosen now 2-OMe or 2-F, substituents that display singlets in the ^1H and ^{19}F NMR spectra at a range free from overlap with other signals.



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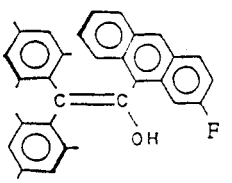
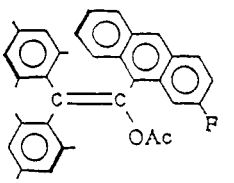


10



11

The two enols (**9** and **10**) were prepared by reaction of dimesityl ketene with the 2-substituted 9-anthryl lithium, which was prepared in turn from n-BuLi and the 9-bromo derivative. The common precursor to the latter was 2-aminoanthraquinone. Diazotation gave the diazonium salt, which on decomposition in water gave the 2-OH derivative, and which with HBF_4 and pyrolysis gave the 2-F derivative. Reduction with HI gave the 2-substituted anthracenes. The 2-F compound was brominated at C-9, while the 2-OH compound was acetylated, and the 2-OAc was brominated at C-9, hydrolyzed to the phenolate and methylated with dimethyl sulfate.

Both **9** and **10** have at room temperature the proper number of signals (with some accidental overlap) in the ^1H NMR spectrum, expected for a mixture of diastereomers where rotations around the Ar-C= bonds are frozen. There are 16 Ant-H, 12- Mes-Me, 8- Mes-H, 2 OH and 2 MeO (or F) signals. Complete assignments of the location of each of these was achieved by a combination of COSY and NOESY techniques.

On raising the temperature, the usual DNMR behavior, i.e., broadening, coalescence and sharpening of signals were observed. For example, with **9** the OMe signals coalesce at T_c = 310 K and the two H-8 anthryl doublets (which are at the extreme low field end of the spectrum and hence easy to follow) coalesce at 321.5 K. The calculated rotational barriers $\Delta G_c^{\#}$ for both probes are 15.7 kcal/mol. This process reduces the number of Ant-H protons by half. At 413 K the β-*o*-Me signals coalesce with $\Delta G_c^{\#}$ of 21.9 kcal/mol. The Mes-H signals of the β'-ring slightly broaden but do not coalesce up to 430 K.

Similar spectral changes take place with **10**. However, here three coalescence processes were observed, with a different $\Delta G_c^{\#}$ value for each ring, as shown in Table 2.

The lower barrier in both cases is for the 3-ring flip and it follows the order: 2-F > 2-H > 2-OMe, although the differences are small. The next higher barrier is for the α,β-2 ring flip. The various barriers, as well as that for **11**, the acetate of **10** (see below) are given in Table 3. The α,β-2-ring flip barrier of 21.9 kcal/mol indicates that the enols have a good chance to be resolved on an optically active column. The related system Mes_2C=C(OAc)MesOMe-3 was previously resolved on an optically active column and its

barrier for the β,β'-2-ring flip enantiomerization (22.0 kcal/mol) is higher than that (19.0 kcal/mol) for the 3-ring flip diastereomerization.[12]

Table 2. DNMR behavior of **10** in $C_6D_5NO_2$

Signal	Δν (slow ex) Hz	k_c, s^{-1}	T_c,K	$\Delta G_c^{\#}$ kcal/mol
F	754 (295 K)	1674	376.5	16.7
H-8	129.3 (295 K)	287.3	346	16.5
β-Mes-H	15.4 (410 K)	34.2	430	22.5
β'-Mes-H	3.2 (420 K)	7.1	444.6	24.6

Table 3. Barriers in $C_6D_5NO_2$

Ring flip	9	10	11	12a, b, c
α,β,β'-3	15.7	16.7	16.6	15.9
α,β-2	21.9	22.5		21.1
α,β'-2		24.6		23.1
β,β'-2		**22**	26.3	25.2
		(est 26.5)		

We estimate the barrier for the β,β'-2-ring flip of **10** as 26.5 kcal/mol by two tools. the barrier for the analogous process for the acetate **11** is 26.3 kcal/mol (see below) and an approximate extrapolation from the various barriers for trimesitylvinyl isopropyl ethers,**12a-c** (Table 3), assuming that the quantitative order of values will be retained in **9**.

m-MeOMesC(Mes)=C(OPr-i)Mes Mes$_2$C=C(OPr-i)MesOMe-*m*
12a (E) **12b** (Z) **12c**

Since NMR cannot be used to measure this barrier, resolution of both **9** and **10** on an optically active amylose (3,5-dimethylphenyl carbamate) column coated with silica gel was tried. Separation was incomplete for **9**, but a complete separation of the 1:1 enantiomer mixture of **10** was achieved by HPLC using a 98:1:1 hexane: EtOH:i-PrOH elution solvent.

According to our estimated barrier, the enantiomers of **10** should be stable for days at room temperature. However, to our surprise, the pure enantiomers racemized in less than 1 h at room temperature and rapidly even at 0 °C. The rate constant of the "spontaneous" racemization was $k_{rac} = 2\ k_{enant} = 1.1 \times 10^{-3}\ s^{-1}$ at 25.5 °C, which gives $\Delta G_c^{\#} = 21.9$ kcal/mol.

It is therefore clear that another low energy route, which does not involve rotation of the rings in the neutral enol, is responsible for the racemization. The evidence below suggests that this new mechanism involves reaction at the O-H group, but we are unable to explain as yet some of the results.

The effect of added triethylamine (TEA) or trifluoroacetic acid (TFA) on the racemization rate were investigated. The effect of TEA is complex. At substrate concentration of 5.3×10^{-5} M (at 26 °C in 98:1:1 hexane: EtOH; i-PrOH) the reaction is accelerated on increasing the [TEA] in the range of 1.8×10^{-5} - 1.8×10^{-4} M and the first order plots are non-linear. However, on further increase in the concentration the rate starts to increase again, the plots become linear and at 9×10^{-4} M [TEA] the rate becomes approximately identical with the "spontaneous" rate. Further increase in the [Et_3N] to 9×10^{-3} M [Et_3N] decreases the racemization by ca. 10-fold and $k_{rac} \sim 10^{-4}\ s^{-1}$. Several linear and non-linear first order plots at different TEA concentrations are shown in Figure 3. The slow racemization at 9×10^{-3} M TEA enables collection of the pure enantiomers, and a CD spectrum of both of them had been obtained.

What is the mechanism of the "spontaneous" racemization of **10**? The amine catalysis at low concentration indicates that ionization of the enolic O-H group is involved. When the solvent used was 98:1:1 hexane: EtOD: i-PrOH, the "spontaneous" racemization was 1.5-fold slower, i.e., k_H/k_D = 1.5, another indication of a proton transfer.

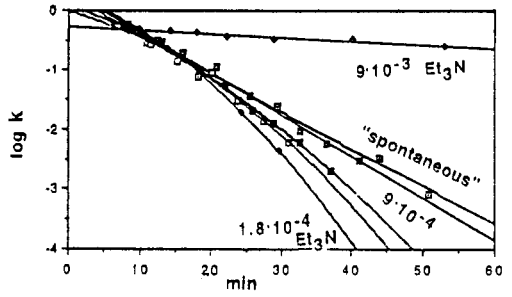
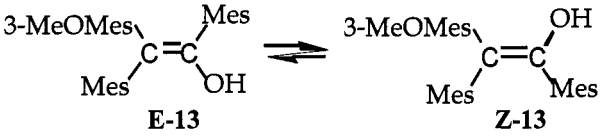


Fig 3. Racemization of **10** in the presence of Et_3N.

In order to check this hypothesis the acetate **11** of enol **10** was prepared. X-ray diffraction showed that the fluorine is at C-2, and a propeller conformation with Ar-C=C torsion angles of 65.5° (α-anthryl), 55.9° (β-Mes) and 58.6° (β'-Mes). Dynamic ^{1}H NMR gave a low

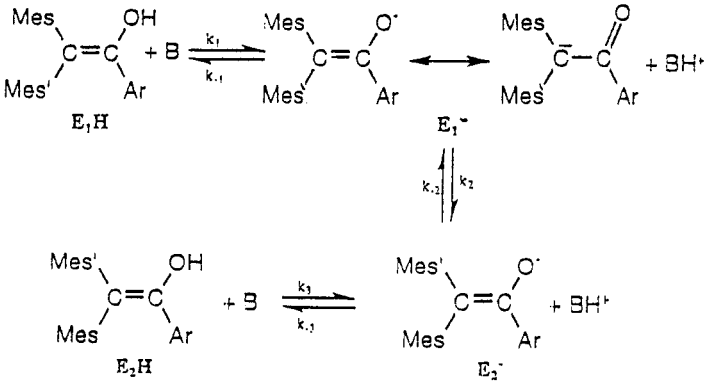
3-ring flip barrier of 16.6 kcal/mol, i.e., identical with that for **10**. **11** could not be resolved with the same solvent mixture used for resolution of **10**, but it was resolved using 80:20 hexane:i-PrOH. Interestingly, integration showed that the two enantiomeric acetates are present in a 0.77 ratio, shwoing that one enantiomer is preferred. The resolved optically active acetates were relatively stable to racemization. At 37 °C, 55 °C and 70 °C, the racemization took ca. 8.5 days, 10 hrs and 80 min, respectively (10^6 k_{rac} = 3.6, 48 and 290 s^{-1}, respectively). The derived $\Delta G^{\#}$ for the β,β'-2-ring flip is 26.3 kcal/mol and from Arrhenius plot $\Delta H^{\#}$ = 27.6 kcal/mol, $\Delta S^{\#}$ =4.3 e.u. Hence, a "normal" racemization mechanism is indicated for the acetate. Indeed, 1.8 x 10^{-5} - 10^{-2} M of either TEA or TFA do not affect the racemization rate of **11**.

Finally, an interesting result is that these characteristic features of the racemization are shared by the E/Z isomerization of β-*m*-methoxymesityl-α,β-dimesitylethenol[10] (eq 5). This reaction shows an isotope effect of 2.1 when the deuteriated enol is used, pyridine



(5)

affects the isomerization rate in the same way that Et_3N affects the racemization rate of **10**, and the corresponding i-Pr ethers **12a** and **12b** are stable to isomerization in the presence of a base.



(6)

A mechanism for racemization of **10** which takes account of the normal behavior of **11**, the amine catalysis at low [Et_3N], the isotope effect and the similarity with the isomerization of **13** is shown in equation 6. The base generates the enolate, which then undergoes a rotation around the C-C bond, followed by reprotonation of the isomeric enolate. Whereas this process is sufficient to isomerize **13**, it

does not necessarily lead to racemization of **10**. The α-ring should also flip or rotate. In the transition state for this rotation the ArCO plane is orthogonal to the Mes_2C^- plane and rotation of the aryl ring becomes easy.

The main unsolved question is how to explain the effect of the high amine concentration. It is unlikely that the anion is involved in the rotation stage, and it should increase the ionization rate. Does it operate at the enolate reprotonation step? At these base concentrations the proton may be attached to two amines (homoconjugation), so that different species may be involved in the protonation at low and high amine concentration. However, at yet this is only a speculation.

Addition of TFA increases the racemization rate. The first order plots are linear and the rate is higher at a higher TFA concentration, although the increase is not linear with [TFA}. A 50-fold increase in [TFA] from 6.8×10^{-5} to 3.4×10^{-3} M increase k by only 50%. The effect is more pronounced at low TFA. The rate increases 6-fold at 3.4×10^{-3} in TFA over the spontaneous rate.

A mechanism involving double bond protonation followed by rotation around the C-C bond in the protonated species, followed by expulsion of the proton seems likely. However, ionization to an α-anthrylvinyl cation, whose α-anthryl ring can undergo easy rotation cannot be excluded without evidence. In addition, the acid may decrease the rate of "spontaneous" racemization by decreasing the concentration of the intermediate enolate ion.

In conclusion, an optically active enol could be prepared and resolved, but it is shorter lived than predicted due to the intervention of a racemization route which probably initiates by ionization of the OH group.

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