Asymmetric Substituent Effect on the Reaction of (*R*)- and (*S*)-Indan-1-carboxylic Acids with (*S*)-α-Phenylethylamine Derivatives

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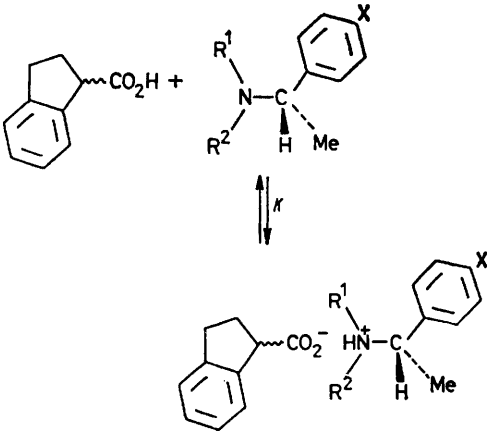
Summary In the reaction of (*R*)- and (*S*)-indan-1-carboxylic acids with (*S*)-α-phenylethylamines, the substituent effect is highly stereoselective and the equilibrium constants K_{SS} and K_{RS} are affected by inductive and resonance effects of the substituent at the *para* position of phenylethylamine rather than by steric hindrance.

We report a substituent effect on the reaction of chiral acids with chiral amines. The reaction of (*R*)- and (*S*)-indan-1-carboxylic acid with *para*-substituted (*S*)-α-phenylethylamines in carbon tetrachloride can be illustrated by equation (1).



(1)

The i.r. spectrum of the reaction system shows maxima at 1755 and 1710 cm^{-1} (monomeric and dimeric stretching vibrations of the carboxy group), and 1380 cm^{-1} (symmetric stretching vibrations of the carboxylate ion), with molecular extinction coefficients of 920, 1410, and 300, respectively. The equilibrium constants for ionization, K_{SS} and K_{RS} [(*S*)-acid–(*S*)-amine and (*R*)-acid–(*S*)-amine pairs, respectively], were evaluated by the procedure previously described,[1] and are summarized in the Table.

Table. Equilibrium constant (l mol^{-1}) for the reaction of (*R*)- and (*S*)-indan-1-carboxylic acids (6 mmol l^{-1}; $[\alpha]_D$ + 43·3 and −47·0 benzene, *c* 0·1) with (*S*)-α-phenylethylamines in CCl_4 at 30 °C.

Amine substituents			$[\alpha]_D$ (neat)	[Amine] 3 mmol l^{-1}		6 mmol l^{-1}	
R^1	R^2	X		K_{SS}	K_{RS}	K_{SS}	K_{RS}
H	H	H	−40·7	1380	1170	2080	1880
"	"	Me	−34·3	1250	1500	1800	2100
"	"	F	−30·7	3880	1160	2340	1590
"	"	Cl	−33·9	870	320	1130	840
"	"	Br	−30·0	1500	1220	2010	1350
"	"	CN	−29·4	< 100		< 100	
"	"	OMe	−31·1	5690	2780	4580	2830
H	Me	H	−78·9	2200	4720	1690	1740
"	"	Me	−46·9	4290	8900	2890	3540
"	"	Cl	−65·2	800	740	700	800
Me	Me	H	−66·5	126	145	72	119
"	"	Me	−64·2	145	165	123	155
"	"	Cl	−65·9	85	90	55	82
(*S*)-(+)-indan-1-amine			+26·0	2930	2470	3870	2670

In spite of the structural difference the ratios K_{SS}/K_{RS} for phenylethylamine and the rigid indan-1-amine systems are almost equal, the extent of ionization of the (*S*)–(*S*) pair being larger than that of the (*R*)–(*S*) pair. Electron releasing substituents such as methyl groups on the aromatic ring and nitrogen atom, favour the ionization of the (*R*)–(*S*) pair, while resonant substituents such as methoxy and halide groups favour ionization of the (*S*)–(*S*) pair. These facts indicate that the stereoselective substituent effect arises from the electronic nature of the substituent and the resonance effect governs stereoselectivity. Although here we cannot elaborate on the correlation between the electronic effect and the stereoselectivity, we would expect these stereoselective interactions to be common in chiral systems. The data in the Table show a linear correlation with the induced circular dichroism intensities in 4-benzoylbenzoic acid–chiral amine systems.[2] The electronic effect observed in the asymmetric reaction of carbonyl compounds[3] may be an analogous phenomenon.

(*Received, 29th March 1978; Com. 335.*)

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